Research Article
Cirrhosis and Liver Failure

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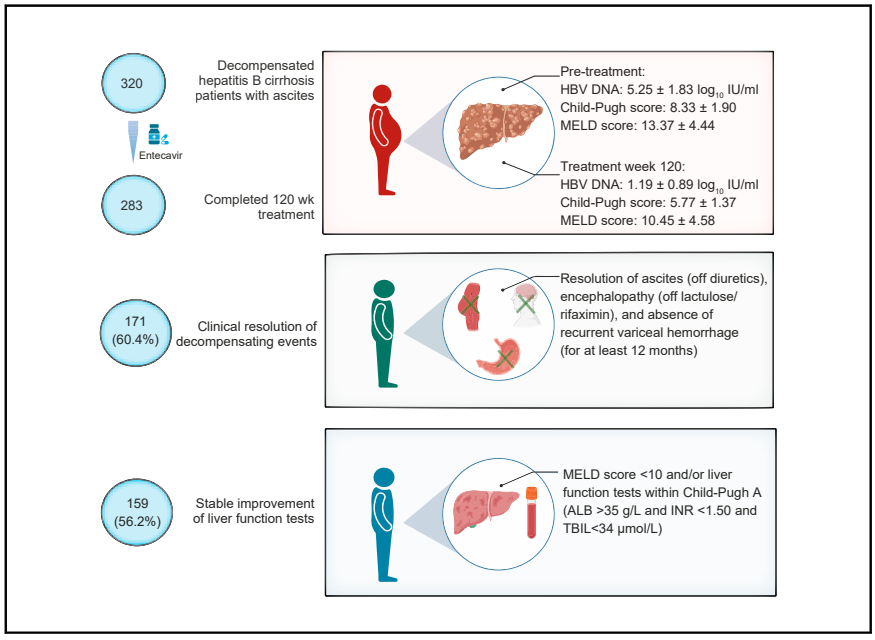
Graphical abstract



Highlights

- This is the first prospective validation of the Baveno VII recompensation definition in patients with HBV-related cirrhosis.
- A stable improvement of liver function tests was defined as MELD <10 and/or ALB & INR & TBIL within Child-Pugh A.
- On-treatment MELD scores may be more predictive of the probability of recompensation than baseline MELD scores.
- Prompt antiviral therapy is effective for patients with HBV-related cirrhosis, even under severe conditions.

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Lay summary

Decompensation of cirrhosis marks the point at which the liver is no longer able to function normally (and symptoms become apparent). Recently the idea of recompensation was proposed for individuals who may experience an improvement in liver function if the underlying cause of their liver disease is addressed (*e.g.* antivirals for viral cirrhosis). Herein, we show that over 50% of patients with hepatitis B-related decompensated cirrhosis treated with antivirals could recompensate and we propose laboratory criteria which could be used to define recompensation.

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Validation of Baveno VII criteria for recompensation in entecavir-treated patients with hepatitis B-related decompensated cirrhosis

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Background & Aims: Antiviral therapy improves the clinical outcomes of patients with chronic hepatitis B (CHB), including those with cirrhosis. In the present study, we validated the Baveno VII definition of recompensation and explored the criteria for stable improvement of liver function tests in entecavir-treated patients with CHB-related decompensated cirrhosis.

Methods: In this multicentre prospective study, patients with decompensated (ascites) CHB-related cirrhosis were enrolled and treated with entecavir for 120 weeks. Patients were followed up for clinical events, viral and biochemical tests, and ultrasonography every 6 months. The recompensation rate per Baveno VII criteria was calculated. Multivariate regression models were used to identify the predictors of recompensation. Finally, the criteria for stable improvement of liver function tests were explored.

Results: Of the 320 recruited patients, 283 completed the 120-week study, with 261/283 (92.2%) achieving HBV DNA levels <20 IU/ml and 171/283 (60.4%) achieving resolution of ascites, encephalopathy, and absence of recurrent variceal bleeding for at least 12 months. We identified model for end-stage liver disease <10 and/or liver function tests within Child-Pugh Class A (albumin >35 g/L, international normalised ratio <1.50 and total bilirubin <34 μmol/L) as the criteria for stable improvement of liver function tests. Accordingly, 56.2% (159/283) of patients fulfilled the Baveno VII definition of recompensation with a stable improvement of liver function tests defined by the current study.

Conclusions: Our study defined the criteria for a stable improvement of liver function tests required by the Baveno VII definition of recompensation in patients with CHB-related decompensated cirrhosis on antiviral therapy. The criteria derived from this multicentre prospective study warrant further validation in patients with cirrhosis of other aetiologies.

Lay summary: Decompensation of cirrhosis marks the point at which the liver is no longer able to function normally (and symptoms become apparent). Recently the idea of recompensation was proposed for individuals who may experience an improvement in liver function if the underlying cause of their liver disease is addressed (*e.g.* antivirals for viral cirrhosis). Herein, we show that over 50% of patients with hepatitis B-related decompensated cirrhosis treated with antivirals could recompensate and we propose laboratory criteria which could be used to define recompensation.

Introduction

HBV infection is a major public health issue that affects approximately 296 million people and causes 820,000 deaths globally per annum, mostly from cirrhosis and hepatocellular carcinoma (HCC).[1] Over 80 million people are chronically infected with HBV in China, accounting for about one-third of all HBV chronic infections in the world.[2]

Treatment with nucleos(t)ide analogues (NAs) can lead to profound viral suppression, thereby leading to amelioration of necroinflammation and regression of fibrosis in most patients with chronic hepatitis B (CHB).[3] Many studies have also demonstrated that NAs can improve the long-term prognosis of patients with cirrhosis, even those in the decompensated stage.[4–6] Therefore, the concept of recompensation has been proposed,[7,8] which means no further occurrence of decompensating events (including ascites, gastroesophageal variceal bleeding [VB], and hepatic encephalopathy [HE]) for an extended period (at least 1 year) as a result of the removal or effective control of the underlying aetiology.[9]

However, explicit definitions and criteria for recompensation were lacking until the most recent publication of the BAVENO VII

Keywords: recompensation; chronic hepatitis B; decompensated cirrhosis; predictors; cut-off values; stable improvement of liver function tests.
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consensus, which proposed a consensus definition of recompensation: at least partial regression of the structural and functional changes of cirrhosis after removal of the aetiology of cirrhosis.[10] The Baveno VII recompensation criteria require fulfilment of all 3 items: (1) removal/suppression/cure of the primary aetiology of cirrhosis; (2) resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin), and absence of recurrent variceal haemorrhage (for at least 12 months); (3) stable improvement of liver function tests (albumin [ALB], international normalised ratio [INR], bilirubin).[10] However, these criteria did not define the cut-off values for stable improvement of liver function tests.[10]

Therefore, in the present report, we validated the Baveno VII definition of recompensation and explored the cut-off values for stable improvement of liver function tests. The data were generated in a multicentre prospective cohort study investigating the clinical efficacy of 120-week entecavir therapy for patients with CHB-related decompensated cirrhosis and new-onset ascites.

Patients and methods

Study population

This multicentre, prospective, single-arm study recruited treatment-naïve patients with CHB-related decompensated cirrhosis at 10 participating hospitals from September 2016 to December 2018. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The informed consent processes were approved by the ethics committees at the leading site, Beijing Ditan Hospital, Capital Medical University (Approval No.: 2017-009-02), and each participating hospital.

The inclusion criteria were: (1) aged 18–70 years; (2) antiviral treatment-naïve CHB or starting antiviral therapy within 6 months of enrolment; (3) met the clinical, biochemical, haematological, radiological, or histological diagnostic criteria of cirrhosis; (4) detectable HBV DNA levels at the time of screening; (5) with ascites as the first presentation of decompensation; (6) provided informed consent.

The exclusion criteria were: (1) other concomitant chronic liver diseases, including hepatitis C, alcohol-related liver disease, severe non-alcoholic fatty liver disease, drug-induced liver injury, autoimmune liver disease, or genetic liver diseases; (2) history of gastroesophageal VB, HE, hepatorenal syndrome, or hepatopulmonary syndrome; (3) a Child-Pugh score >12 points; (4) creatinine >1.5× the normal upper limit at screening; (5) complicated with any malignant tumour (excluding cured ones); (6) dysfunction of the heart, lungs, kidneys, brain, blood, or other vital organs; (7) serious mental illness; (8) pregnant and breast-feeding females.

Treatment and follow-up

The baseline date was defined as the date of the first entecavir prescription. Patients' demographics, clinical characteristics and test results of biochemistry and virology, and ultrasonography were collected.

According to the Chinese HBV guidelines,[11] all patients were treated with oral entecavir 0.5 mg daily for 120 weeks. Switch-to or add-on tenofovir disoproxil fumarate once virological breakthroughs occur. A virological breakthrough was defined as a greater than 1 log IU/ml increase in the HBV DNA level or a detectable HBV DNA level after it became undetectable.

All patients were evaluated every 12 weeks for 120 weeks. Data on entecavir dosing, concurrent medications, and cirrhotic complications (*e.g.*, ascites, VB, and HE) were recorded. Laboratory tests at each visit included biochemistry, complete blood cell counts, INR, HBV DNA, and alpha-fetoprotein (AFP). The HBV serological markers were tested every 48 weeks. HBV DNA was quantified by a real-time PCR assay with a lower limit of quantification of 20 IU/ml.

Abdominal ultrasonography was performed at baseline and every 12 weeks thereafter. The presence and severity of ascites were evaluated by ultrasonography: Grade 1 (mild), ascites with a depth <3 cm; Grade 2 (moderate), 3–10 cm; and Grade 3 (severe), ≥10 cm.[12] When HCC was suspected on ultrasonography or by AFP measurement, enhanced multiphasic CT or MRI was used to confirm the diagnosis. Endoscopy was performed when the patient had VB.

A longer-term follow-up (144 weeks–288 weeks) was conducted in a subgroup of patients recruited at the leading site (Beijing Ditan Hospital, Capital Medical University).

The outcome assessment

The primary outcome was the clinical resolution of decompensating events, which was defined as resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin), and absence of recurrent VB for at least 12 months under antiviral treatment (Baveno VII).

The secondary outcomes included the following: 1) HBV DNA suppression; 2) changes in Child-Pugh scores, model for end-stage liver disease (MELD) scores, and other important indicators.

The exploratory endpoint was the cut-off values for the stable improvement of liver function tests that support the recompensation definition of the Baveno VII consensus.

Statistical analysis

Continuous variables are expressed as mean ± SD or median (IQR), while categorical variables are presented as n (%). Qualitative and quantitative differences between subgroups were analysed by the chi-square or Fisher's exact test for categorical variables, and the Student's *t* test or Mann-Whitney *U* test for continuous variables, as appropriate.

The paired-samples *t* test or ANOVA was used to compare the differences in MELD scores and Child-Pugh scores between time points. Sankey diagram was plotted to represent the change of Child-Pugh scores from baseline to treatment week 120. Multivariate logistic regression analysis was used to estimate the odds ratios (ORs) and their 95% CIs.

All statistical tests were 2-sided. Statistical significance was set at p <0.05. Statistical analysis was performed with IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NK, USA), GraphPad Prism Version 8.0.0 (http://www.graphpad.com), and R version 4.0.4 (http://www.r-project.org).

Results

Patients enrolment and baseline characteristics

During the study period, 490 patients with CHB-related decompensated cirrhosis were screened for eligibility at the 10 participating hospitals. After excluding 159 patients for various reasons, 331 patients were enrolled. We further excluded 11 patients who were diagnosed with HCC within 24 weeks of

enrolment. Of the remaining 320 patients, 283 completed the 120-week study with outcome data collected (Fig. 1).

The patients' baseline characteristics are shown in Table 1. Their mean age was 52 ± 11 years, with 61.9% (198/320) being males. The mean HBV DNA level was 5.25 ± 1.83 log10 IU/ml. The median alanine aminotransferase (ALT) level was 53.0 (IQR 35.1–100.9) IU/L, with 66.9% (214/320) of them having elevated ALT (>40 IU/L). The mean Child-Pugh and MELD scores were 8.33 ± 1.90 and 13.37 ± 4.44, respectively.

The number of patients with ascites Grades of 1, 2, and 3 was 178 (55.6%), 110 (34.4%), and 32 (10.0%), respectively. Among these 320 patients with cirrhosis and ascites, furosemide combined with spironolactone was given to 81 patients (25.3%), furosemide alone to 1 patient (0.3%), and spironolactone alone to 6 patients (1.9%). The details of the diuretic dosages are presented in Table S1.

The efficacy of entecavir on viral load, biochemistry, Child-Pugh and MELD scores

At week 120, the mean HBV DNA level in all patients significantly decreased from baseline (from 5.25 ± 1.83 to 1.19 ± 0.89 log10 IU/ml, p <0.001). Among the 283 patients who had completed the study, 92.2% achieved HBV DNA levels below the lower limit of quantification.

The liver function tests were remarkably improved, as shown in Table 2. The ALB levels were significantly increased from the baseline (31.7 ± 6.4 *vs.* 42.4 ± 6.2, p <0.001), whereas the INR and total bilirubin (TBIL) levels were significantly decreased from baseline (p <0.05 and p <0.001, respectively). Similarly, ALT and aspartate aminotransferase (AST) levels were also decreased significantly from baseline (both p <0.001).

After 120 weeks of entecavir therapy, the Child-Pugh scores and MELD scores significantly reduced from 8.33 ± 1.90 to 5.77 ± 1.37 (p <0.001) and from 13.37 ± 4.44 to 10.45 ± 4.58 (p <0.001), respectively.

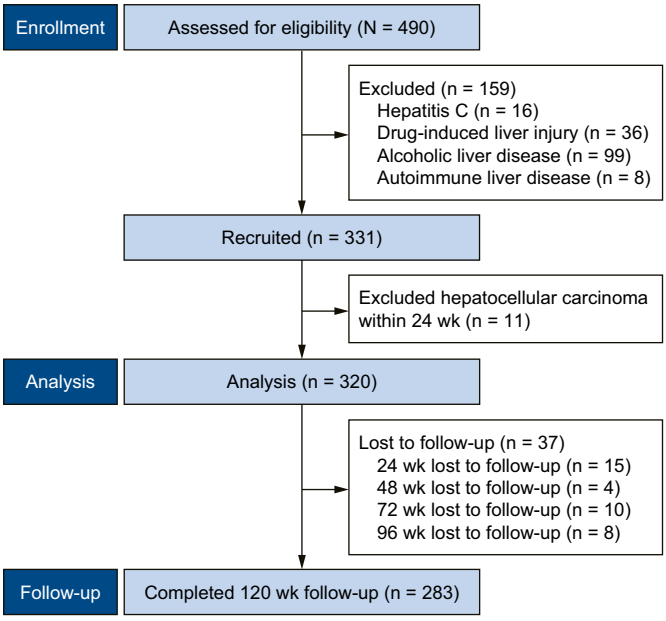

Fig. 1. Flow chart of patient characteristics.

Table 1. Baseline characteristics of 320 patients with decompensated cirrhosis due to HBV.

Characteristic	
Age (years)	52 ± 11
Male sex	198 (61.9%)
Laboratory results	
HBV DNA (Log_{10} IU/ml)	5.25 ±1.83
PLT (10^9/L)	73.0 (52.0, 97.0)
INR	1.37 (1.20, 1.56)
ALT (IU/L)	53.0 (35.1, 100.9)
AST (IU/L)	66.4 (45.0, 111.9)
TBIL (μmol/L)	32.9 (22.1, 52.0)
ALB (g/L)	31.7 ± 6.4
Na+ (μmol/L)	139.5 ± 3.4
AFP (ng/ml)	14.5 (5.4, 62.4)
Child-Pugh scores	8.33 ± 1.90
MELD scores	13.37 ± 4.44

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalised ratio; MELD, model for end-stage liver disease; PLT, platelet count; TBIL, total bilirubin.
Continuous variables were expressed as mean ± SD or median (IQR), while categorical variables were presented as n (%).

Efficacy of entecavir on clinical outcomes

During the 120 weeks of follow-up, 14 patients died and 2 had liver transplants, giving a combined death/liver transplant rate of 5.0%. Nineteen patients developed HCC between weeks 24 and 120, 11 patients developed VB (with 1 patient developing VB twice), and 4 patients developed HE.

Among the 283 patients who completed the 120-week follow-up, 171 patients (60.4%) achieved the clinical recompensation defined by Baveno VII, which means the resolution of ascites (off diuretics) and encephalopathy (off lactulose/rifaximin), and the absence of recurrent VB for at least 12 months.

Baseline and on-treatment characteristics in patients with or without clinical resolution of decompensating events

We stratified patients into those with (n = 171) and without (n = 112) clinical resolution of decompensating events to compare their baseline and on-treatment variables.

There was no difference in Child-Pugh and MELD scores at baseline between these 2 groups (8.39 ± 1.90 *vs.* 8.26 ± 1.86, p = 0.580; 13.67 ± 4.49 *vs.* 12.88 ± 4.15, p = 0.143). Interestingly, the patients with clinical resolution of decompensating events had higher baseline HBV DNA, platelet count (PLT), ALT, AST, TBIL, Na^+, and AFP than those without clinical resolution of decompensating events (Table S2).

The patients with clinical resolution of decompensating events at week 48 had lower INR, AST, TBIL, Child-Pugh scores, and MELD scores but higher PLT and ALB than those without clinical resolution of decompensating events (Table S2). Compared with those without clinical resolution of decompensating events, patients with clinical resolution of decompensating events had more profound improvement in Child-Pugh scores and MELD scores from treatment week 24 up to 120 (Fig. 2).

We plotted the Sankey diagram to represent the change of Child-Pugh scores from baseline to week 120, which showed remarkably more favourable results in the group with clinical resolution of decompensating events (Fig. 3). Although both groups achieved improvement in liver function tests during the 120-week treatment, the proportion of stable improvement of

Table 2. Baseline and on-treatment characteristics of the cohort.

Variables	Baseline (n = 320)	Week 48 (n = 301)	Week 120 (n = 283)
Laboratory results			
HBV DNA (Log_{10} IU/ml)	5.25 ± 1.83	1.30 ± 1.03*	1.19 ± 0.89#/ns
WBC (10^9/L)	4.10 ± 1.97	4.22 ± 1.80ns	4.32 ± 1.69ns/ns
RBC (10^{12}/L)	3.79 ± 0.64	4.34 ± 0.65*	4.46 ± 0.60#/$
HGB (g/L)	120.5 ± 19.7	135.5 ± 21.3*	138.0 ± 24.3#/ns
PLT (10^9/L)	73.0 (52.0–97.0)	72.0 (52.0–103.0) ns	79.0 (58.0–128.0)#/$
INR	1.37 (1.20–1.56)	1.20 (1.09–1.32)*	1.15 (1.06–1.30)#/ns
ALT (IU/L)	53.0 (35.1–100.9)	26.3 (20.2–34.1)*	22.0 (16.9–29.5)#/$
AST (IU/L)	66.4 (45.0–111.9)	33.4 (26.4–40.5)*	26.6 (21.9–33.8)#/$
TBIL (μmol/L)	32.9 (22.1–52.0)	19.8 (13.8–29.6)*	20.8 (15.4–20.8)#/ns
ALB (g/L)	31.7 ± 6.4	40.5 ± 7.3*	42.4 ± 6.2#/$
Na^+ (μmol/L)	139.5 ± 3.4	140.5 ± 3.4*	140.9 ± 3.5#/ns
AFP (ng/ml)	14.5 (5.4–62.4)	4.2 (3.0–6.7)*	2.7 (1.9–3.6)#/$
Child-Pugh scores	8.33 ± 1.90	5.97 ± 1.66*	5.77 ± 1.37#/ns
MELD scores	13.37 ± 4.44	10.55 ± 3.58*	10.45 ± 4.58#/ns

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HGB, haemoglobin; INR, international normalised ratio; MELD, model for end-stage liver disease; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; WBC, white blood cell count.
Quantitative differences were analysed by the Student's *t* test or Mann-Whitney *U* test for continuous variables, as appropriate.
*Week 48 *vs.* baseline, p <0.05.
#Week 120 *vs.* baseline, p <0.05.
$Week 120 *vs.* week 48, p <0.05; ns: no significance.

liver function tests was significantly higher in the group with clinical resolution of decompensating events, as shown in Fig. 4.

Factors associated with clinical resolution of decompensating events

Univariate logistics analyses revealed several baseline variables associated with clinical resolution of decompensating events, including higher HBV DNA, ALT, AST, Na^+, and AFP (all p <0.05). Multivariate analysis showed that the following 2 baseline variables independently associated with clinical resolution of decompensating events: higher AST (odds ratio [OR] 0.996; 95% CI 0.993–0.999; p = 0.011) and higher Na^+ (OR 0.890; 95% CI 0.823–0.963; p = 0.004) (Table 3).

Further univariate analyses showed that at treatment week 48, white blood cell count, red blood cell count, haemoglobin, PLT, INR, AST, TBIL, and ALB were associated with clinical resolution of decompensating events (all p <0.05). Multivariate analysis demonstrated that at treatment week 48 the following variables were independently associated with clinical resolution of decompensating events: higher PLT (OR 0.988; 95% CI 0.979–0.996; p = 0.006) and higher ALB (OR 0.926; 95% CI 0.886–0.968; p = 0.001) (Table 3).

The cut-off values for stable improvement of liver function tests supporting the Baveno VII definition of recompensation

Overall, all 283 patients who completed 120 weeks of entecavir therapy achieved viral suppression. Among them, 171/283 (60.4%) achieved resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin), and absence of recurrent VB for at least 12 months.

At treatment week 48, 130 of these 171 patients achieved an improvement of liver function tests within Child-Pugh A (ALB >35 g/L & INR <1.50 & TBIL <34 μmol/L); and 142 of these 171 patients had MELD scores below 10 points. Overall, 150 of these

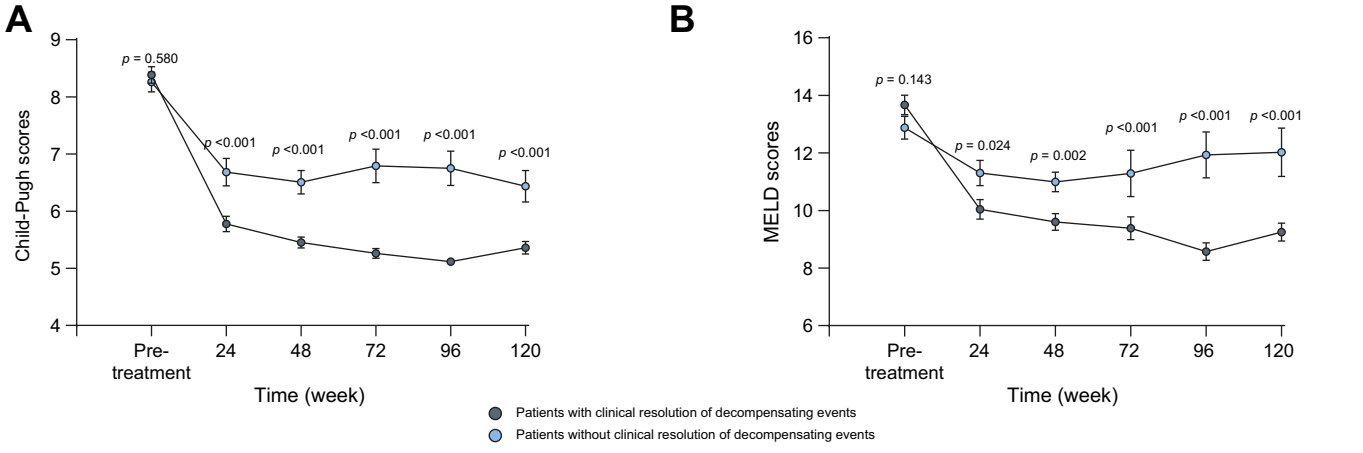

Fig. 2. The changes in Child-Pugh/MELD scores in patients with/without clinical resolution of decompensating events during 120 weeks of treatment. (A) Mean Child-Pugh scores at baseline and follow-up in patients with or without clinical resolution of decompensating events (bars represent SEM). The differences in Child-Pugh scores in these 2 groups at each time point were compared using Student's *t* tests. (B) Mean MELD scores at baseline and follow-up in patients with or without clinical resolution of decompensating events (bars represent SEM). The differences in MELD scores in these 2 groups at each time point were compared using Student's *t* tests. MELD, model for end-stage liver disease.

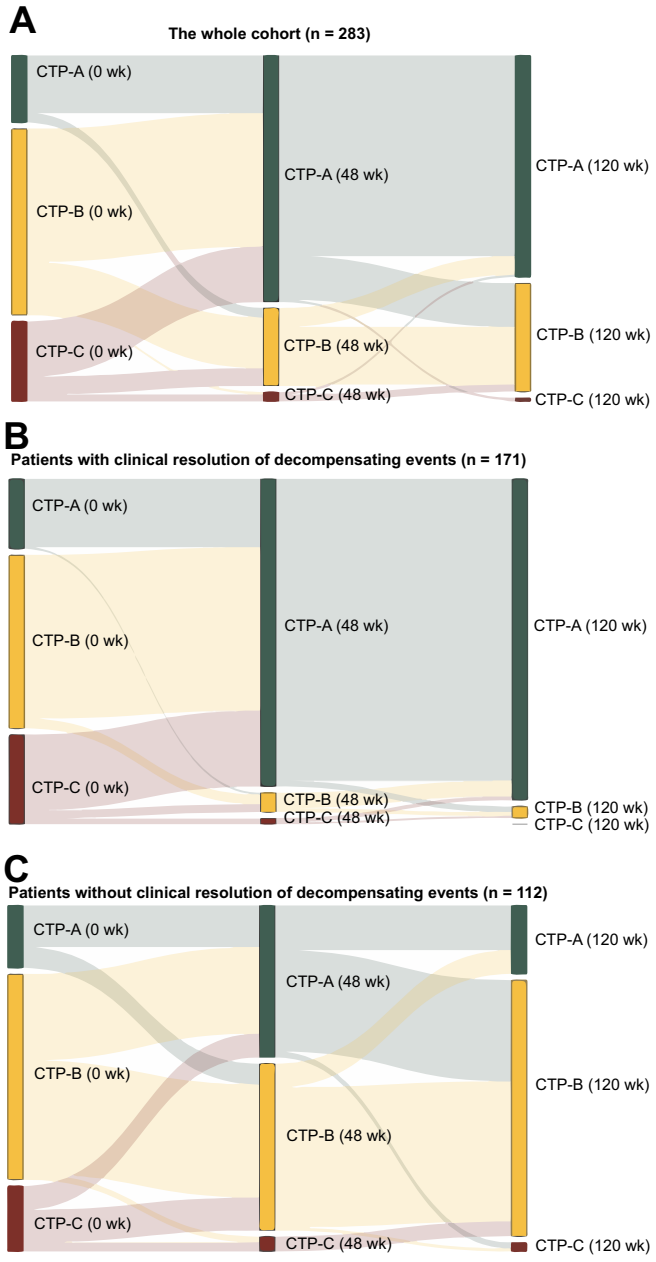

Fig. 3. Sankey diagrams for the change of Child-Pugh scores from baseline to treatment week 120. Sankey diagrams were used to show the major transfers or flows of patients. The colours of the columns represent patients with different Child-Pugh classifications, with green representing Child-Pugh-A, yellow representing Child-Pugh-B, and red representing Child-Pugh-C. The length of the column represents the proportion of patients. The thicker the line, the greater the number of patients involved. (A) The whole cohort (n = 283). (B) Patients with clinical resolution of decompensating events (n = 171). (C) Patients without clinical resolution of decompensating events (n = 112).

171 patients achieved stable improvement of liver function tests that were within Child-Pugh A (ALB >35 g/L & INR <1.50 & TBIL <34 μmol/L) and/or MELD <10 at treatment week 48 (Fig. 5). Therefore, we would propose to use these cut-off values as the criteria for stable improvement of liver function tests, which is a key component of the Baveno VII definition for recompensation.

Accordingly, 53.0% of the patients (150/283) would fulfil the Baveno VII criteria of recompensation by treatment week 48. By the same criteria, 56.2% of the patients (159/283) would fulfil the Baveno VII criteria of recompensation by treatment week 120.

Recompensation rate in patients with more severe liver disease

We further assessed the outcomes of patients who had a higher MELD score or higher levels of bilirubin, INR, ALT, or AST at baseline.

Notably, among the 74 patients with MELD scores >15 points at baseline, 3 died between week 48 to week 120 (with MELD scores of 15.32, 17.86, and 20.36, respectively), 1 received a liver transplant at week 24 (with a MELD score of 20.59), 3 developed VB between week 72 to week 96 (with MELD scores of 16.85, 15.77, and 16.98, respectively), and 1 developed HE at week 48 (MELD score of 17.04).

Despite these detrimental outcomes in some patients, those with MELD scores >15 points at baseline had an even higher recompensation rate than those with MELD scores ≤15 points at baseline (50/74, 67.6% *vs.* 109/209, 52.2%; $p = 0.029$). However, 0 of the 5 patients with a MELD score >15 after 48 weeks of treatment achieved recompensation within 120 weeks.

Similarly, among the 32 patients with higher levels of total bilirubin (>200 μmol/L), INR (>2.5), or ALT or AST (>500 IU/L) at baseline, 1 patient died and 1 patient developed HCC, but no one developed HE or VB. Notably, 22 of the 32 patients achieved recompensation by week 120, which was not statistically different from the rest of the cohort (22/32, 68.8% *vs.* 137/251, 54.6%; $p = 0.136$).

Lastly, as shown in Fig. 3, the number of patients with Child-Pugh C cirrhosis also dramatically reduced from baseline to treatment weeks 48 and 120.

Recompensation rate in patients with or without new-onset VB or HE

Overall, 15 patients developed either VB (11 patients) or HE (4 patients) from week 24 to week 120 and from week 48 to week 120, respectively. More details of these 15 patients are provided in Table S3. The baseline characteristics of those with or without new-onset VB or HE were shown in Table S4. Actually, compared to those without new-onset VB or HE, neither more advanced cirrhosis (fibrosis-4 scores: 8.30 [5.17–8.94] *vs.* 6.77 [4.99–10.29], $p = 0.981$), nor more severe hepatitis flare (log HBV DNA: 4.90 [2.79–6.10] *vs.* 5.33 [3.66– 6.31], $p = 0.623$) was observed in those with new-onset VB or HE.

We further performed univariate analysis to reveal the factors associated with new-onset VB or HE in 15 patients with VB or HE and 88 patients without VB or HE. We found that none of the variables had a significant odds ratio for the new-onset VB or HE (Table S5).

Not surprisingly, only 3 of these 15 patients with new-onset VB or HE achieved recompensation by week 120, which was significantly lower than in the rest of the cohort (3/15, 20.0% *vs.* 156/268, 58.2%; $p = 0.006$).

Recompensation states in patents with follow-up beyond 120 weeks

Among the 110 patients recruited at the leading site (Beijing Ditan Hospital, Capital Medical University), 55 patients were

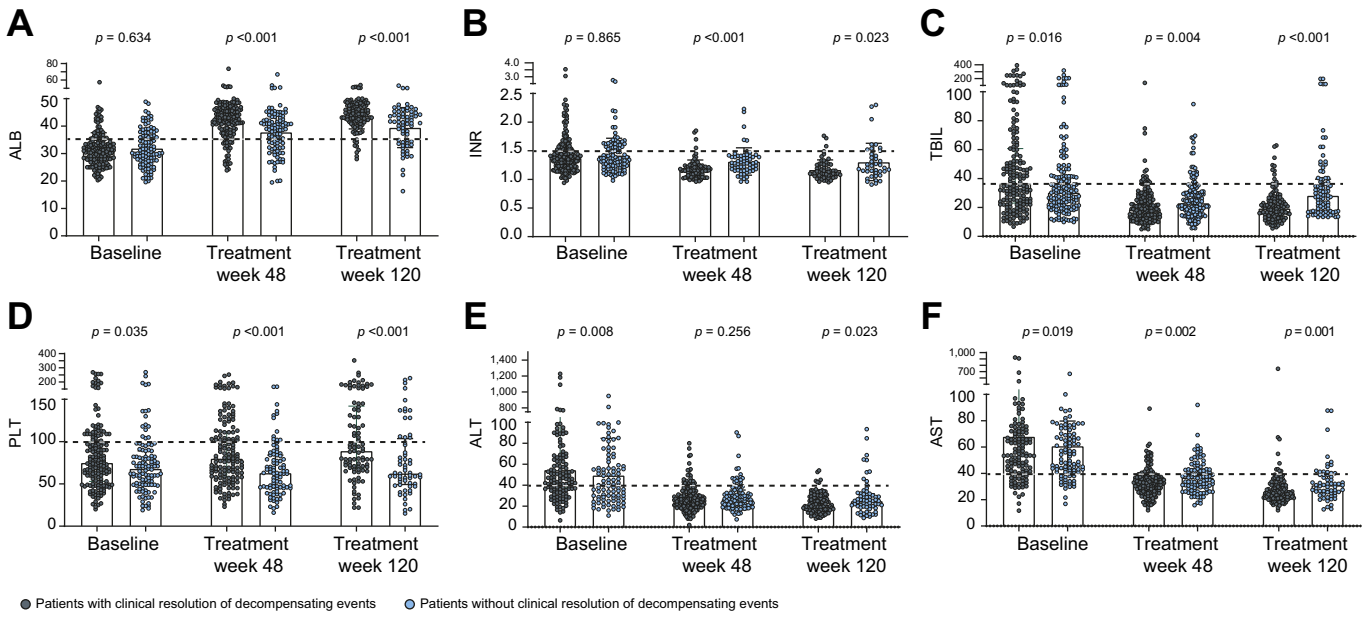

Fig. 4. The dynamic changes in liver function tests in patients with/without clinical resolution of decompensating events. The values of different liver function tests at baseline, week 48, and week 120 for patients with and without clinical resolution of decompensating events are shown in the grey and blue scatter diagrams. At each time point, the differences in liver function tests in these 2 groups were compared. (A) ALB (Student's *t* test). (B) INR (Mann-Whitney *U* test). (C) TBIL (Mann-Whitney *U* test). (D) PLT (Mann-Whitney *U* test). (E) ALT (Mann-Whitney *U* test). (F) AST (Mann-Whitney *U* test). ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalised ratio; PLT, platelet count; TBIL, total bilirubin.

followed beyond week 120, with a median follow-up time of 144 weeks.

Among the 34 patients who achieved recompensation by week 120, 31 (91.2%) did not experience any decompensated events thereafter, and 3 were diagnosed with HCC between weeks 144 and 240.

In contrast, among the 21 patients who did not achieve recompensation by week 120, 8 patients (38.1%) developed detrimental outcomes (1 developed VB, 3 developed moderate-severe ascites, 2 developed HCC, 1 developed pancreatic cancer, and 1 died of chronic liver failure) between weeks 144 and 288.

These findings provide further support to the criteria for recompensation required by the Baveno VII and suggested by the current study.

Discussion

Our current study revealed that after 120 weeks of antiviral therapy, 92.2% of the patients (261/283) achieved HBV DNA suppression; 60.4% (171/283) achieved clinical resolution of ascites without the use of diuretics, no HE without the use of lactulose or rifaximin, and absence of recurrent VB for at least 12 months. Importantly, 56.2% (159/283) of patients achieved a stable improvement in liver function tests as defined by the present study (MELD score <10 and/or ALB & INR & TBIL within Child-Pugh A). Therefore, we propose the use of these criteria to define a stable improvement of liver function tests for patients with HBV-related decompensated cirrhosis, which supports the recompensation definition proposed by the Baveno VII consensus.

Table 3. Logistics analyses for prediction of clinical resolution of decompensating events.

	Univariate analysis			Multivariate analysis		
Characteristic	**Odds ratio**	**95%CI**	***p* value**	**Odds ratio**	**95%CI**	***p* value**
Pre-treatment						
HBV DNA (Log_{10} IU/ml)	0.867	0.761–0.988	0.032	0.920	0.799–1.060	0.248
ALT (IU/L)	0.998	0.996–1.000	0.031	1.000	0.998–1.003	0.977
AST (IU/L)	0.996	0.993–0.999	0.012	0.996	0.993–0.999	0.011
Na^+ (μmol/L)	0.910	0.845–0.980	0.013	0.890	0.823–0.963	0.004
AFP (ng/ml)	0.998	0.996–1.000	0.022	0.999	0.997–1.001	0.146
Treatment week 48						
WBC (10^9/L)	0.826	0.691–0.986	0.034	1.048	0.835–1.316	0.684
RBC (10^{13}/L)	0.488	0.311–0.764	0.002	0.749	0.305–1.840	0.529
HGB (g/L)	0.985	0.972–0.997	0.018	1.009	0.983–1.037	0.491
PLT (10^9/L)	0.980	0.971–0.988	<0.001	0.988	0.979–0.996	0.006
INR	1.039	1.017–1.062	<0.001	1.020	0.997–1.044	0.094
AST (IU/L)	1.018	1.001–1.034	0.039	1.011	0.993–1.030	0.229
TBIL (μmol/L)	1.020	1.002–1.039	0.029	0.998	0.971–1.024	0.858
ALB (g/L)	0.921	0.887–0.957	<0.001	0.926	0.886–0.968	0.001

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HGB, haemoglobin; INR, international normalised ratio; MELD, model for end-stage liver disease; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; WBC, white blood cell count.
Odds ratios were estimated using logistic regression.

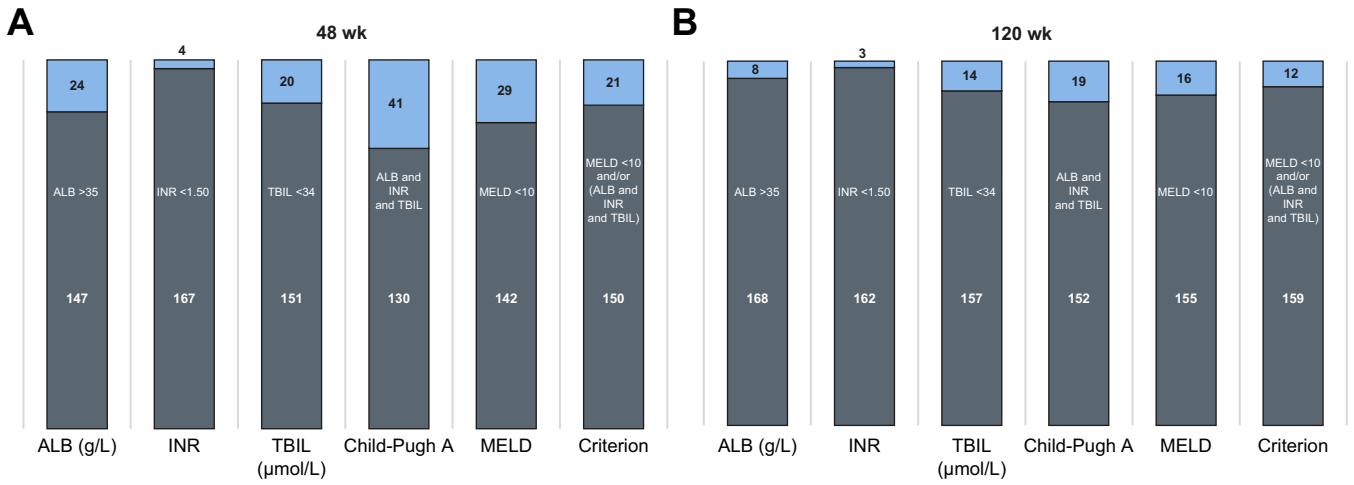

Fig. 5. The number of patients under different standards at treatment weeks 48 and 120. (A) At treatment week 48. (B) At treatment week 120. From left to right, the grey columns represent the number of patients with ALB >35 g/L, INR <1.50, TBIL <34 μmol/L, ALB & INR & TBIL, MELD <10, and the criterion (MELD <10 and/or ALB & INR & TBIL), respectively. The blue columns represent the number of patients who did not meet the standards. ALB, albumin; INR, international normalised ratio; MELD, model for end-stage liver disease; TBIL, total bilirubin.

To our knowledge, this is the first multicentre prospective study validating the Baveno VII definition of recompensation and defining the criteria for stable improvement of liver function tests required by this definition. There was no universal definition for recompensation,[13,14] although this concept was well supported by many studies which had shown antiviral therapy remarkably improves clinical outcomes, including decreases in MELD and Child-Pugh scores, the incidence of HCC, the need for liver transplantation, and liver-related death.[5,15,16]

For the first time, Baveno VII proposed an explicit definition and 3 requirements for recompensation, namely: removal or control of the underlying aetiology; free from decompensating events for at least 12 months; and stable improvement of liver function tests.[10] However, different variables and cut-off values had been used in previous studies on clinical outcomes of decompensated cirrhosis due to various aetiologies.[17,18] Obviously, detailed criteria for stable improvement of liver function tests are still needed.

Our current study also suggested that MELD score <10 and/or liver function tests within Child-Pugh A (ALB >35 g/L & INR <1.50 & TBIL <34 μmol/L) would be used as a criterion for stable improvement of liver function tests. Although Child-Pugh and MELD scores have been widely used for the assessment of prognosis in cirrhosis,[19–21] we did not directly use the whole original Child-Pugh score for the following reasons. First, Child-Pugh score includes variables which are subjective or not accurately measured, such as the severity of ascites and HE.[22,23] Second, prothrombin time used in the Child-Pugh score can vary widely between laboratories due to variations in the reagents and procedures, whereas INR is a more stable indicator with 2 "correction factors" (although it was originally established for monitoring anticoagulation therapy in the non-liver disease setting[24]). We hope the criteria based on these objective variables would be more clinically relevant and easy to use in day-to-day medical care.

Notably, data on patients with follow-up beyond 120 weeks further demonstrated that patients were very stable if they achieved clinical recompensation as defined by Baveno VII and stable improvement of liver function tests defined by the present study. These data provide further evidence supporting the use of clinical definition and liver function test criteria for recompensation in future study or clinal practice.

Interestingly, we found that high pre-treatment AST was independently associated with a higher recompensation rate on entecavir therapy for 120 weeks. This may indicate that patients with active liver disease, as reflected by higher AST levels, had a better potential for response to antiviral therapy.[25] Similar to previous reports,[26,27] we also found that PLT and ALB at treatment week 48 were associated with recompensation. Not surprisingly, we found high pre-treatment serum Na^+ concentration was independently associated with recompensation, as shown by previous studies.[28,29]

Similarly, we found that patients who were quite acutely ill at baseline, reflected by higher levels of AST, TBIL and INR, seemed to share a similar recompensation rate with the rest of the patients in the cohort. This suggested that prompt antiviral therapy is effective, at least for some patients, even in severe conditions, which may be unique to hepatitis B-related decompensated cirrhosis.[30,31]

Furthermore, patients who had a baseline MELD score >15 did not have a lower recompensation rate than those who had a baseline MELD score ≤15. However, none of the patients who had a MELD score >15 after 48 weeks of treatment achieved recompensation within 120 weeks. These results indicate that on-treatment MELD scores are more important than the baseline values in predicting recompensation in patients on antiviral therapy.[32]

In our study, 3 patients achieved HBsAg seroclearance. In clinical fields, persistent HBsAg positivity, reflecting the deregulation of innate and adaptive immune systems, has long served as a diagnostic marker for chronic HBV infection.[33] The decreased level or even loss of HBsAg is associated with the recovery of the host's immune system and the reduced risk of HCC.[34] Since the number of patients with HBsAg was too small, further analysis is not feasible. Obviously, the development of novel drugs aimed at clearing HBsAg (*i.e.* to achieve a functional cure) is crucial to further improve long-term clinical outcomes.

Our study has some limitations. First, there was no untreated control group for ethical reasons, since antiviral therapy has become the standard of care. Second, follow-up beyond 120 weeks is available only in a subgroup of the cohort. Still, the limited data indicate that most of those who achieved recompensation at week 120 remained stable thereafter. In contrast, few who did not achieve recompensation at week 120 had a favourable outcome. Third, we only included patients with decompensated cirrhosis due to hepatitis B; therefore, whether these criteria can be extrapolated to patients with other aetiologies of cirrhosis warrants further validation.

In summary, we validated the Baveno VII definition of recompensation and proposed the stable improvement of liver function tests be defined as MELD score <10 and/or liver function tests within Child-Pugh A (ALB >35 g/L & INR <1.50 & TBIL <34 μmol/L). These results may warrant further validation in decompensated cirrhosis of other aetiologies.

Abbreviations

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalised ratio; MELD, model for end-stage liver disease; NAs, nucleos(t)ide analogues; OR, odds ratio; PLT, platelet; TBIL, total bilirubin; VB, variceal bleeding; WBC, white blood cell.

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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

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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.jhep.2022.07.037.

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Author names in bold designate shared co-first authorship

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