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Durability and on-treatment predictors of recompensation in entecavir-treated patients with hepatitis B and decompensated cirrhosis

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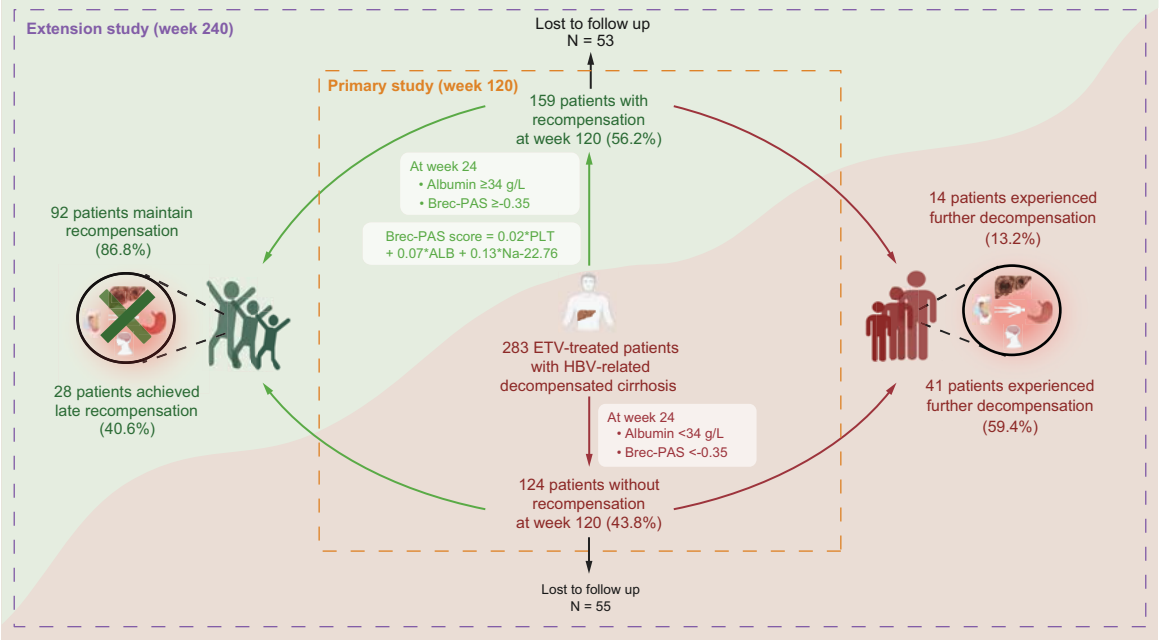
Graphical abstract



Highlights:

- A serum albumin level ≥34 g/L at treatment week 24 reliably predicted recompensation by week 120.
- The Brec-PAS score emerged as an easy-to-use tool for the prediction of recompensation by week 120.
- Recompensation achieved by week 120 of NA treatment is maintained in >80% of patients in the long term.
- Some patients may achieve recompensation only after >120 weeks of NA treatment.
- HCC incidence was reduced but not completely abolished after achieving recompensation.

Impact and implications:

Our research provides a meaningful contribution to understanding the long-term prognosis of recompensation in patients with chronic hepatitis B and decompensated cirrhosis, as well as to evaluating the predictive value of serum albumin levels, offering a comprehensive view of clinical outcomes after recompensation. The significance of early biomarkers in guiding therapeutic decisions is highlighted, shedding light on the continued benefits and possible risks after recompensation. This enhances the capability for more precise prognostic evaluations and informed therapeutic strategies. For healthcare providers, these insights afford a detailed perspective on patient monitoring and intervention planning, underscoring the need for ongoing assessment past the initial recompensation phase.

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Durability and on-treatment predictors of recompensation in entecavir-treated patients with hepatitis B and decompensated cirrhosis

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Background & Aims: Hepatic recompensation may be achieved in patients with decompensated cirrhosis due to chronic hepatitis B (CHB) upon effective suppression of viral replication by nucleos(t)ide analogues (NAs). However, the optimal timing and predictors of recompensation and the subsequent clinical course of patients with CHB with *vs.* without recompensation are not well-defined.

Methods: This study was a retrospective extension of a multi-centre prospective cohort, focusing on patients with CHB and decompensated cirrhosis treated with entecavir. We followed patients beyond treatment week 120 until a second decompensation event or June 2023. We identified the optimal timing and predictors of recompensation by week 120, evaluated durability of recompensation in patients fulfilling recompensation criteria by week 120 and examined late recompensation in those who did not fulfil it by week 120.

Results: At treatment week 24, serum albumin ≥34 g/L predicted recompensation by week 120. The Brec-PAS model offered good predictive ability for recompensation by week 120. Of the 283 patients who finished 120 weeks of therapy, 175 were followed beyond week 120 (median follow-up: 240 weeks). Among the 106 patients achieving recompensation by week 120, 92 (86.8%) maintained recompensation for another 120 (72-168) weeks. Among the 69 patients without recompensation by week 120, 40.6% attained late recompensation during the subsequent 120 (72-168) weeks. Additionally, hepatocellular carcinoma incidence was lower in the recompensated group (5.0% *vs.* 16.13%, $p = 0.002$).

Conclusions: A serum albumin ≥34 g/L at treatment week 24 predicted recompensation by week 120. Recompensation achieved by week 120 of NA treatment is maintained in >80% of patients in the long term. Some patients may achieve recompensation only after >120 weeks of NA treatment. The incidence of hepatocellular carcinoma was reduced but not completely abolished after recompensation.

Introduction

Hepatitis B is a global health concern, affecting approximately 296 million people and causing an estimated 820,000 deaths annually,[1] mainly due to cirrhosis and hepatocellular carcinoma (HCC).[2] Long-term antiviral therapy with potent nucleos(t)ide analogues (NAs) can profoundly suppress HBV replication, attenuate necroinflammation, and lead to regression of fibrosis, which ultimately reduces progression to decompensation and development of HCC.[3–5] Even in patients with decompensated cirrhosis, NA therapy has shown the potential for recompensation.[6,7]

The BAVENO VII consensus has proposed an explicit definition of recompensation.[8] Based on a prospective cohort study on entecavir (ETV)-treated patients with CHB and ascites, we have established a criterion of stable improvement of liver function tests (LFTs), which is required by the BAVENO VII definition of recompensation.[7] However, there is limited knowledge on the subsequent clinical course of patients who do or do not achieve initial recompensation.

Therefore, our present study aimed to identify the optimal timing and predictors for recompensation, and to investigate the durability of the initial recompensation and the chance for

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late recompensation, in those who did not achieve initial recompensation among ETV-treated patients with CHB and decompensated cirrhosis.

Patients and methods

Study population and extended follow-up

This study was a retrospective extension of a prospective cohort study involving patients with CHB and decompensated cirrhosis who were treated with ETV. The primary study design, inclusion and exclusion criteria, and participant characteristics have been published elsewhere.[7] The study protocol adhered to the ethical guidelines outlined in the 1975 Declaration of Helsinki. The informed consent procedures were initially approved by the ethics committees at the coordinating centre, Beijing Ditan Hospital, Capital Medical University (Approval No.: 2017-009-02), and subsequently at each participating centre.

The primary study assessed the rate of recompensation by treatment week 120. A longer follow-up was conducted in the present study, using electronic medical records and telephone interviews, observing clinical outcomes, including decompensation events in patients who achieved initial recompensation by week 120, and late recompensation in those who did not, up until June 2023.

Clinical outcome assessment

The current study aimed to identify the optimal timing and predictors for recompensation by week 120, evaluate the durability of recompensation in patients who initially achieved recompensation by week 120, and examine the late attainment of recompensation in patients who did not achieve it by week 120. Furthermore, the study aimed to identify factors at week 120 that were associated with durable recompensation at week 240.

The definition of recompensation was as follows:[7,8] (1) suppression of HBV DNA (<lower limit of quantification); (2) resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin), and absence of recurrent variceal haemorrhage for at least 48 weeks; and (3) stable improvement of LFTs (model for end-stage liver disease [MELD] score <10 and/or within Child-Pugh class A [albumin (ALB) >35 g/L, international normalised ratio <1.50 and total bilirubin (TBIL) <34 μmol/L]).

Exploration of baseline and on-treatment predictors for recompensation by week 120

Univariate logistic regression was conducted to analyse baseline and on-treatment factors associated with recompensation by week 120. Factors that demonstrated a significant association with recompensation (p <0.05) were then included in the multivariate logistic regression. The optimal prediction timing was determined by comparing the AUROCs of combined models with independent predictors at each time point. The optimal cut-off values were determined using the Youden index principle.

Development of a predictor model for assessing recompensation by week 120

Logistic regression analyses were initially performed to identify significant predictors and their associated regression coefficients (Beta values). These Beta values were transformed into scores, assigning a base score to the reference variable with the highest Beta value. Scores for other variables were calculated based on their Beta value ratios to this reference. The total score correlates with the probability of the desired outcome, using the logistic regression formula: $p = \exp(\beta0 + \beta1X1 + \beta2X2 + \ldots + \beta nXn)/(1 + \exp(\beta0 + \beta1X1 + \beta2X2 + \ldots + \beta nXn))$,[9] where p is the recompensation probability, $\beta0$ is the intercept, and $\beta1$, $\beta2$, …, βn are coefficients for each predictor. This score-to-probability relationship facilitated the creation of a nomogram, which allows for inputting specific predictors for each patient, offering a visual representation of the total score and its corresponding predicted probability. An interactive, dynamic nomogram was created using the 'shiny' package in R, allowing users to input specific parameter values and obtain predictive results. The discriminatory performance of the newly developed model was compared with MELD and fibrosis-4 (FIB-4) scores using AUROC and the DeLong test. Decision curve analysis was performed to assess whether the prediction model provided more clinical benefits than harm. A calibration curve was created by comparing the observed and projected recompensation rates.

Exploration of factors at week 120 associated with durable recompensation by week 240

Univariate logistic regression was performed to examine the relationship between factors at week 120 and the durability of recompensation by week 240. Factors that demonstrated a significant association with recompensation (p <0.05) were included in subsequent multivariate logistic regression analysis.

Statistical analysis

Quantitative variables were reported as mean ± SD or median (IQR), while categorical variables were presented as numbers (percentages). Student's t or Mann-Whitney U tests were used for comparing quantitative variables, and chi-square or Fisher's exact tests were used for analysing categorical variables, as appropriate. Kaplan-Meier survival curves were generated to illustrate patient survival probabilities over time, with differences between curves assessed using the log-rank test. To effectively illustrate the temporal sequence of patients, we constructed a Sankey diagram.

All statistical tests were two-sided. P values <0.05 were considered significant. Statistical analysis was performed with R 4.0.4 (http://www.r-project.org) and GraphPad Prism 8.0.0 (http://www.graphpad.com).

Results

Patient enrolment and baseline characteristics

During the primary study, a total of 283 patients completed the 120-week treatment and follow-up period. Among them, 159 (56.2%) patients achieved recompensation at week 120, while 124 (43.8%) patients did not, as reported previously.[7] Out of the 283 patients who had finished the initial 120-week study, 175 patients (106 achieved and 69 did not achieve recompensation by week 120) received an extended follow-up and were analysed in the current study (Fig. S1), with a median follow-up time of 240 weeks (range 192-288 weeks).

The baseline characteristics of the included patients are presented in Table 1. Mean age was 52.1 ± 10.5 years and 61.8% (175/283) were males. The mean HBV DNA level was 5.25 ± 1.85 log_{10} IU/ml, and the mean ALB level was 31.7 ± 6.3 g/L. The median alanine aminotransferase (ALT) level was 52.5 (IQR 35.2–99.6) IU/L. The mean MELD score was 13.4 ± 4.3, and the median FIB-4 score was 6.8 (IQR 4.4–10.9).

We delineated the baseline and on-treatment characteristics of patients who participated in the extended follow-up compared to those who did not (Tables S1–S3). Patients who completed the extended follow-up showed lower white blood cell counts and higher ALB levels at baseline (Table S1). Additionally, they had lower ALT and gamma-glutamyltransferase levels at week 24 (Table S2). However, there was no significant difference in all these variables between the two groups at week 120 (Table S3).

Baseline and on-treatment characteristics in patients with and without recompensation by week 120

We stratified the patients into those with (n = 159) and without (n = 124) recompensation by week 120 to compare their baseline and on-treatment variables.

At baseline, there was no significant difference in MELD and FIB-4 scores between the two groups (13.7 ± 4.6 *vs.* 13.0 ± 4.0, $p = 0.153$; 6.3 (4.2, 11.0) *vs.* 7.3 (5.2, 10.7), $p = 0.151$). Interestingly, at baseline, patients with recompensation had higher HBV DNA, platelet count (PLT), ALT, aspartate aminotransferase (AST), TBIL, direct bilirubin (DBIL), and Na^+ than those without recompensation (Table 1).

Patients who achieved recompensation by week 120 had higher ALB but lower ALT, AST, TBIL, and DBIL at treatment week 12 than those without recompensation by week 120 (Table S4). Similarly, at week 24, patients with recompensation exhibited higher white blood cell count, red blood cell count, PLT, ALB and Na^+ but lower INR, ALT, AST, TBIL, DBIL, globulin, gamma-glutamyltransferase, MELD and FIB-4 scores (Table 2).

Factors and optimal timing for prediction of recompensation by week 120

We conducted univariate and multivariate logistic analyses, including factors readily available in routine clinical practice. The multivariate analyses revealed that higher baseline levels of HBV DNA, DBIL, and Na^+, but lower TBIL levels were independently associated with recompensation by week 120 (Table S5). At treatment week 12, higher ALB levels were the only independent factor related to recompensation by week 120 (Table S6). At week 24, we found that higher PLT (odds ratio [OR] 1.020; 95% CI 1.010–1.033; p <0.001), ALB (OR 1.080; 95% CI 1.026–1.144; $p = 0.005$), and Na^+ (OR 1.116; 95% CI 1.007–1.243; $p = 0.041$) were independently associated with recompensation by week 120 (Table 3).

To determine the optimal timing for predicting recompensation, we evaluated the predictability of these prognostic factors at different time points. The AUROC for all individual baseline parameters was below 0.6 (Fig. S2), with the model based on these factors yielding an AUROC of 0.696 (0.635-0.757) (Fig. 1A). At treatment week 12, the AUROC for ALB was

Table 1. Baseline characteristics of study patients with and without recompensation by week 120.

Characteristics	Overall (N = 283)	Patients with recompensation (n = 159)	Patients without recompensation (n = 124)	*p* value
Age (years)	52.1 ± 10.5	51.2 ± 10.4	53.4 ± 10.7	0.085
Male sex	175 (61.8%)	94 (59.1%)	81 (65.3%)	0.324
Laboratory results				
HBV DNA (Log_{10} IU/ml)	5.25 ± 1.85	5.48 ± 1.78	4.94 ± 1.90	0.014
WBC (10^9/L)	3.99 ± 1.84	4.11 ± 2.00	3.84 ± 1.61	0.209
RBC (10^{12}/L)	3.78 ± 0.62	3.73 ± 0.63	3.84 ± 0.61	0.168
PLT (10^9/L)	72.0 (51.5, 96.0)	76.0 (58.5, 103.0)	66.5 (49.0, 82.3)	0.003
Hb (g/L)	120.1 ± 19.2	118.1 ± 20.0	122.6 ± 17.9	0.052
INR	1.37 (1.23, 1.56)	1.37 (1.22, 1.54)	1.37 (1.23, 1.56)	0.859
ALT (IU/L)	52.5 (35.2, 99.6)	59.0 (38.9, 117.0)	45.0 (30.0, 82.4)	0.001
AST (IU/L)	65.7 (45.0, 105.0)	71.3 (47.5, 139.0)	58.3 (43.0, 78.3)	0.006
TBIL (μmol/L)	33.0 (22.1, 51.5)	35.6 (22.4, 62.5)	31.2 (21.7, 43.1)	0.045
DBIL (μmol/L)	15.3 (9.2, 29.6)	17.6 (8.9, 37.6)	13.1 (9.6, 23.2)	0.023
ALB (g/L)	31.7 ± 6.3	31.7 ± 6.0	31.7 ± 6.6	0.998
GLB (g/L)	33.0 ± 7.7	32.5 ± 7.9	33.6 ± 7.5	0.219
ALP (IU/L)	110.9 (84.1, 142.6)	104.0 (84.1, 142.9)	117.5 (86.3, 142.4)	0.398
GGT (IU/L)	57.0 (34.2, 85.8)	58.5 (37.4, 94.0)	49.7 (32.0, 79.4)	0.157
BUN (mmol/L)	4.89 ± 1.68	4.73 ± 1.46	5.09 ± 1.92	0.072
Cr (μmol/L)	65.1 ± 16.9	64.3 ± 15.6	66.2 ± 18.5	0.342
Na+ (μmol/L)	139.6 ± 3.3	140.0 ± 3.2	139.0 ± 3.4	0.016
MELD scores	13.4 ± 4.3	13.7 ± 4.6	13.0 ± 4.0	0.153
FIB-4 scores	6.8 (4.4, 10.9)	6.3 (4.2, 11.0)	7.3 (5.2, 10.7)	0.151

Qualitative and quantitative differences were analysed by the chi-squared or Fisher's exact test for categorical variables, and the Student's *t* test or Mann-Whitney *U* test for continuous variables, as appropriate.

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; DBIL, direct bilirubin; FIB-4, fibrosis-4; GLB, globulin; GGT, gamma-glutamyltransferase; Hb, haemoglobin; INR, international standard ratio; MELD, model for end-stage liver disease; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; WBC, white blood cell count.

Table 2. Treatment week 24 characteristics in patients with and without recompensation.

Characteristics	Overall (N = 283)	Patients with recompensation (n = 159)	Patients without recompensation (n = 124)	*p* value
Laboratory results				
HBV DNA (Log_{10} IU/ml)	1.72 ± 1.09	1.73 ± 1.10	1.71 ± 1.08	0.920
WBC (10^9/L)	4.09 ± 1.48	4.35 ± 1.60	3.75 ± 1.23	0.001
RBC (10^{12}/L)	4.14 ± 0.57	4.23 ± 0.60	4.03 ± 0.51	0.004
PLT (10^9/L)	73.0 (57.0, 98.5)	86.0 (64.0, 110.5)	65.3 (47.0, 79.3)	<0.001
Hb (g/L)	130.7 ± 17.9	132.1 ± 19.0	128.8 ± 16.2	0.127
INR	1.25 (1.17, 1.35)	1.22 (1.15, 1.29)	1.31 (1.21, 1.42)	<0.001
ALT (IU/L)	31.0 (22.0, 42.1)	29.3 (20.8, 39.8)	35.0 (25.0, 44.3)	0.007
AST (IU/L)	40.0 (32.0, 51.3)	36.4 (30.2, 47.1)	45.0 (36.7, 55.6)	<0.001
TBIL (μmol/L)	23.5 (16.4, 31.7)	20.4 (14.8, 28.9)	26.4 (20.3, 33.9)	<0.001
DBIL (μmol/L)	8.9 (6.1, 12.7)	7.5 (5.5, 10.4)	10.6 (8.0, 14.5)	<0.001
ALB (g/L)	38.5 ± 7.0	40.2 ± 6.6	36.3 ± 6.9	<0.001
GLB (g/L)	32.2 ± 7.9	31.3 ± 5.8	33.3 ± 9.8	0.031
ALP (IU/L)	99.5 (79.2, 128.5)	95.6 (79.6, 122.1)	107.3 (78.9, 139.3)	0.156
GGT (IU/L)	42.0 (27.0, 68.0)	40.0 (26.8, 53.4)	46.5 (27.9, 78.1)	0.030
BUN (mmol/L)	5.59 ± 2.51	5.47 ± 2.26	5.73 ± 2.80	0.394
Cr (μmol/L)	66.7 ± 19.2	65.0 ± 17.2	68.8 ± 21.3	0.097
Na^+ (μmol/L)	140.3 ± 2.9	140.8 ± 2.5	139.7 ± 3.2	0.002
MELD scores	11.0 ± 2.5	10.5 ± 2.3	11.7 ± 2.7	<0.001
FIB-4 scores	5.3 (3.5, 7.9)	4.4 (3.0, 6.7)	6.7 (4.8, 9.0)	<0.001

Quantitative differences were analysed by the Student's *t* test or Mann-Whitney *U* test for continuous variables, as appropriate.
ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; DBIL, direct bilirubin; FIB-4, fibrosis-4; GLB, globulin; GGT, gamma-glutamyltransferase; Hb, haemoglobin; INR, international standard ratio; MELD, model for end-stage liver disease; PLT, platelet count; RBC, red blood cell; TBIL, total bilirubin; WBC, white blood cell.

0.618 (0.551-0.685) (Fig. S3). Moving to treatment week 24, the AUROC for PLT, ALB, and Na^+ were 0.687, 0.676, and 0.607, respectively (Fig. S4), while the model combining these factors had an AUROC of 0.749 (0.691-0.808) (Fig. 1B). The AUROC for the week 48 model was 0.746 (0.689-0.803) (Fig. 1C). Thus, treatment week 24 was the optimal timing for predicting recompensation by week 120.

Exploration of ALB cut-off value for predicting recompensation by week 120

There was no difference in baseline ALB levels between patients with and without recompensation by week 120. However, after starting antiviral treatment, serum ALB levels steadily increased and remained stable for the subsequent 24 weeks; patients with recompensation by week 120 had a significantly higher ALB level than those without (Fig. S5).

At treatment weeks 12 and 24, ALB levels were independent predictors of recompensation by week 120. According to the Youden index principle, the optimal cut-off value for ALB at week 12 was 34.4 g/L, similar to 34.2 g/L at week 24 (Table S7). At week 12, 120 out of 190 patients (63.2%) who had ALB ≥34 g/L achieved recompensation by 120 weeks, a rate significantly higher than the 39 out of 93 patients (41.9%) with ALB <34 g/L (*p* <0.001). Similarly, at week 24, patients with ALB

Table 3. Logistics analyses of treatment week 24 characteristics for recompensation prediction.

Characteristics	β	Odds ratio (95%CI)	*p* value	β	Odds ratio (95%CI)	*p* value
Laboratory results						
HBV DNA (Log_{10} IU/ml)		1.011 (0.815-1.260)	0.919			
WBC (10^9/L)	0.32	1.373 (1.144-1.675)	0.001		1.201 (0.956-1.529)	0.120
RBC (10^{12}/L)	0.63	1.864 (1.215-2.923)	0.005		0.625 (0.329-1.163)	0.142
PLT (10^9/L)	0.02	1.021 (1.013-1.030)	<0.001	0.02	1.020 (1.010-1.033)	<0.001
Hb (g/L)	0.01	1.010 (0.997-1.024)	0.128			
INR	-1.93	0.981 (0.966-0.995)	0.009		1.029 (0.999-1.062)	0.062
ALT (IU/L)	-0.005	0.995 (0.987-1.001)	0.135			
AST (IU/L)	-0.01	0.988 (0.978-0.997)	0.017		0.992 (0.981-1.000)	0.099
TBIL (μmol/L)	-0.02	0.983 (0.968-0.996)	0.014		1.012 (0.991-1.035)	0.276
DBIL (μmol/L)	-0.02	0.984 (0.963-1.002)	0.102			
ALB (g/L)	0.10	1.100 (1.056-1.148)	<0.001	0.07	1.080 (1.026-1.144)	0.005
GLB (g/L)	-0.04	0.964 (0.930-0.996)	0.038		0.972 (0.930-1.010)	0.191
ALP (IU/L)	-0.01	0.994 (0.989-1.000)	0.038		0.999 (0.992-1.005)	0.715
GGT (IU/L)	0.0001	1.000 (0.999-1.001)	0.847			
BUN (mmol/L)	-0.04	0.960 (0.867-1.055)	0.399			
Cr (μmol/L)	-0.01	0.989 (0.976-1.002)	0.107			
Na^+ (μmol/L)	0.14	1.146 (1.051-1.259)	0.003	0.13	1.116 (1.007-1.243)	0.041
MELD scores*	-0.19	0.825 (0.741-0.912)	<0.001			
FIB-4 scores*	-0.22	0.805 (0.740-0.869)	<0.001			

Variable selection for the multivariate regression model was performed using stepwise forward selection.
ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; DBIL, direct bilirubin; FIB-4, fibrosis-4; GLB, globulin; GGT, gamma-glutamyltransferase; Hb, haemoglobin; INR, international standard ratio; MELD, model for end-stage liver disease; PLT, platelet count; RBC, red blood cell; TBIL, total bilirubin; WBC, white blood cell.
*MELD score and FIB-4 score did not include in multivariate regression.

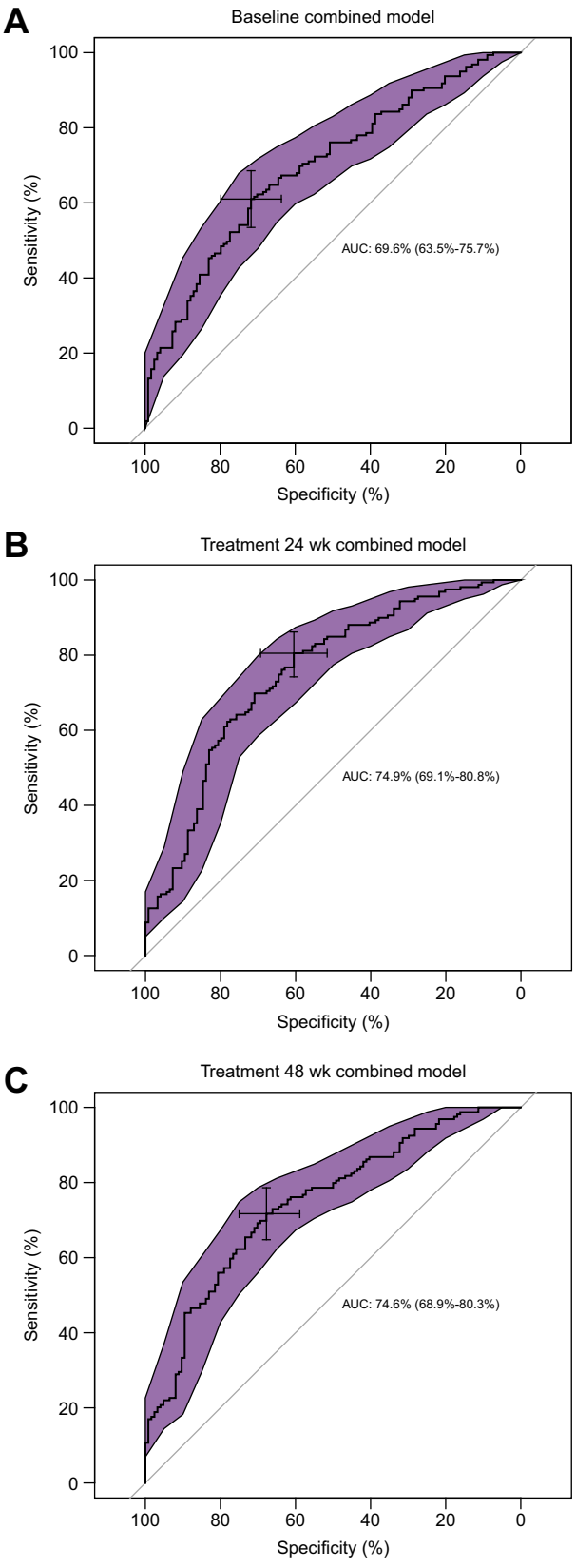

Fig. 1. ROC curves of the baseline, treatment week 24, treatment week 48 combined models for recompensation prediction. (A) The baseline combined model. (B) The treatment week 24 combined model. (C) The treatment week 48 combined model.

≥34 g/L showed a significantly higher recompensation rate (137/214, 64.0%) than those with ALB <34 g/L (22/69, 31.9%, p <0.001). Therefore, an ALB level of ≥34 g/L within 24 weeks of antiviral therapy may be a reliable threshold for predicting recompensation by week 120.

Of note, 54 patients (19.1%) underwent low-dose ALB administration as part of their initial treatment, receiving an average of 72.6 g of ALB per individual. However, at baseline and treatment week 12, there were no significant differences in age, sex, key baseline laboratory results, or MELD scores between these two groups, except for ALB levels (Table S8). Additionally, we observed a progressive increase in ALB levels across both patient groups throughout the antiviral therapy duration. Interestingly, by week 120, the rates of recompensation were statistically indistinguishable between the cohorts that received ALB infusions and those that did not.

Models for predicting recompensation by week 120

After identifying platelet count, serum ALB and sodium levels at week 24 as optimal predictors for recompensation, we built a score using the regression coefficients from the multivariate model as follows: score = 0.02*PLT + 0.07*ALB + 0.13*Na - 22.76 (PLT in 10^9/L; ALB in g/L and Na^+ in μmol/L) (Table 3). We refer to this score as the hepatis B RECompensation prediction using Platelet count, serum Albumin, and Sodium score (Brec-PAS score). The Brec-PAS score allows us to estimate the possibility of recompensation for an individual patient: Recompensation prediction =exp (Brec-PAS)/[1 + exp (Brec-PAS)].[9]

To aid in the prediction of recompensation, a nomogram, which is a graphical representation of the Brec-PAS score, has been created (Fig. 2). Clinicians can use the nomogram to easily determine a patient's likelihood of recompensation by drawing a line upward from the patient's score on each variable axis to the total points axis. Additionally, an online calculator has been developed to streamline the prediction process, accessible at https://Brec-PAS.shinyapps.io/dynnomapp/.

To identify a high-probability group, we stratified the Brec-PAS scores of all patients using a cut-off value of -0.35 (based on the Youden index principle). In our study, 150 patients were categorized into the high-probability group, which exhibited a considerably higher recompensation rate compared to the low-probability group (75.5% *vs.* 34.6%, p <0.001).

Discrimination and calibration of the Brec-PAS score

The discrimination ability of the Brec-PAS model was assessed by comparing its AUROC with those of the MELD and FIB-4 scores. For predicting the recompensation by week 120, the AUROC of the Brec-PAS score was 0.749 (0.691-0.808), which was significantly superior to that of the MELD score (0.629, p = 0.002) and the FIB-4 score (0.702, p = 0.097) (Fig. 3A). The model's calibration for predicting recompensation by week 120 was satisfactory (Fig. 3B), and the decision curve analysis indicated that the model, to some extent, outperformed the MELD scores and FIB-4 scores (Fig. 3C). The finding is further supported by the Brec-PAS model's predictive accuracy in subgroups defined by age, sex, baseline MELD scores, and FIB-4 scores (Table S9).

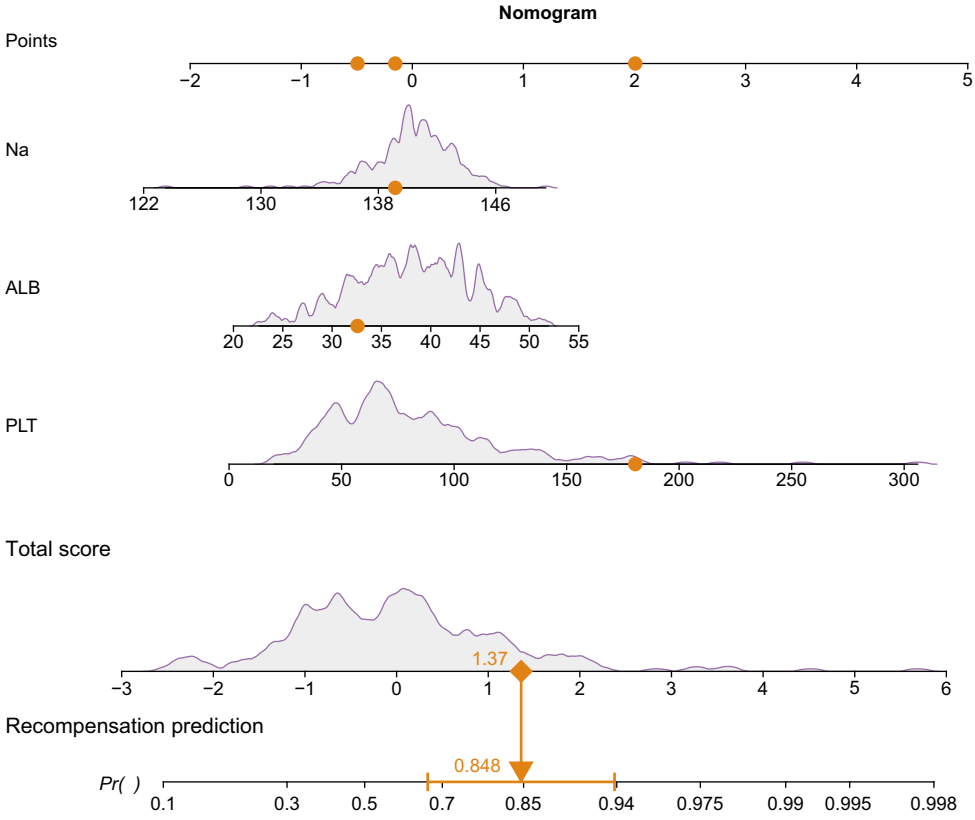

Fig. 2. Nomogram to predict the 120-week recompensation. To use, locate 'Na' axis; draw a line straight up to the 'Points' axis to determine the score associated with the Na. Repeat for the other two variables. Sum the scores and locate the total score on the 'Total score' axis. Draw a line straight downward to the 'Recompensation prediction' axis to obtain the 120-week recompensation probability. ALB, albumin; PLT, platelet count.

The durability of recompensation achieved by week 120

Most patients (86.8%, 92/106) who achieved recompensation by week 120 did not experience any subsequent decompensating events (Fig. 4). Among them, four patients (3.8%, 4/106) developed HCC without subsequent mortality, two (1.9%, 2/106) experienced variceal bleeding, two (1.9%, 2/106) developed moderate-severe ascites, and six (5.7%, 6/106) died. Of these six patients, two died due to advanced-stage HCC with portal vein tumour thrombosis, while the other four died from liver failure: two had concurrent infections, one succumbed to complications from gastrointestinal bleeding, and another, with a history of irregular medication adherence, showed virologic positivity upon admission, suggesting that viral rebound might have been a contributing factor.

The late attainment of recompensation in patients who did not achieve it by week 120

Among the 69 patients who did not achieve recompensation by week 120, a subset of them (40.6%, 28/69) did not experience any further decompensating events and achieved late recompensation. Additionally, four patients (5.8%, 4/69) developed HCC without subsequent mortality, one (1.4%, 1/69) experienced variceal bleeding, 10 (14.5%, 10/69) developed moderate-severe ascites, and 26 (37.7%, 26/69) died from liver-related causes (14 patients died within the 120 weeks) (Fig. 4).

Factors at week 120 associated with durable recompensation by week 240

We categorized patients into two groups: those with durable recompensation (n = 92) and those without (n = 14). Upon comparing their variables at week 120, we observed that patients with durable recompensation exhibited lower blood urea nitrogen levels (Table S10). However, further logistic analyses revealed that no factor was independently associated with durable recompensation (all p >0.05) (Table S11).

Incidence of HCC and mortality in patients with and without recompensation

Of the 283 patients, 28 patients developed HCC between weeks 24 and 288. In the initial study, patients diagnosed with HCC within the first 24 weeks were excluded due to the potential of pre-existing HCC. Of those who developed HCC later, eight were in the recompensation group and 20 were in the non-recompensation group (8/159, 5.0% *vs.* 20/124, 16.13%, p = 0.002). Among the 28 patients who developed HCC, nine subsequently died (2 from the recompensation group and 7 from the non-recompensation group).

Throughout the follow-up period, 32 patients died, six in the recompensation group and 26 in the non-recompensation group. Mortality was significantly lower among patients who achieved recompensation, as indicated by the higher cumulative survival rates in the recompensation group compared to

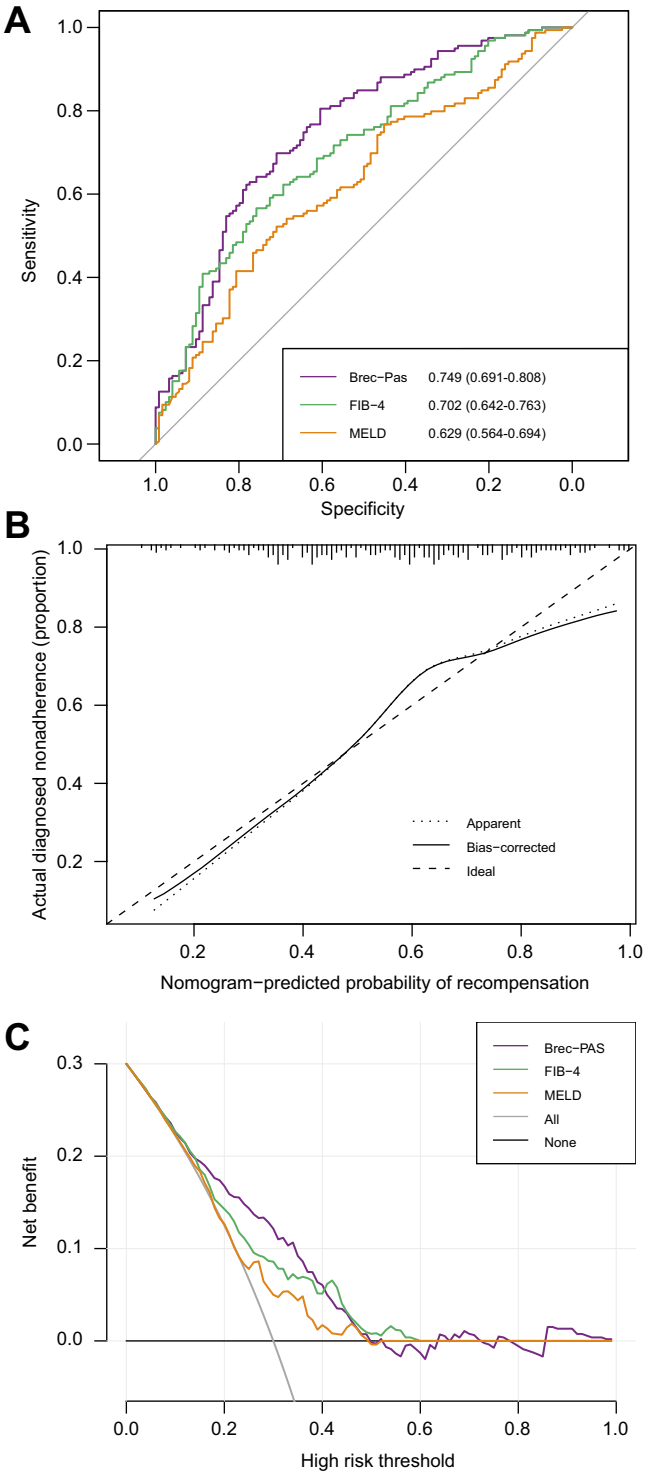

Fig. 3. ROC curves, calibration curves and decision curves of Brec-PAS score and conventional models for predicting recompensation. (A) The Brec-PAS score had the highest AUC for 120-week recompensation compared with the conventional prognostic models, including MELD and FIB-4 scores, in the whole cohort. (B) The nomogram-predicted recompensation probabilities were stratified in equally sized subgroups. Apparent line indicates the reference line, indicating where an ideal nomogram would lie. (C) Decision curve analysis plot depicting the standardized net benefit of Brec-PAS score as a continuous predictor for recompensation.

the non-recompensation group (100%, 99.1%, and 94.5% *vs.* 96.0%, 88.7%, and 69.9% at 1, 3, and 5 years of follow-up, respectively; p <0.001) (Fig. 5A). Additionally, the recompensation group exhibited higher HCC-free survival rates than the non-recompensation group (98.7%, 96.8%, and 92.6% *vs.* 98.3%, 86.1%, and 76.5% at 1, 3, and 5 years, respectively; p <0.001) (Fig. 5B).

Discussion

Our study revealed important findings in ETV-treated patients with CHB and decompensated cirrhosis. We found that an ALB level of ≥34 g/L at 24 weeks was associated with a higher likelihood of recompensation by week 120. Among those who achieved recompensation by week 120, 86.8% maintained stability during the subsequent 120 weeks, with a range of 72-168 weeks, of antiviral therapy. Furthermore, 40.6% of patients who did not achieve recompensation by week 120 could attain late recompensation in the following 120 weeks, with a range of 72-168 weeks.

One of the major findings of the study is that the predictability of ALB levels at treatment week 24 for recompensation by week 120 outperformed the baseline values. This outcome aligns with the expected improvements in baseline factors after initiating antiviral therapy.[10,11] Several studies have emphasized the connection between serum ALB levels and recompensation in patients with cirrhosis. For instance, Aravinthan *et al.* identified low MELD scores and high serum ALB levels as independent predictors for removing candidates with alcohol-related liver disease from the transplant list.[12] Similarly, in a study on HCV-related cirrhosis, El-Sherif *et al.* found that the absence of ascites or hepatic encephalopathy, along with high ALB levels, were critical pre-treatment factors associated with the restoration of liver function to Child-Pugh A.[13] Besides baseline ALB levels, the patient's response to treatment and ALB levels during treatment are also closely associated with recompensation.[14]

It is crucial to emphasize the dual role of ALB levels within the context of cirrhosis. ALB levels are not only integral to the recompensation process but also hold significant predictive value for the eventual achievement of recompensation. In the early stages of cirrhosis, dynamic fluctuations in ALB levels often precede the manifestation of clinical symptoms, especially since recompensation assessment typically requires 48 weeks or more. This perspective is supported by various studies that have identified ALB levels as a critical early predictive marker in liver disease.[13,14] The prognostic utility of ALB is rooted in its sensitivity to changes in hepatic synthetic function and its roles in antioxidant activities, immune modulation, and endothelial protection.[15] Recognizing the dual perspective of ALB levels as both indicators of ongoing recompensation and predictors of future recompensation not only aids in monitoring immediate progress but also provides insight into the likely trajectory of the disease.

We found that achieving an ALB level of 34 g/L or higher at treatment week 24 was associated with a significantly higher recompensation rate in patients with decompensated cirrhosis due to CHB. This finding aligns with previous reports that maintaining higher ALB concentrations through repeated infusion of human serum ALB is associated with improved clinical

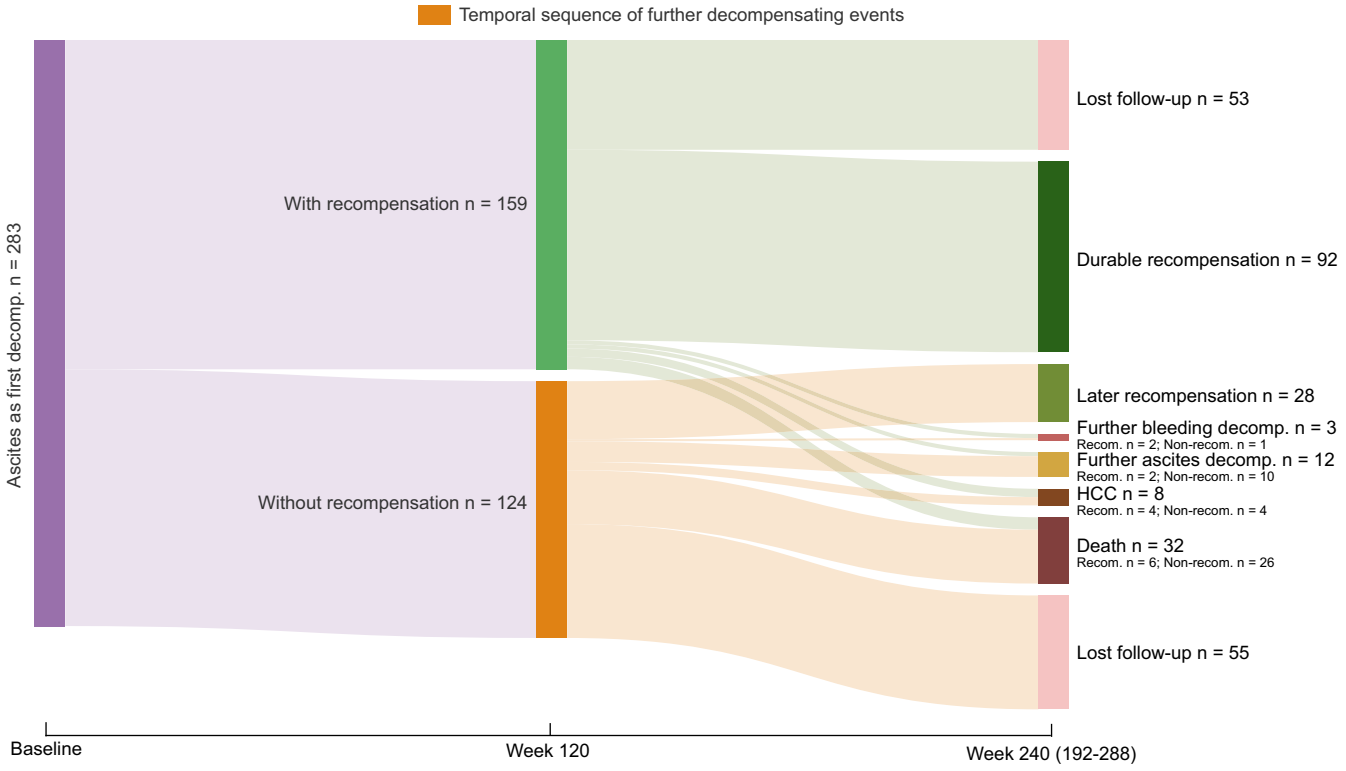

Fig. 4. Temporal sequence of further decompensating events at baseline, at treatment 120 weeks, and at treatment 240 weeks. The Sankey chart presents the temporal sequence of further decompensating events in patients over a period of 240 weeks, highlighting key time points at baseline, 120 weeks, and 240 weeks. The flow of patients between different decompensating events is depicted using varying thickness of the arrows, with wider arrows indicating a higher frequency or occurrence of the respective events. Some patients were diagnosed with HCC and subsequently succumbed to their illness, in this chart, these cases are solely classified and denoted as 'death'. HCC, hepatocellular carcinoma.

outcomes in patients with decompensated cirrhosis.[16–18] However, the target threshold for serum ALB and its clinical benefit remains a topic of discussion.[11,19,20] The ANSWER study indicated that patients with ALB levels above 40 g/L 1 month after treatment had significantly higher survival rates.[19] In contrast, the Barcelona study did not observe a significant difference in survival rates,[17] which might be related to the inclusion of more patients with severe conditions.

A distinct aspect of our study is the application of the Baveno VII definition of recompensation, which focuses on controlling the underlying cause rather than on ALB infusion.[8] In our study, less than one-fifth of the patients received a short period of low-dose ALB infusion. Interestingly, despite the recognized role of ALB in the management of cirrhosis,[15,18] our analysis did not reveal a significant difference in recompensation rates between patients who received ALB infusions during the initial treatment phase and those who did not. This may suggest that the beneficial impact of ALB infusions on the likelihood of recompensation is less pronounced than the therapeutic effect of antiviral medications, or that the variables related to ALB infusion, such as dosing and duration, require optimization to influence recompensation outcomes. Current literature presents divergent views on this matter, indicating both potential benefits and negligible effects of ALB infusions in different patient populations and clinical scenarios.[17,19,21,22] Our study's limitations, including its sample size and observational design, could have contributed to these findings, underscoring the necessity for further prospective trials. These future studies should aim to delineate the precise role of ALB infusions in enhancing liver function recovery, providing a clearer direction for clinical interventions in the management of cirrhosis.

Current research suggests that the pro-inflammatory and pro-oxidative environment during cirrhosis alters the structure of ALB molecules, leading to post-translational modifications and the production of various functionally impaired ALB subtypes.[23,24] Hence, the concept of "effective ALB concentration" has been proposed, emphasizing that the functional characteristics of ALB are as important as its quantity.[25] Therefore, targeting effective ALB, rather than trying to achieve a given concentration, might improve outcomes.

To facilitate clinical decision-making, we developed a model called the Brec-PAS score, which incorporated platelet, ALB, and sodium levels at treatment week 24. Patients with higher Brec-PAS scores are likely to respond more favourably to antiviral therapy, which may result in improved liver synthetic function.[15,19,26,27] The Brec-PAS score showed superior discriminative performance to MELD and FIB-4 scores, which have been used to select liver transplant candidates and evaluate liver fibrosis.[28,29] While prior research has explored the prediction of "recompensation" in patients with cirrhosis of various aetiologies, it is important to note that these studies were conducted before the explicit criteria for recompensation were defined.[6,12,30] The Brec-PAS model has the potential to

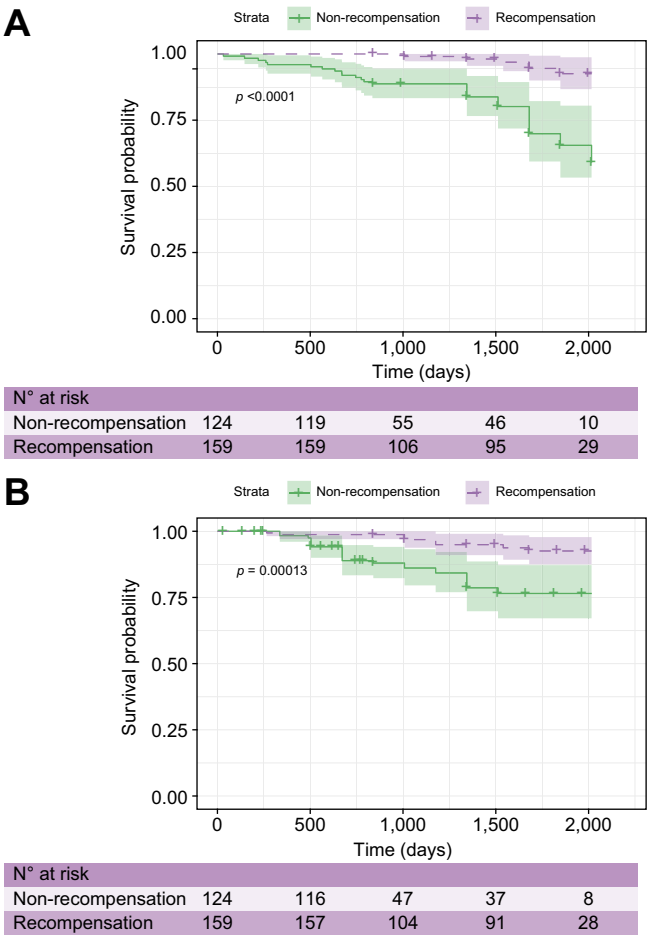

Fig. 5. Survival analysis of patients with chronic hepatitis B and decompensated cirrhosis based on recompensation status. (A) All-cause survival stratified by recompensation status. (B) Hepatocellular carcinoma-free survival stratified by recompensation status.

facilitate the creation of personalized treatment plans for individuals suffering from HBV-related decompensated cirrhosis.

An additional key finding of our study is that most patients (86.8%) who achieved recompensation by week 120 remained stable thereafter, with only a minor proportion (13.2%) experiencing a second decompensation event. Obviously, understanding the factors that influence recompensation durability in these patients is of clinical relevance.[8,31] Further research with longer-term follow-up is necessary to better elucidate these issues and optimize monitoring and treatment approaches.

Last but not least, we found that patients who did not achieve recompensation by week 120 still had a 40.6% chance of later recompensation, underlining the value of sustained antiviral therapy or intensified treatment. Thus, it is crucial to encourage these patients to continue with effective antiviral therapy, as there is still a substantial chance of achieving late recompensation.[5,32]

While the Baveno VII criteria have played a critical role in standardizing patient assessment, the rationale for the 12-month timeframe – predominantly based on expert opinion rather than empirical evidence – deserves further exploration. Several studies in this field have traditionally employed a 1-year timeframe to assess clinically significant outcomes, and their findings have significantly shaped the consensus regarding this period.[30,33–35] These studies have reported considerable clinical improvements within a year, affirming the utility of this timeline. Nonetheless, in light of the dynamic nature of cirrhosis and its management, we must consider whether a shorter timeframe might also be adequate for determining persistent patient improvement.[6,12]

Our study has some limitations. Firstly, 38.2% of patients were lost to extended follow-up. Despite no significant differences in clinical characteristics at baseline, week 24 and week 120 between those followed and those lost (Tables S1–3), this loss could still potentially lead to overestimation or underestimation of the treatment effect. Secondly, the Brec-PAS score showed only moderate performance in predicting recompensation by week 120, with an AUROC below 0.8. Nonetheless, it outperformed existing scoring systems currently in use, suggesting its potential as a predictive tool in clinical practice. Thirdly, we restricted our inclusion criteria to patients with CHB and decompensated cirrhosis, who presented with ascites as their initial decompensating event and received ETV as their initial treatment. Additionally, we excluded patients with comorbidities such as obesity and alcohol-related liver disease. This approach likely introduces a potential selection bias, potentially skewing our results towards a more favourable prognosis. Therefore, the selection criteria may limit the generalizability of our findings to a broader, more heterogeneous cohort of patients with a variety of comorbidities and decompensating events.

In summary, we demonstrated that a serum ALB level of 34 g/L or greater at antiviral treatment week 24 predicts recompensation by treatment week 120. The Brec-PAS score is an easy-to-use online tool for predicting recompensation during antiviral therapy. Initial recompensation was durable in 86.8% of patients, while 40.6% of the patients who did not achieve initial recompensation by week 120 achieved late recompensation.

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Abbreviations

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; DBIL, direct bilirubin; ETV, entecavir; FIB-4, fibrosis-4; INR, international normalised ratio; MELD, model for end-stage liver disease; PLT, platelet count; TBIL, total bilirubin.

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Conflict of interest

J.J. received research grants, consulting fees, or speaker honoraria from BMS, Gilead, and GSK. Y.N., X.X., H.Y. and W.X. received speaker honoraria from BMS, Gilead, and GSK. Calvin Q. Pan received research grants and speaker honoraria from Gilead. Other authors have nothing to be disclosed.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: Jidong Jia, Wen Xie, Xiaoyuan Xu, You Deng, Hong Zhao, and Qi Wang. Data acquisition: You Deng, Haiyan Kang, Huiling Xiang, Yuemin Nan, Jinhua Hu, Qinghua Meng, Qi Wang, Hong Zhao, Xiaoyuan Xu, Jilian Fang, Jie Xu, Xiaoming Wang. Analysis and interpretation of data: You Deng, Haiyan Kang, Huiling Xiang, Yuemin Nan, Jinhua Hu, Qinghua Meng, Xiaoyuan Xu, Wen Xie, and Jidong Jia. Manuscript writing, critical revision of the manuscript, and statistical analysis: Jidong Jia, Wen Xie, Xiaoyuan Xu, You Deng, and Haiyan Kang. All the authors vouch for the veracity and completeness of the data and analyses presented. The final version of the manuscript has been reviewed and approved by all authors.

Data availability statement

Data are available upon request and an appropriate institutional collaboration agreement.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101091.

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Author names in bold designate shared co-first authorship

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