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***Retrospective Cohort Study***

**Pegylated interferon  $\alpha$ -2b add-on to nucleos(t)ide analogues reduces hepatocellular carcinoma and decompensation in advanced fibrotic chronic hepatitis B**

Li XY *et al.* Peg-IFN $\alpha$ -2b add-on therapy in advanced CHB

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ACCEPTED

## Abstract

### BACKGROUND

The current therapeutic strategy of adding pegylated interferon (Peg-IFN)  $\alpha$ -2b to nucleos(t)ide analogues (NAs) is primarily aimed at achieving functional cure. However, its value in improving prognosis and the suitable candidates for this combination strategy in patients with hepatitis B virus (HBV)-related advanced fibrosis or compensated cirrhosis remain to be further explored.

### AIM

To evaluate the long-term prognosis benefit of add-on Peg-IFN $\alpha$ -2b therapy in patients with HBV-related advanced fibrosis or compensated cirrhosis.

### METHODS

This retrospective cohort study enrolled patients diagnosed with HBV-related advanced fibrosis or compensated cirrhosis. Participants were divided into two groups: (1) Those receiving combination therapy (Peg-IFN $\alpha$ -2b add-on to ongoing NA treatment); and (2) Those receiving NA monotherapy. A 1:1 propensity score matching approach was applied to balance baseline characteristics between groups. In survival analysis, the outcomes of hepatocellular carcinoma (HCC) and decompensated cirrhosis were stratified by baseline clinical features and established HCC risk scores.

### RESULTS

The analysis included 302 matched pairs, with a median follow-up duration of 220 weeks. Combination therapy was associated with a significantly lower risk of developing HCC (hazard ratio = 0.22; 95%CI: 0.11-0.48) and decompensated cirrhosis (hazard ratio = 0.39; 95%CI: 0.20-0.77) than NA monotherapy. These benefits were particularly pronounced among patients classified as intermediate-to-high risk by validated HCC prediction models and in those with persistent biochemical abnormalities lasting > 12 months.

## CONCLUSION

Add-on therapy with Peg-IFN $\alpha$ -2b to NAs is significantly associated with reduced HCC and decompensation in high-risk patients with HBV-related advanced fibrosis or cirrhosis, supporting its use in this population.

**Key Words:** Chronic hepatitis B; Hepatitis B-related cirrhosis; Pegylated interferon  $\alpha$ -2b add-on therapy; Risk stratification; Hepatocellular carcinoma; Decompensated cirrhosis; Therapeutic strategy

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**Core Tip:** This large-scale, propensity score-matched cohort study provides evidence that a pegylated interferon  $\alpha$ -2b add-on strategy reduces the risk of hepatocellular carcinoma and decompensated cirrhosis among patients with hepatitis B virus-related advanced fibrosis or compensated cirrhosis. The benefits of combination therapy were particularly pronounced in patients classified as having an intermediate-to-high risk of hepatocellular carcinoma. A persistently elevated transaminase level for > 12 months also identified a patient population that derived significant benefit from this approach. These results indicate that a prognosis-oriented approach with pegylated interferon  $\alpha$ -2b add-on therapy should be considered.

## INTRODUCTION

Chronic hepatitis B (CHB) is a primary cause of cirrhosis and hepatocellular carcinoma (HCC) globally. In 2021, hepatitis B virus (HBV)-related cirrhosis affected 283000000 individuals, causing 432000 annual deaths, while HBV-related HCC accounted for an additional 206400 deaths[1]. Despite reduction in hepatitis B

surface antigen (HBsAg) prevalence in younger individuals[2,3], several infected individuals remain at risk of disease progression owing to the lack of a sterilizing cure that eradicates the virus.

Current guidelines recommend antiviral agents, such as nucleos(t)ide analogues (NAs) and interferon-based therapies, as first-line therapy for managing CHB and controlling disease progression[4-7]. NAs, such as tenofovir alafenamide, tenofovir disoproxil fumarate, and entecavir, are the most commonly used agents for managing CHB. They suppress viral replication, delay disease progression, improve prognosis, and have a favourable safety profile and low resistance rates[4,5,8]. Interferons inhibit viral replication, reduce HCC incidence, and slow fibrosis progression. However, it is not widely prescribed as monotherapy owing to lower response rates, a narrower scope of application, and more frequent side effects[4,9,10].

Given their complementary mechanisms of action[4,11,12], combining pegylated interferon (Peg-IFN)  $\alpha$  with NAs has attracted interest. The main advantage of combination therapy lies in its potential to attain a functional cure, defined as sustained HBsAg loss ( $\geq 24$  weeks) with or without hepatitis B surface antibody seroconversion, while maintaining HBV DNA levels below the lower limit of detection[13,14]. Achieving a functional cure carries clinical implications as it decreases the incidence of HCC and decompensated cirrhosis, enhancing patient prognosis[15,16]. The “update on the treatment navigation for functional cure of CHB: Expert consensus 2.0”, published in January 2025, suggests that, to achieve a functional cure, a 48-week to 96-week course of interferon combined with NAs should be offered to patients who achieve virological responses below the detection limit after NA therapy and have an HBsAg titre  $< 3000$  IU/mL[14]. Other major clinical guidelines recommend combination therapy aimed at functional cure only for specific populations or have not yet issued guidance on this approach[4,5,14].

Cure-oriented strategies may overlook patients with advanced liver fibrosis or compensated cirrhosis. According to current guidelines, patients who are not considered candidates for functional cure should continue NA monotherapy and have their HBsAg levels monitored[17,18]. Patients who have progressed to cirrhosis

have a high risk of developing decompensated cirrhosis or HCC even with continuous NA therapy[19,20]. Add-on Peg-IFN $\alpha$  therapy reduces HCC incidence and contributes to better long-term outcomes[21], leading hepatologists to question whether Peg-IFN $\alpha$  add-on therapy can also be used to improve prognosis in patients with advanced liver fibrosis or compensated cirrhosis.

Currently, direct evidence regarding the effectiveness of Peg-IFN $\alpha$  and NA combination therapy in reducing the incidence of HCC and decompensated cirrhosis in patients with advanced fibrosis or cirrhosis is insufficient to determine which patients, based on different risk profiles, would benefit more from combination therapy. This study compared the long-term outcomes of Peg-IFN $\alpha$ -2b combined with NA *vs* NA monotherapy in patients with HBV-related advanced fibrosis or compensated cirrhosis, stratified by risk profiles.

## **MATERIALS AND METHODS**

### ***Study design and participants***

This propensity score-matched retrospective cohort study enrolled patients diagnosed with HBV-related advanced liver fibrosis or compensated cirrhosis treated at Third Affiliated Hospital of Sun Yat-sen University between June 1, 2017 and December 31, 2025.

**Inclusion criteria:** (1) HBsAg positive for more than 6 months; (2) Ongoing long-term treatment with NAs; (3) HBV DNA suppressed to undetectable level and hepatitis B e antigen negative, with or without hepatitis B e antibody seroconversion; and (4) Advanced liver fibrosis or compensated cirrhosis based on abdominal ultrasonography or liver stiffness measurement.

**Exclusion criteria:** (1) Non-compliance with the treatment regimen, discontinuation of treatment due to adverse effects, or inability to continue therapy; (2) Loss to follow-up; (3) Comorbid conditions affecting liver function, such as other viral hepatitis or secondary liver tumours; and (4) Request to withdraw or patient deemed unsuitable for inclusion for other reasons.

### *Data collection and analysis*

Patients were divided into two groups: The monotherapy group continued NA monotherapy, whereas the combined therapy group received Peg-IFN $\alpha$ -2b combined with an NA for 48-96 weeks, followed by continued NA monotherapy.

A 1:1 propensity score matching (calliper = 0.02) was performed to minimise baseline differences. Based on seven studies of predictive factors for HCC and decompensated cirrhosis[22-28], matching factors included age, sex, family history of HCC, history of diabetes, alpha fetoprotein level (using 10 ng/mL as the cut-off), history of alcohol consumption, and definitive imaging-confirmed cirrhosis.

Survival analysis was applied to estimate and graphically depict (*via* Kaplan-Meier curves) the cumulative incidence of HCC and decompensated cirrhosis. The log-rank test was used to determine significance. Stratified analyses were performed based on HBsAg titres and achievement of early biochemical normalization. Six HCC prediction models [mREACH-B[22], mPAGE[23], AASL-HCC[24], REAL-B[25], cirrhosis, age, male sex, and diabetes mellitus (CAMD)[26], and aMAP[27]] were selected according to the guidelines and stratified survival analyses were conducted using log-rank tests according to the HCC risk group. Cox regression was used to calculate hazard ratios (HRs) with 95% CIs, with the monotherapy group as the reference. Prognostic outcomes were compared between the combination and monotherapy groups across patient subgroups defined by HBsAg titres, inflammation levels, and risk groups.

$\chi^2$  tests were used to evaluate the rates of HBsAg clearance, biochemical normalization, and maintained virological response (MVR) between groups, to assess the relative effectiveness of the two regimens.

Changes in three non-invasive liver fibrosis scores, fibrosis-4 (FIB-4) index, the aspartate aminotransferase-to-platelet ratio index (APRI), and gamma-glutamyl transferase-to-platelet ratio (GPR), were calculated before and after treatment. The degree of change was defined by the following equation: (posttreatment score - pretreatment score)/pretreatment score.

The two treatment groups were compared for their degree of improvement

using analysis of covariance or the Mann-Whitney *U* test, depending on whether the data were normally or non-normally distributed.

### ***Definitions***

HCC and decompensated cirrhosis were diagnosed according to the Chinese clinical practice guidelines[29,30]. Stratification was based on the guideline-recommended HBsAg cut-offs for combination therapy, resulting in three groups: (1) < 500 IU/mL; (2) 500-3000 IU/mL; and (3) > 3000 IU/mL[14,15]. Early biochemical normalization was defined according to the European Association for the Study of the Liver guidelines as stable biochemical normalization within 12 months after starting treatment[6,31]. HCC risk grouping was based on the original risk categories recommended by the respective prediction models[22-25], with intermediate and high-risk groups combined for the analysis[26-28]. The upper limits of normal values for various biochemical indices were based on the hospital's laboratory standards (aspartate aminotransferase,  $\leq 40$  U/L for men and  $\leq 35$  U/L for women; alanine aminotransferase,  $\leq 35$  U/L for men and  $\leq 40$  U/L for women; and gamma-glutamyl transferase,  $\leq 60$  U/L for men and  $\leq 45$  U/L for women).

### ***Statistical analysis***

Data analysis and figure generation were conducted using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, United States) and GraphPad Prism version 9.5 (GraphPad Software, San Diego, CA, United States), respectively. Statistical significance was defined at two-sided *P* values < 0.05.

### ***Ethics***

Ethical approval for this study was provided by Third Affiliated Hospital of Sun Yat-sen University Medical Ethics Committee (approval No. II-2026-098-01). All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. Patients provided informed consent for the use of their medical data for scientific research.

## **RESULTS**

### ***Study patients***

Among 808 patients, 416 received monotherapy and 392 received combination therapy. Among the 392 patients who received interferon therapy, after excluding those with pre-existing pancytopenia at baseline due to hypersplenism or other causes, a total of 199 patients (50.8%) developed bone marrow suppression following treatment. This included 79 cases of grade I myelosuppression, 73 case of grade II myelosuppression, and 47 case of grade III higher myelosuppression by the World Health Organization grading criteria. Three patients experienced thyroid dysfunction. All adverse events were transient, and no patient required modification or discontinuation of the treatment regimen. Other interferon-related side effects, such as anxiety, nausea, and flu-like symptoms, could not be reliably captured due to the retrospective nature of the study.

The 1:1 propensity score matching yielded 302 well-matched pairs for subsequent analysis. Follow-up was conducted for a median duration of 220 weeks (interquartile range: 112-276). The two groups were well-balanced in terms of age, sex, family history of HCC, diabetes, alfa-fetoprotein level, history of alcohol consumption, and imaging-confirmed cirrhosis (Table 1).

Certain variables, such as the duration of prior NA therapy and type of NA used, were not included in the propensity score matching. There might be distribution between treatment groups. However, in multivariable Cox regression analysis, these variables showed no significant association with clinical outcomes (Supplementary Table 1).

### ***Incidence of HCC and decompensated cirrhosis before matching***

Among 416 patients in the monotherapy group, 60 (14.4%) developed HCC and 43 (10.3%) developed decompensated cirrhosis. Among 392 patients in the combination therapy group, 14 (3.6%) developed HCC and 12 (3.1%) developed decompensated cirrhosis. The monotherapy group demonstrated significantly higher rates of HCC and decompensated cirrhosis in the survival analysis ( $P < 0.001$ ). This difference was observed in separate survival analyses for each clinical endpoint (Figure 1A and B).

### ***Incidence of HCC and decompensated cirrhosis after matching***

Among 302 matched pairs, 41 (13.6%) cases of HCC and 32 (10.6%) of decompensated cirrhosis occurred in the monotherapy group and 9 (3.0%) cases of HCC and 12 (4.0%) of decompensated cirrhosis occurred in the combination therapy group. In the survival analysis with HCC as the endpoint, the incidence of HCC was significantly lower in the combination therapy group than that in the monotherapy group (HR = 0.22, 95%CI: 0.11-0.48;  $P < 0.001$ ; Figure 1C). Similarly, in the survival analysis with decompensated cirrhosis as the endpoint, the combination therapy group showed a decreased incidence (HR = 0.39, 95%CI: 0.20-0.77;  $P = 0.005$ ; Figure 1D).

### ***Incidence of HCC and decompensated cirrhosis stratified by the HBsAg titre***

Among 302 patients in the monotherapy group, 78, 99, and 125 had HBsAg titres of  $< 500$  IU/mL, 500-3000 IU/mL, and  $> 3000$  IU/mL, respectively. Among 302 patients in the combination therapy group, 93, 138, and 71 had HBsAg titres of  $< 500$  IU/mL, 500-3000 IU/mL, and  $> 3000$  IU/mL, respectively. The survival analysis stratified by these groups is shown in Figure 2.

Across the overall cohort, the combination therapy group demonstrated a significantly lower incidence of HCC and decompensated cirrhosis than that in the monotherapy group. However, the results differed according to HBsAg strata. Using HCC as the endpoint, the combination therapy group showed a significantly lower incidence of HCC than the monotherapy group in all HBsAg strata ( $P_A = 0.048$ ,  $P_C < 0.001$ , and  $P_E = 0.011$ ; Figure 2A, C, and E). The difference was most marked and the HR was lowest in the 500-3000 IU/mL stratum (HR = 0.18, 95%CI: 0.06-0.56; Figure 2C). Using the decompensated cirrhosis endpoint, in the  $< 500$  IU/mL stratum, the incidence of decompensated cirrhosis was significantly lower in the combination therapy group than that in the monotherapy group (HR = 0.15, 95%CI: 0.03-0.70;  $P = 0.006$ ; Figure 2B). In contrast, decompensated cirrhosis incidence did not significantly differ between groups within the other two strata (Figure 2D and F).

### ***Incidence of HCC and decompensated cirrhosis stratified by early biochemical normalization status***

The proportion of patients with early biochemical normalization within 12 months was similar in the monotherapy (194/302, 64.2%) and combination therapy (196/302, 64.9%) groups. Stratified analysis based on achieving early biochemical normalization revealed that, in patients who did not achieve early biochemical normalization, the combination therapy group had a significantly lower risk of HCC ( $P = 0.003$ ; Figure 3A) and decompensated cirrhosis ( $P = 0.036$ ; Figure 3B) than that in the monotherapy group. In patients with early biochemical normalization, a significant reduction in HCC incidence was observed with combination therapy ( $P = 0.002$ ; Figure 3C); for decompensated cirrhosis, no significant intergroup difference was noted ( $P = 0.154$ ; Figure 3D).

Although the study baseline did not coincide with the initiation of antiviral therapy, multivariable Cox regression confirmed that lack of biochemical normalization within 12 months remained an independent risk factor for HCC (HR = 1.75, 95%CI: 1.01-3.03,  $P = 0.047$ ) and decompensated cirrhosis (HR = 3.85, 95%CI: 2.02-7.21,  $P < 0.001$ ).

### ***Incidence of HCC and decompensated cirrhosis stratified by different model risk scores***

Using mREACH-B for risk stratification, patients were categorised into the following groups[22]: (1) A low-risk stratum (mREACH-B score 0-9) with 264 patients (129 monotherapy and 134 combination therapy); and (2) High-risk stratum (mREACH-B score 10-16) with 341 patients (174 monotherapy and 168 combination therapy). In patients in the low-risk stratum, the significant difference in HCC incidence favoured the combination therapy group over the monotherapy group ( $P = 0.002$ ; Figure 4A); however, the risk of decompensated cirrhosis did not differ significantly among both groups ( $P = 0.388$ ; Figure 4B). In patients in the high-risk group, the combination therapy group had a significantly lower incidence of HCC ( $P = 0.001$ ; Figure 4C) and decompensated cirrhosis ( $P = 0.005$ ; Figure 4D) than that in the monotherapy group.

Based on mPAGE-B, patients were stratified into the following groups[23]: (1) Low-risk (mPAGE-B score 0-8; 156 patients, 62 monotherapy and 94 combination therapy); and (2) Intermediate-to-high risk (mPAGE-B score 9-21; 448 patients, 240 monotherapy and 208 combination therapy) strata. In patients in the low-risk stratum, the incidence of HCC ( $P = 0.129$ ; Figure 5A) and decompensated cirrhosis ( $P = 0.112$ ; Figure 5B) was not significantly different between the monotherapy and combination therapy groups. Patients in the intermediate-to-high-risk stratum experienced significantly more favourable outcomes for HCC ( $P = 0.001$ ; Figure 5C) and decompensated cirrhosis ( $P = 0.002$ ; Figure 5D) when treated with combination *vs* monotherapy.

Age, albumin, sex, liver cirrhosis (AASL)-HCC classified[24] patients into the low-risk (AASL-HCC score 0-5; 90 patients, 49 monotherapy and 41 combination therapy) and intermediate-to-high risk (AASL-HCC score 6-29; 514 patients, 253 monotherapy and 261 combination therapy) strata. In the low-risk stratum, five patients (10%) in the monotherapy group and no patients in the combination therapy group developed HCC ( $P = 0.027$ ; Supplementary Figure 1A). In the low-risk stratum, no patients in either treatment group developed decompensated cirrhosis; therefore, survival analysis was not feasible for this endpoint. Combination therapy group demonstrated a clear advantage in the intermediate-to-high-risk stratum, significantly lowering the incidence of HCC ( $P < 0.001$ ; Supplementary Figure 1B) and decompensated cirrhosis ( $P = 0.005$ ; Supplementary Figure 1C) compared with monotherapy.

REAL-B was used to divide the cohort into[25] low-risk (REAL-B score 0-3) and intermediate-to-high risk (REAL-B score  $\geq 4$ ) strata. In the low-risk stratum, survival analysis with HCC as the endpoint showed that the incidence of HCC was significantly higher in the monotherapy group than that in the combination therapy group ( $P = 0.010$ ; Supplementary Figure 2A); however, the HR was not significant. In the low-risk stratum, no patients in either treatment group developed decompensated cirrhosis; therefore, the survival analysis was not feasible for this endpoint. In the intermediate-to-high-risk stratum, combination therapy corresponded to HRs of 0.27 for HCC (95%CI: 0.13-0.57,  $P < 0.001$ ; Supplementary

Figure 2B) and 0.42 for decompensated cirrhosis (95%CI: 0.21-0.82,  $P = 0.008$ ; Supplementary Figure 2C), indicating reduced risk *vs* monotherapy.

Based on CAMD, patients were stratified into[26] the low-risk (CAMD score 0-7; 169 patients) and intermediate-to-high risk (CAMD score 8-19; 435 patients) strata. In the low-risk stratum, the incidence of HCC was significantly higher in the monotherapy group than that in the combination therapy group ( $P = 0.036$ ; Supplementary Figure 3A). Survival analysis with decompensated cirrhosis as the end point was not estimable in this stratum because no events occurred in either group. In patients in the intermediate-to-high-risk stratum, combination therapy conferred a significantly better prognosis than monotherapy for HCC ( $P < 0.001$ ; Supplementary Figure 3B) and decompensated cirrhosis ( $P = 0.007$ ; Supplementary Figure 3C).

The aMAP classified patients into[27]: (1) Low-risk (aMAP score  $< 50$ ; 182 patients); and (2) Intermediate-to-high risk (aMAP score  $> 50$ ; 422 patients) strata. Within the low-risk stratum, combination therapy was linked to a significantly reduced risk of HCC ( $P = 0.036$ , Figure 6A); however, the risk of decompensated cirrhosis remained comparable between treatment groups ( $P = 0.882$ ; Figure 6B). Within the intermediate-to-high-risk stratum, the probability of HCC or decompensated cirrhosis was lower in the combination therapy group ( $P < 0.001$  for HCC, Figure 6C;  $P = 0.002$  for decompensated cirrhosis, Figure 6D).

#### ***Effects of combination treatment on biochemical normalization, sustained virological response, and seroconversion***

At baseline, 198 patients in the monotherapy group and 180 patients in the combination therapy group had abnormal transaminase levels. The rates of achieving biochemical normalization within 12 months were comparable between groups (45.5% and 41.1%, respectively;  $P = 0.395$ ; Table 2). Over the follow-up period, biochemical normalization rates increased but remained similar between the monotherapy and combination therapy groups (79.3% and 80.0%, respectively;  $P = 0.865$ ; Table 3).

The combination therapy group demonstrated a higher probability of achieving

MVR than that in the monotherapy group (98.3% and 83.1%, respectively;  $P < 0.001$ ; Table 4). Further, the combination therapy group demonstrated a higher probability of achieving HBsAg clearance than the monotherapy group (19.2% and 0.7%, respectively;  $P < 0.001$ ; Table 5). Although the baseline HBsAg titre and follow-up duration were not balanced during the matching process, multivariable Cox regression analysis including the baseline log-transformed HBsAg titre as a covariate confirmed that patients in the combination therapy group had a significantly higher probability of seroconversion (Supplementary Figure 4).

### *Comparison of treatment effects on reducing the degree of liver fibrosis*

Owing to the non-normal distribution of changes in fibrosis scores (FIB-4, APRI, GPR) as determined by the Kolmogorov-Smirnov test, the Mann-Whitney  $U$  test was used for intergroup comparisons. The median change in APRI score was less than 0 in both treatment groups, indicating a reduction in the fibrosis score after therapy, with no significant intergroup difference ( $P = 0.064$ ; Supplementary Figure 5). In contrast, improvements in FIB-4 and GPR scores were more pronounced in the monotherapy group than those in the combination therapy group (FIB-4,  $P = 0.001$ , and GPR,  $P = 0.005$ ; Supplementary Figure 5).

## **DISCUSSION**

Overall, this large-scale, propensity score-matched cohort study provides evidence that a Peg-IFN $\alpha$ -2b add-on strategy reduces the risk of HCC and decompensated cirrhosis among patients with HBV-related advanced fibrosis or compensated cirrhosis. This benefit was particularly pronounced in patients stratified as having an intermediate-to-high risk of disease progression. Current clinical practice for initiating interferon add-on therapy is primarily guided by the goal of functional cure[13,14]. Our results highlight that the value of combination therapy in improving prognosis should not be overlooked in high-risk patients who have entered a critical window of disease progression and in whom a functional cure may not be obtainable.

The principle finding of this study, that combining Peg-IFN $\alpha$ -2b with NAs was

associated with a significantly reduced risk of HCC and decompensated cirrhosis, is consistent with recent research. An interim analysis of the PARADISE multicentre randomised controlled trial, published in 2024, demonstrated that patients with CHB at intermediate-to-high risk participants who received interferon combined with NAs for 96 weeks had a significantly lower incidence of HCC than those who received NA monotherapy[32]. This study provides an extended evaluation of the Peg-IFN $\alpha$ -2b and NA combination therapy benefit in a larger, multiple risk-stratified cohort, specifically in patients with confirmed HBV-related cirrhosis or advanced liver fibrosis.

The clinical benefits of combination therapy varied depending on the level of risk. Stratified analyses based on six internationally recognised HCC risk-prediction models consistently showed that combination therapy was linked with a significantly reduced risk of both HCC and decompensated cirrhosis, especially in patients with a relatively high risk of disease progression. The effects of combination therapy did not differ significantly from those of monotherapy in some low-risk strata. For patients identified as having an intermediate-to-high risk of disease progression according to these models, combination therapy should be actively considered to improve long-term outcomes, regardless of their HBsAg level.

In the present study, the baseline was not the initiation of antiviral therapy; therefore, our definition of “early biochemical normalization” differs from that used in the original study cited by European Association for the Study of the Liver[31]. Nevertheless, a persistently elevated transaminase level for > 12 months was linked to an elevated risk of disease progression. In this subgroup of patients with a poor long-term biochemical response, a prognosis-oriented approach with Peg-IFN $\alpha$ -2b add-on therapy should also be considered, even though it did not show a clear advantage over NA monotherapy in facilitating biochemical normalization in this study.

For patients with a low-risk of disease progression, the potential treatment benefit might be obscured in this study owing to the generally small sample size in the low-risk strata (because this study focused on patients with advanced fibrosis/compensated cirrhosis) and inherently low incidence of HCC and

decompensated cirrhosis in low-risk strata. Larger prospectively designed cohorts are required to determine whether Peg-IFN $\alpha$ -2b add-on therapy benefits patients with CHB in low-risk strata defined according to various models.

The benefits of combination therapy are likely multifaceted. In the present study, the combination therapy group had significantly higher rates of MVR and HBsAg clearance, consistent with a previous study[33]. Maintenance of viral suppression and immunomodulation are critical for halting disease progression. The paradoxical worsening of non-invasive fibrosis scores (*e.g.*, FIB-4 and GPR) in the combination therapy group should be interpreted with caution. Peg-IFN $\alpha$ -2b causes bone marrow suppression and immune activation[34], leading to decreased platelet counts and elevated transaminases[10] that artificially inflate these scores. This pharmacodynamic confounding is not unique to interferon therapy: A TDF monotherapy study with serial liver biopsies similarly found that APRI and FIB-4 correlated with Ishak stage yet showed extensive overlap across stages, rendering them inaccurate for fibrosis staging[35]. The investigators speculated that post-treatment increases in platelet counts and declines in transaminase levels affected the non-invasive assessments. Given interferon's even more pronounced hematological effects, the score changes observed herein are also plausibly laboratory artifacts rather than true histological progression. Non-invasive fibrosis indices are therefore unreliable for monitoring fibrosis trajectory during interferon-based therapy. Liver stiffness measurement or biopsy, which is not recommended for routine long-term follow-up in the guidelines[4,5], was not available in our study. The benefit of Peg-IFN add-on therapy for reversing liver fibrosis remains a matter of debate[36,37]. Further prospective multicentre studies, ideally randomised controlled trials, that use more accurate methods, such as liver stiffness measurement or biopsy, to measure liver stiffness, are warranted to evaluate the anti-fibrotic effects of NA plus Peg-IFN $\alpha$ -2b combination therapy.

This study had several limitations. Firstly, despite propensity score matching, the retrospective design may allow for residual confounding. Longitudinal virological or biochemical profiles prior to study baseline were not systematically available for the entire cohort, while this may influence long-term outcomes.

Secondly, some of the subgroups (especially the low-risk stratum in some risk models) had relatively small sample sizes, which reduced the statistical power to discover an effect. Finally, the difference between fibrosis levels was also not evaluated using a valid approach; hence, the impact needs to be clarified in future studies.

## **CONCLUSION**

Peg-IFN $\alpha$ -2b should be used in combination with NA in high-grade fibrosis or compensated cirrhosis with HBV, especially in individuals having a medium-high risk of advanced disease. This combination therapy increases virological and serological responses and lowers the probability of HCC and decompensated cirrhosis, improving prognosis in the long-term. Therapeutic decision-making for this high-risk group in clinical practice must not be limited to the pursuit of functional cure only but must involve a risk-control approach, whereby combination therapy improves treatment outcomes in the target population.

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## Footnotes

**Institutional review board statement:** Ethical approval for this study was provided by Third Affiliated Hospital of Sun Yat-sen University Medical Ethics Committee (approval No. II-2026-098-01).

**Informed consent statement:** Third Affiliated Hospital of Sun Yat-sen University Medical Ethics Committee waived the informed consent form.

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**Data sharing statement:** Raw data were generated at Third Affiliated Hospital of Sun Yat-sen University. Derived data supporting the findings of this study are available from the corresponding author on request.

**STROBE statement:** The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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## Figures and Tables

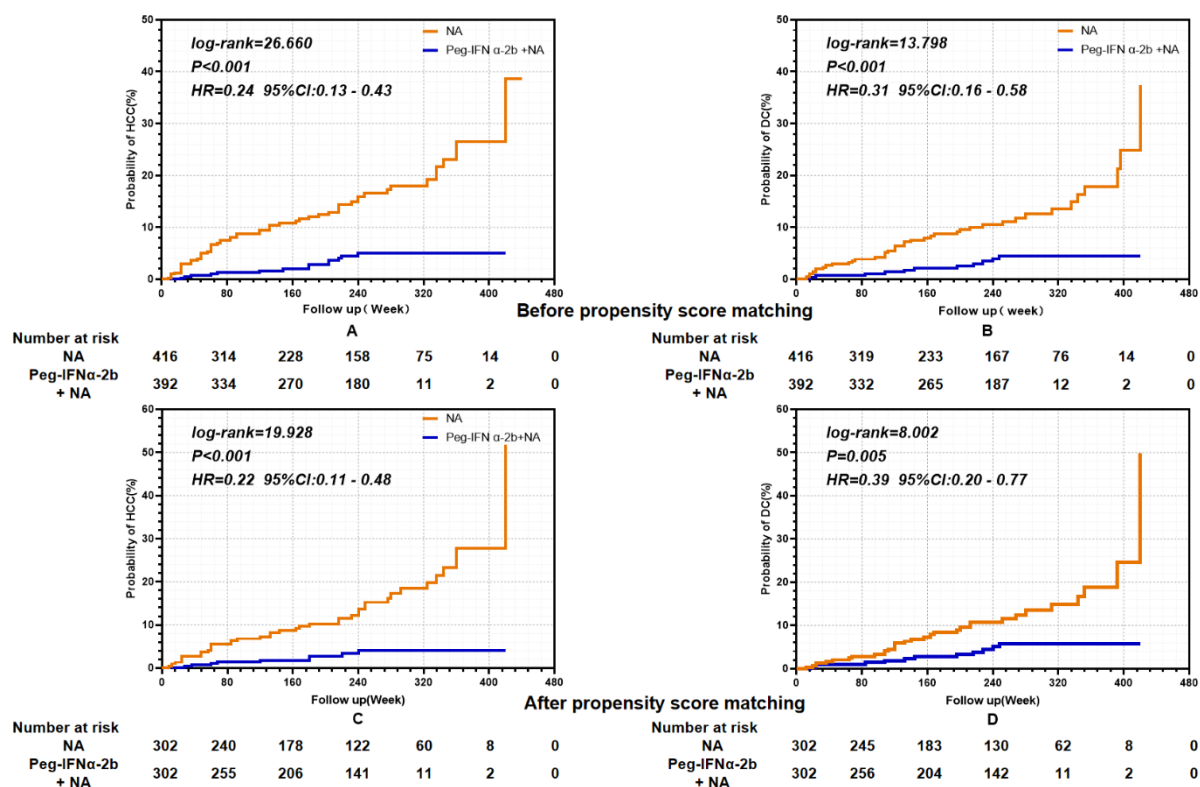


**Figure 1** Kaplan-Meier analysis of survival outcomes before and after propensity score matching: Nucleos(t)ide analogue monotherapy *vs* pegylated interferon α-2b combined with nucleos(t)ide analogues. A: Before propensity score matching, endpoint: Hepatocellular carcinoma; B: Before propensity score matching, endpoint: Decompensated cirrhosis; C: After propensity score matching, endpoint: Hepatocellular carcinoma; D: After propensity score matching, endpoint: Decompensated cirrhosis. HCC: Hepatocellular carcinoma; DC: Decompensated cirrhosis; HR: Hazard ratio; NA: Nucleos(t)ide analogue; Peg-IFNα-2b: Pegylated interferon α-2b.

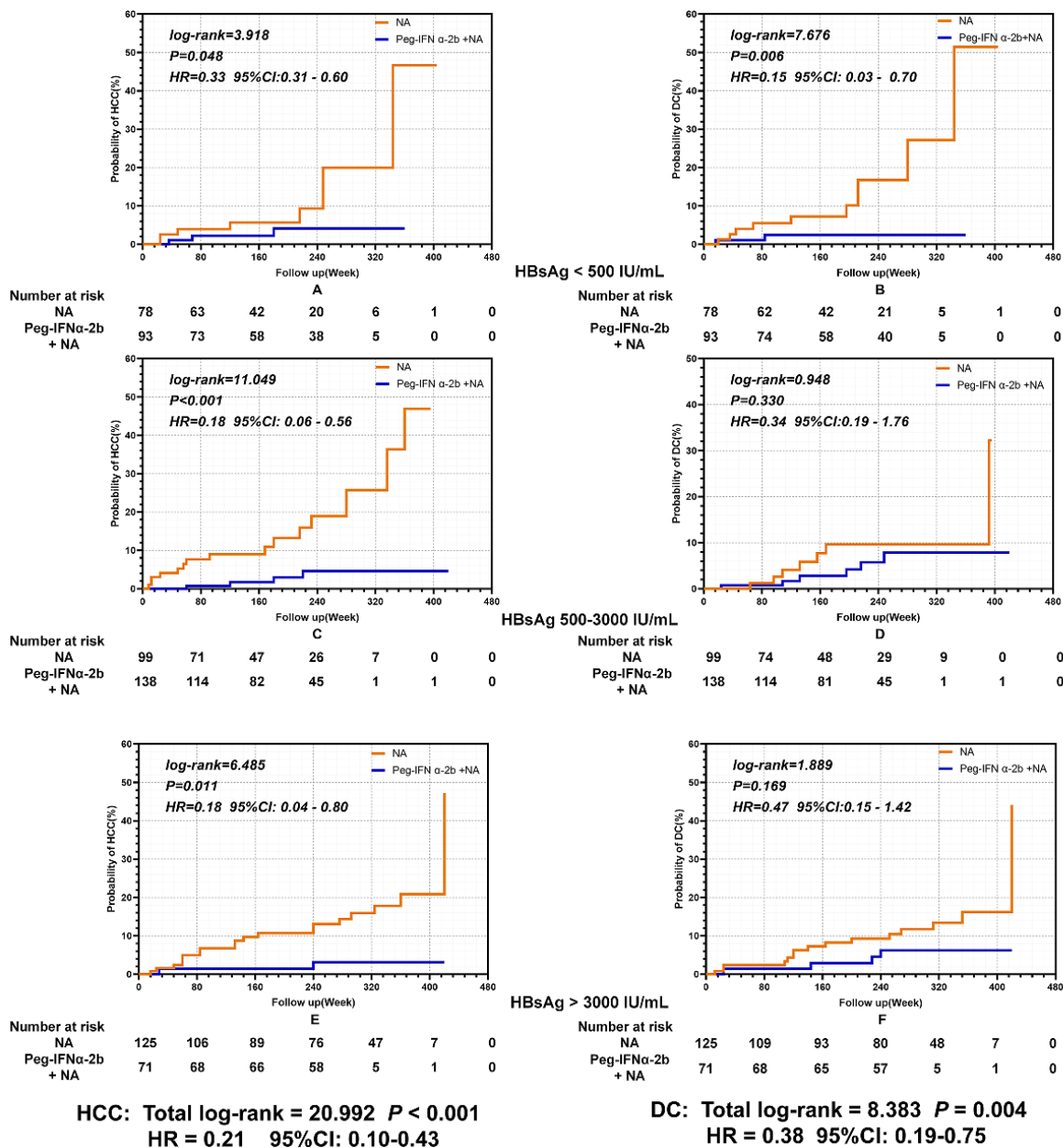


**Figure 2** Survival analysis stratified by baseline serum hepatitis b surface antigen levels: Nucleos(t)ide analogue monotherapy *vs* pegylated interferon α-2b combined with nucleos(t)ide analogues. A: Patients with hepatitis B surface antigen (HBsAg) < 500 IU/mL, endpoint: Hepatocellular carcinoma (HCC); B: Patients with HBsAg < 500 IU/mL, endpoint: Decompensated cirrhosis (DC); C: Patients with HBsAg 500-3000 IU/mL, endpoint: HCC; D: Patients with HBsAg 500-3000 IU/mL, Endpoint: DC; E: Patients with HBsAg > 3000 IU/mL, endpoint: HCC; F: Patients with HBsAg > 3000 IU/mL, endpoint: DC. HCC: Hepatocellular carcinoma; DC: Decompensated cirrhosis; HR: Hazard ratio; NA: Nucleos(t)ide analogue; Peg-IFNα-2b: Pegylated interferon α-2b.

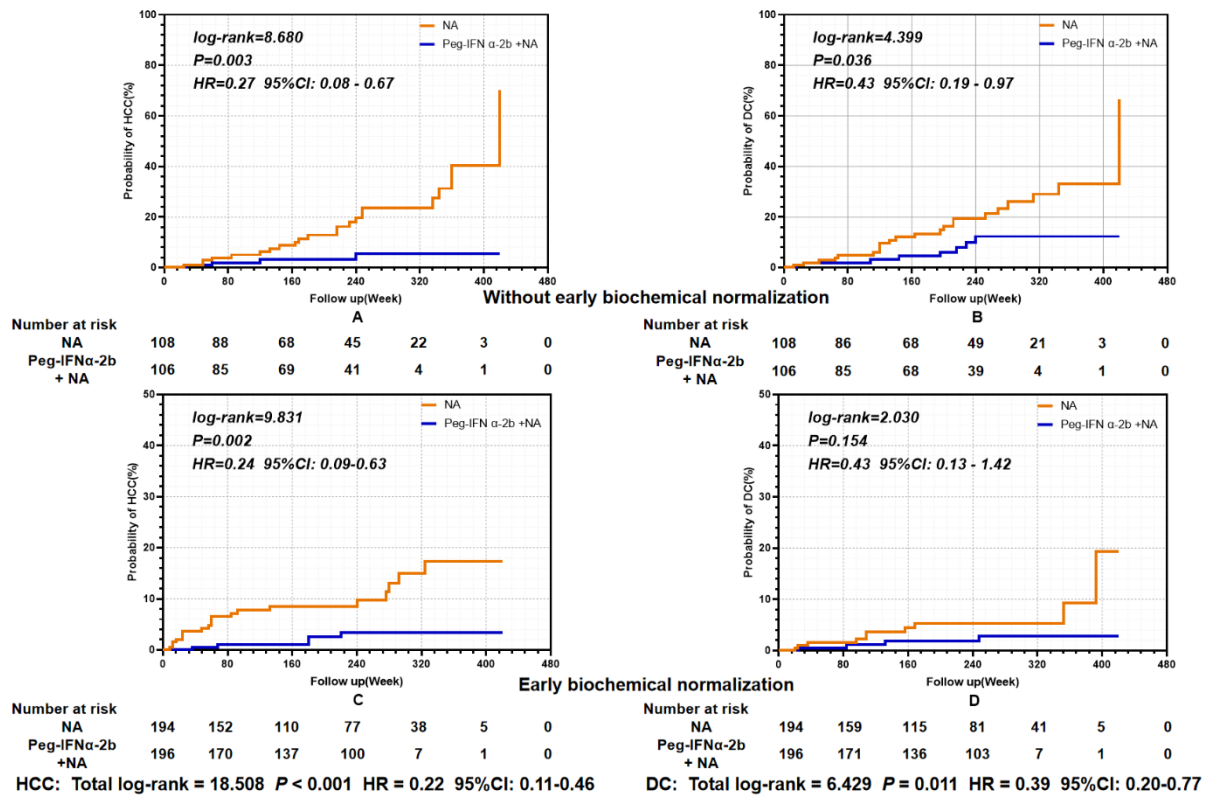


**Figure 3 Survival analysis stratified by achievement of early biochemical normalization: Nucleos(t)ide analogue monotherapy *vs* pegylated interferon  $\alpha$ -2b combined with nucleos(t)ide analogues.** A: Patients without early biochemical normalization, endpoint: Hepatocellular carcinoma; B: Patients without early biochemical normalization, endpoint: Decompensated cirrhosis; C: Patients with early biochemical normalization, endpoint: Hepatocellular carcinoma; D: Patients with early biochemical normalization, endpoint: Decompensated cirrhosis. HCC: Hepatocellular carcinoma; DC: Decompensated cirrhosis; HR: Hazard ratio; NA: Nucleos(t)ide analogue; Peg-IFN $\alpha$ -2b: Pegylated interferon  $\alpha$ -2b.

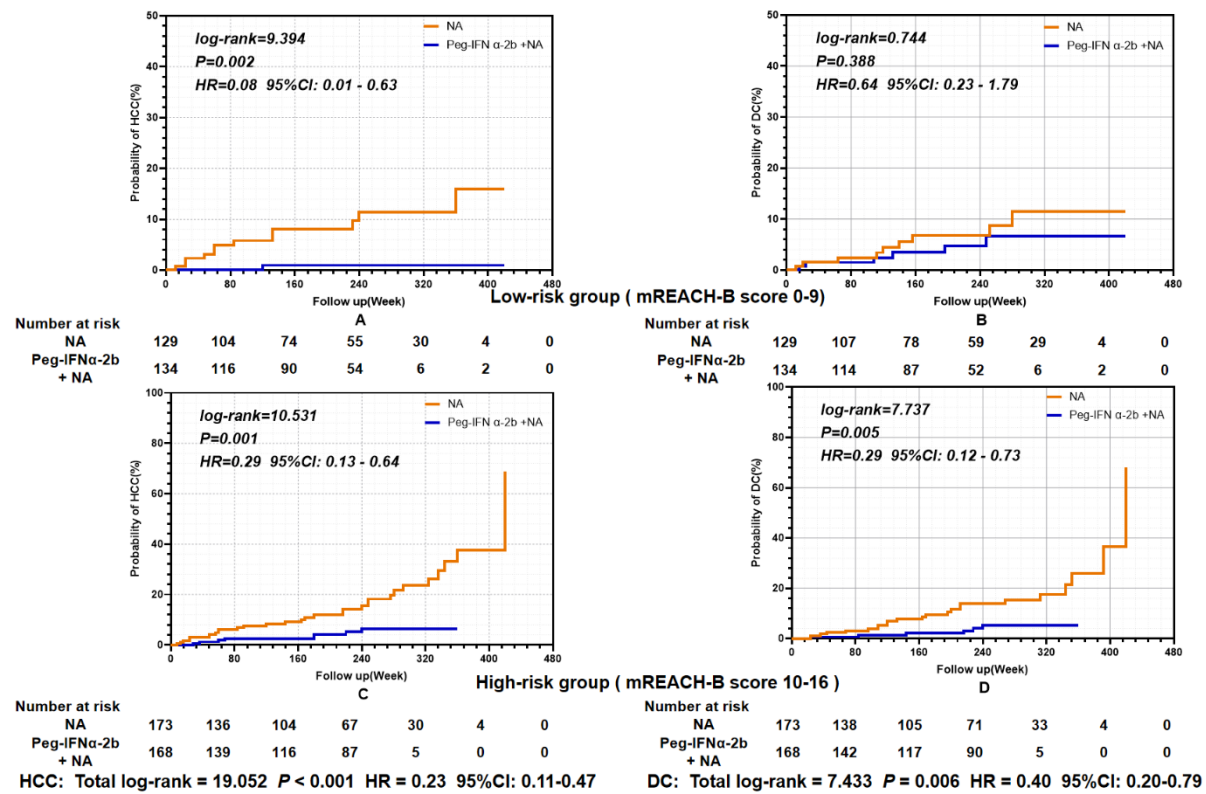


**Figure 4** Survival analysis stratified by mREACH-B model risk score: Nucleos(t)ide analogue monotherapy *vs* pegylated interferon α-2b combined with nucleos(t)ide analogues. A: Low-risk group (mREACH-B score 0-9), endpoint: Hepatocellular carcinoma; B: Low-risk group (mREACH-B score 0-9), endpoint: Decompensated cirrhosis; C: High-risk group (mREACH-B score 10-16), endpoint: Hepatocellular carcinoma; D: High-risk group (mREACH-B score 10-16), endpoint: Decompensated cirrhosis. HCC: Hepatocellular carcinoma; DC: Decompensated cirrhosis; HR: Hazard ratio; NA: Nucleos(t)ide analogue; Peg-IFNα-2b: Pegylated interferon α-2b.

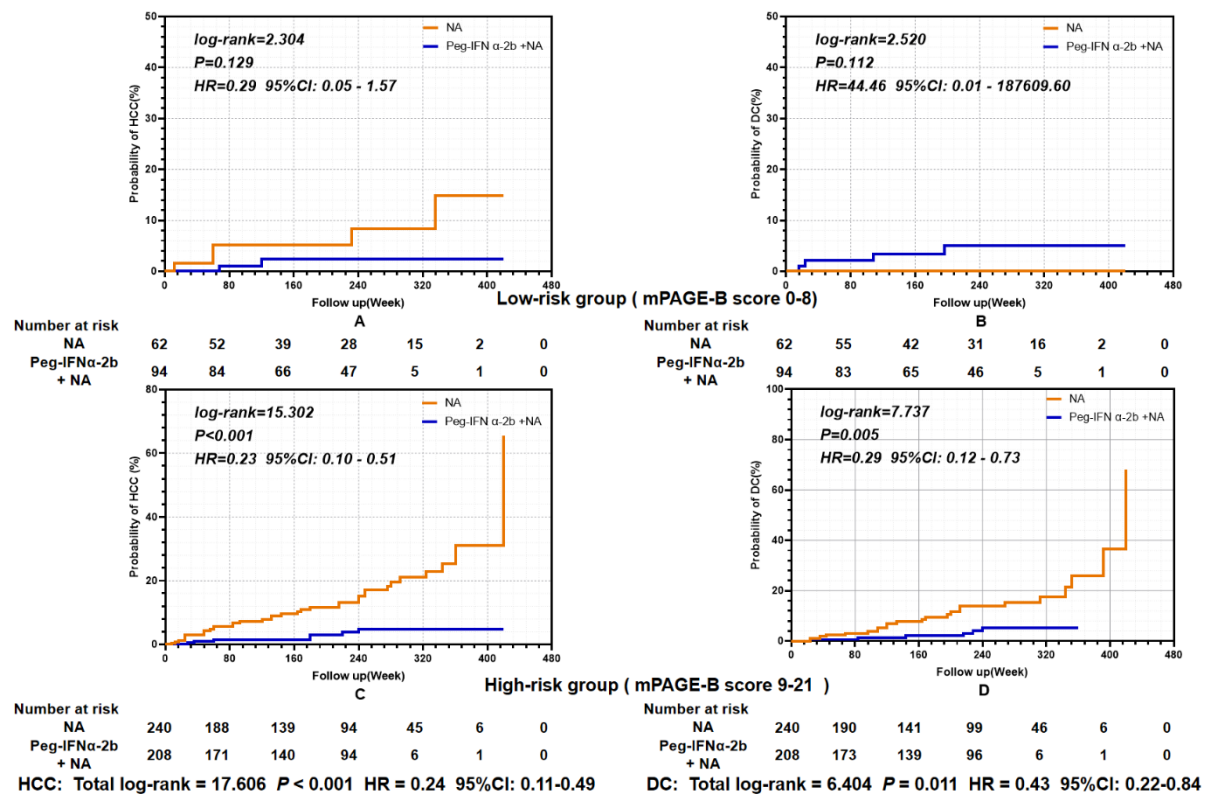


**Figure 5 Survival analysis stratified by mPAGE-B model risk score: Nucleos(t)ide analogue monotherapy *vs* pegylated interferon  $\alpha$ -2b combined with nucleos(t)ide analogues.** A: Low-risk group (mPAGE-B score 0-8), endpoint: Hepatocellular carcinoma; B: Low-risk group (mPAGE-B score 0-8), endpoint: Decompensated cirrhosis; C: Intermediate-to-high-risk group (mPAGE-B score 9-21), endpoint: Hepatocellular carcinoma; D: Intermediate-to-high-risk group (mPAGE-B score 9-21), endpoint: Decompensated cirrhosis. HCC: Hepatocellular carcinoma; DC: Decompensated cirrhosis; HR: Hazard ratio; NA: Nucleos(t)ide analogue; Peg-IFN $\alpha$ -2b: Pegylated interferon  $\alpha$ -2b.

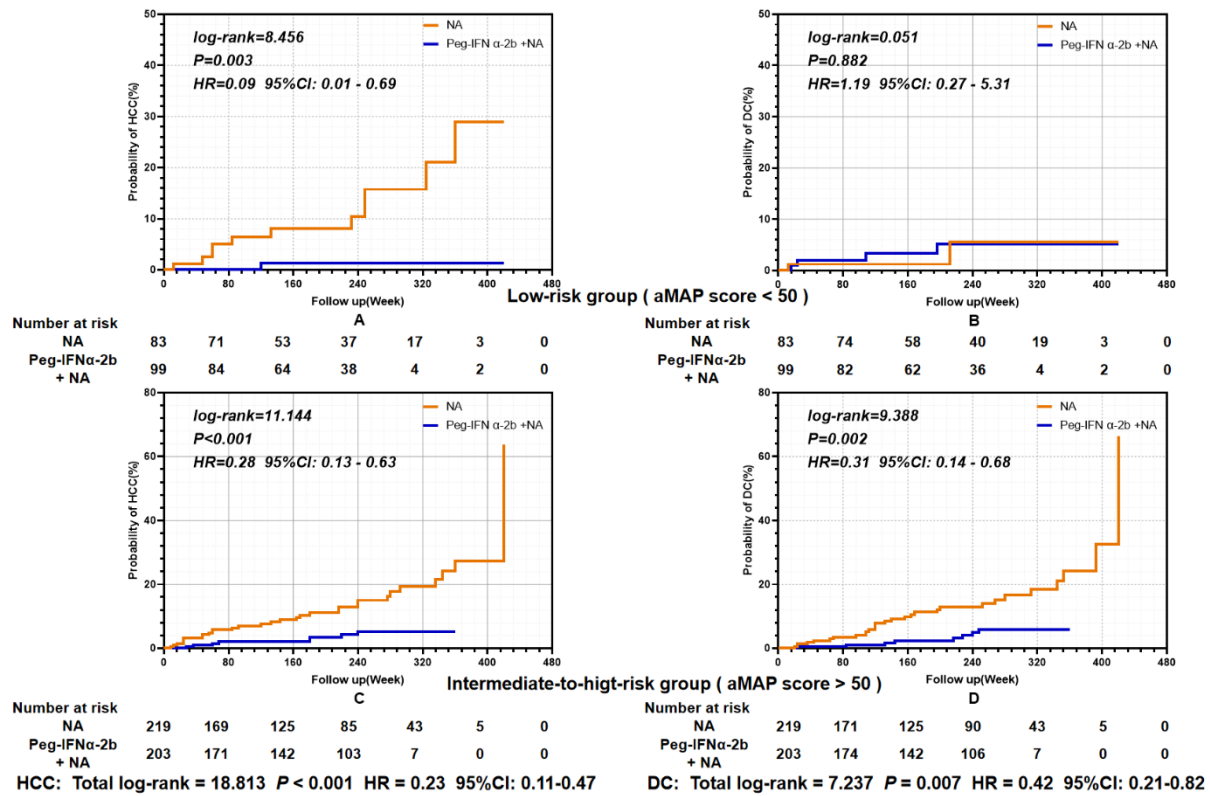


**Figure 6 Survival Analysis stratified by aMAP model risk score: Nucleos(t)ide analogue monotherapy *vs* pegylated interferon α-2b combined with nucleos(t)ide analogues.** A: Low-risk group (aMAP score < 50), endpoint: Hepatocellular carcinoma; B: Low-risk group (aMAP score < 50), endpoint: Decompensated cirrhosis; C: Intermediate-to-high-risk group (aMAP score > 50), endpoint: Hepatocellular carcinoma; D: Intermediate-to-high-risk group (aMAP score > 50), endpoint: Decompensated cirrhosis. HCC: Hepatocellular carcinoma; DC: Decompensated cirrhosis; HR: Hazard ratio; NA: Nucleos(t)ide analogue; Peg-IFNα-2b: Pegylated interferon α-2b.

**Table 1 Baseline characteristics after propensity score matching, median (interquartile range)**

| Characteristics       | NA group<br>(n = 302) | Peg-IFNα-2b + NA<br>group (n = 302) | $\chi^2$ | P value | SMD    |
|-----------------------|-----------------------|-------------------------------------|----------|---------|--------|
| Age (years)           | 46 (39, 54)           | 46 (40, 51)                         | -        | 0.565   | 0.089  |
| Sex (male)            | 265                   | 266                                 | 0.016    | 0.901   | -0.010 |
| Family history of HCC | 23                    | 22                                  | 0.024    | 0.887   | 0.013  |

|                        |     |     |       |         |        |
|------------------------|-----|-----|-------|---------|--------|
| Diabetes mellitus      | 1   | 1   | 0.000 | > 0.999 | 0.000  |
| AFP $\geq$ 10 ng/mL    | 20  | 21  | 0.026 | 0.871   | -0.013 |
| Alcohol use history    | 11  | 10  | 0.049 | 0.824   | 0.018  |
| Radiographic cirrhosis | 173 | 174 | 0.007 | 0.934   | -0.007 |

AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma; NA: Nucleos(t)ide analogue; Peg-IFN $\alpha$ -2b: Pegylated interferon  $\alpha$ -2b; SMD: Standardized mean differences.

**Table 2 Comparison of efficacy measures between the nucleos(t)ide analogue monotherapy *vs* pegylated interferon  $\alpha$ -2b and nucleos(t)ide analogue combination therapy: Early biochemical normalization rates, *n* (%)**

| Group                     | Total | Early biochemical normalization | Non-early biochemical normalization | $\chi^2$ | <i>P</i> value |
|---------------------------|-------|---------------------------------|-------------------------------------|----------|----------------|
| NA                        | 198   | 90 (45.5)                       | 108 (54.5)                          | 0.724    | 0.395          |
| Peg-IFN $\alpha$ -2b + NA | 180   | 74 (41.1)                       | 106 (58.9)                          |          |                |

NA: Nucleos(t)ide analogue; Peg-IFN $\alpha$ -2b: Pegylated interferon  $\alpha$ -2b.

**Table 3 Comparison of efficacy measures between the nucleos(t)ide analogue monotherapy *vs* pegylated interferon  $\alpha$ -2b and nucleos(t)ide analogue combination therapy: Overall biochemical normalization rates, *n* (%)**

| Group                     | Total | Biochemical normalization | Non-biochemical normalization | $\chi^2$ | <i>P</i> value |
|---------------------------|-------|---------------------------|-------------------------------|----------|----------------|
| NA                        | 198   | 157 (79.3)                | 41 (20.7)                     | 0.029    | 0.865          |
| Peg-IFN $\alpha$ -2b + NA | 180   | 144 (80.0)                | 36 (20.0)                     |          |                |

NA: Nucleos(t)ide analogue; Peg-IFN $\alpha$ -2b: Pegylated interferon  $\alpha$ -2b.

**Table 4 Comparison of Efficacy measures between the nucleos(t)ide analogue monotherapy *vs* pegylated interferon  $\alpha$ -2b and nucleos(t)ide analogue combination therapy: Maintained virological response rates, *n* (%)**

| Group                     | Total | MVR        | Non-MVR   | $\chi^2$ | P value |
|---------------------------|-------|------------|-----------|----------|---------|
| NA                        | 302   | 251 (83.1) | 51 (16.9) | 41.647   | < 0.001 |
| Peg-IFN $\alpha$ -2b + NA | 302   | 297 (98.3) | 5 (1.7)   |          |         |

NA: Nucleos(t)ide analogue; Peg-IFN $\alpha$ -2b: Pegylated interferon  $\alpha$ -2b; MVR: Maintained virological response.

**Table 5 Comparison of efficacy measures between the nucleos(t)ide analogue monotherapy *vs* pegylated interferon  $\alpha$ -2b and nucleos(t)ide analogue combination therapy: Hepatitis b surface antigen clearance rates, *n* (%)**

| Group                     | Total | HBsAg clearance | Non-HBsAg clearance | $\chi^2$ | P value |
|---------------------------|-------|-----------------|---------------------|----------|---------|
| NA                        | 302   | 2 (0.71)        | 300 (99.29)         | 50.842   | <       |
| Peg-IFN $\alpha$ -2b + NA | 302   | 52 (19.19)      | 250 (81.81)         |          | 0.001   |

HBsAg: Hepatitis B surface antigen; NA: Nucleos(t)ide analogue; Peg-IFN $\alpha$ -2b: Pegylated interferon  $\alpha$ -2b.