Efficacy and safety of bifidobacterium triple viable capsules combined with entecavir in the treatment of Hepatitis B cirrhosis

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Background. Liver cirrhosis caused by hepatitis B is a critical progression of chronic hepatitis B. It is often accompanied by intestinal dysbiosis and impaired intestinal mucosal barrier function, which further exacerbate hepatic inflammation and fibrosis. Therefore, exploring effective combined therapeutic approaches to improve patient outcomes is of significant importance.

Objective. This study compares the efficacy and safety of entecavir combined with bifidobacterium triple viable capsules versus entecavir alone in treating Hepatitis B cirrhosis.

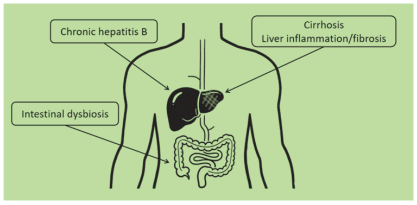
Methods. This retrospective case-control study enrolled 110 patients with Hepatitis B cirrhosis diagnosed and treated from January 2021 to January 2024. The control group received entecavir alone, while the observation group received entecavir combined with bifidobacterium triple viable capsules Efficacy was assessed at 24 weeks and 48 weeks post-treatment. Comparisons were made between the two groups regarding changes in intestinal flora count, intestinal mucosal barrier function, liver function, HBV-DNA negativity rate, liver fibrosis indices, liver stiffness measurement (LSM), inflammatory factor indices, and treatment safety.

Results. At 24 weeks and 48 weeks post-treatment, the observation group exhibited significant modulation of the intestinal microecology, with a notable decrease in the count of pathogenic bacteria (Candida albicans, Enterobacteriaceae, Enterococcus) in feces compared to pre-treatment and the control group (all $P<0.05$), and a significant increase in the count of probiotics (Lactobacillus, Bifidobacterium) (all $P<0.05$). Meanwhile, the observation group showed more significant improvement in intestinal mucosal barrier function, with lower levels of endotoxin, D-lactic acid, and diamine oxidase compared to the control group (all $P<0.05$). Regarding liver-related indices, the observation group demonstrated significantly greater improvement in liver function (ALT, AST, TBIL, ALB), liver fibrosis markers (HA, PC-III, IV-C, LN), and LSM compared to the control group (all $P<0.05$), with more pronounced improvement at 48 weeks than at 24 weeks ($P<0.05$). Notably, the observation group exhibited a higher HBV-DNA negativity rate at 48 weeks (90.91% vs 76.36%, $P=0.039$) and superior regulation of inflammatory factors (decreased TNF-α, IL-6, IL-8, and increased IL-10) (all $P<0.05$). The final clinical efficacy assessment revealed a significantly higher total effective rate in the observation group compared to the control group (83.64% vs 65.45%, $P=0.029$). Adverse event rates were comparable between the observation and control groups (7.27% vs. 10.91%, $P=0.507$), supporting the safety of the intervention.

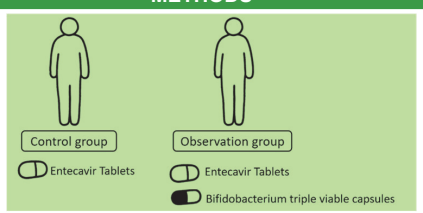
Conclusion. The treatment regimen of bifidobacterium triple viable capsules combined with entecavir is significantly superior to entecavir alone in improving intestinal flora, repairing the intestinal mucosal barrier, promoting liver function recovery, and alleviating liver fibrosis in patients with Hepatitis B cirrhosis. It also demonstrates more pronounced long-term efficacy, a higher HBV-DNA negativity rate, superior overall clinical efficacy, and good safety.

Efficacy And Safety Of Bifidobacterium Triple Viable Capsules Combined With Entecavir In The Treatment Of Hepatitis B Cirrhosis

BACKGROUND



METHODS



RESULTS

1. Intestinal Microecology: Post-treatment (24 & 48 weeks), observation group: Pathogenic bacteria in feces decreased (vs pre-treatment & control, $P<0.05$); probiotics increased ($P<0.05$)
2. Intestinal Mucosal Barrier Function: Observation group: Improved more, with lower endotoxin, D-lactic acid, and diamine oxidase (vs control, $P<0.05$)
3. Liver-Related Indices: Function & Fibrosis: Observation group: Greater improvement in liver function, fibrosis markers, and LSM (vs control, $P<0.05$); more at 48 weeks ($P<0.05$)
4. HBV-DNA: At 48 weeks, observation group had higher negativity rate (90.91% vs 76.36%, $P=0.039$)
5. Inflammation: Observation group: Better regulation (↓TNF-α, IL-6, IL-8; ↑IL-10, $P<0.05$)
6. Clinical Efficacy: Observation group: Higher total effective rate (83.64% vs 65.45%, $P=0.029$)
7. Adverse Events: Rates similar in both groups (7.27% vs 10.91%, $P=0.507$)

Bifidobacterium triple viable capsules + entecavir improve gut health and liver function, reduce liver fibrosis, and show better long-term efficacy and safety in Hepatitis B cirrhosis patients.

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Graphical Abstract

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INTRODUCTION

Hepatitis B cirrhosis represents the terminal phase of chronic HBV infection, marked principally by widespread liver fibrosis, pseudolobule formation, destruction of hepatic parenchymal structure, and progressive liver dysfunction[1]. Among these, hepatic fibrosis is a critical link and a core pathological change in disease development[2]. Persistent hepatic inflammatory responses, abnormal immune responses, and long-term active viral replication induced by HBV infection are important mechanisms driving the continuous progression of hepatic fibrosis[3]. HBV activates hepatic stellate cells through various viral factors such as HBeAg and HBx protein, promoting excessive extracellular matrix deposition. Moreover, the persistent inflammatory microenvironment triggers oxidative stress reactions, further exacerbating liver tissue damage and the fibrosis process[4, 5]. Additionally, the long-term presence of HBV-DNA in the hepatocyte nucleus makes it difficult to completely eradicate the virus[6]. Without timely and effective antiviral treatment and disease monitoring following HBV infection, patients often undergo a progressive development process from chronic hepatitis, hepatic fibrosis, compensated cirrhosis to decompensated cirrhosis, with some patients eventually progressing to hepatocellular carcinoma[7]. Therefore, early implementation of potent antiviral therapy to continuously suppress HBV-DNA replication, combined with antifibrotic treatment, holds significant clinical importance for blocking or even reversing hepatic fibrosis and delaying the progression of liver cirrhosis[8].

Nucleos(t)ide analogues (NAs), as fundamental antiviral agents, are extensively employed for chronic hepatitis B and related cirrhosis treatment. They primarily work by competitively suppressing HBV-DNA polymerase, thereby inhibiting viral replication and markedly lowering serum HBV-DNA levels[9, 10]. Long-term, standardized NAs treatment not only inhibits viral replication but also alleviates hepatic inflammatory responses, partially improves the degree of hepatic fibrosis, thereby delaying the progression of cirrhosis and reducing the risk of liver function decompensation and hepatocellular carcinoma[11]. Among the existing NAs drugs, entecavir is recommended as a first-line anti-HBV medication by international guidelines such as those from the AASLD, EASL, and the Chinese "Guidelines for the Prevention and Treatment of Chronic Hepatitis B" dbecause of its strong ability to suppress viruses and high genetic barrier to resistance[12]. However, clinical practice has revealed that after one year of NAs treatment, the average improvement rate of inflammatory necrosis reaches approximately 68%, while only 35% of hepatic fibrosis cases demonstrate improvement. In the patient population with severe hepatic fibrosis, even after 5 to 10 years of long-term antiviral treatment, the proportion of patients with no improvement in hepatic fibrosis remains as high as 35% (ref.[13]). Despite the ability of long-term NAs therapy to somewhat hinder the progression of hepatic fibrosis and cirrhosis, its capacity to induce fibrosis reversal proves inadequate[14]. Furthermore, even with antiviral treatment, the risk of cirrhosis advancing to hepatocellular carcinoma remains substantial[15]. Therefore, exploring effective antifibrotic treatment methods is particularly crucial.

As research on the microbiome progresses, the relationship between gut bacteria and liver fibrosis has become a key focus in the scientific community[16]. Empirical evidence demonstrates that cirrhotic patients with long-term HBV infection tend to develop gastrointestinal microbiome disturbances, principally showing declines in advantageous bacterial strains and expansion of potentially detrimental microbial populations[17]. This microbial imbalance may compromise gut barrier integrity, allowing endotoxin transfer to the liver through the portal system. This activates Kupffer cells to secrete inflammatory mediators, promoting hepatic stellate cell activation and accelerating fibrosis progression[18]. Against this backdrop, the administration of a triple-viable bifidobacterium preparation may play a positive role in delaying the progression of hepatic fibrosis by regulating gut microecological balance, reducing endotoxin translocation, and inhibiting inflammatory responses. Therefore, combining triple-viable bifidobacterium treatment with antiviral therapy may hold significant clinical importance. Further exploration of the safety and efficacy of this combined treatment regimen is warranted, with the aim of improving patients' quality of life and prolonging survival.

MATERIALS AND METHODS

Study design

The study adopted a controlled, single-center retrospective design, analyzing clinical data from hospitalized patients over a three-year period (January 2021 to January 2024). A total of 135 patients with chronic hepatitis B were initially identified. Following rigorous assessment based on inclusion and exclusion criteria, 110 patients ultimately met the eligibility criteria for this study and were

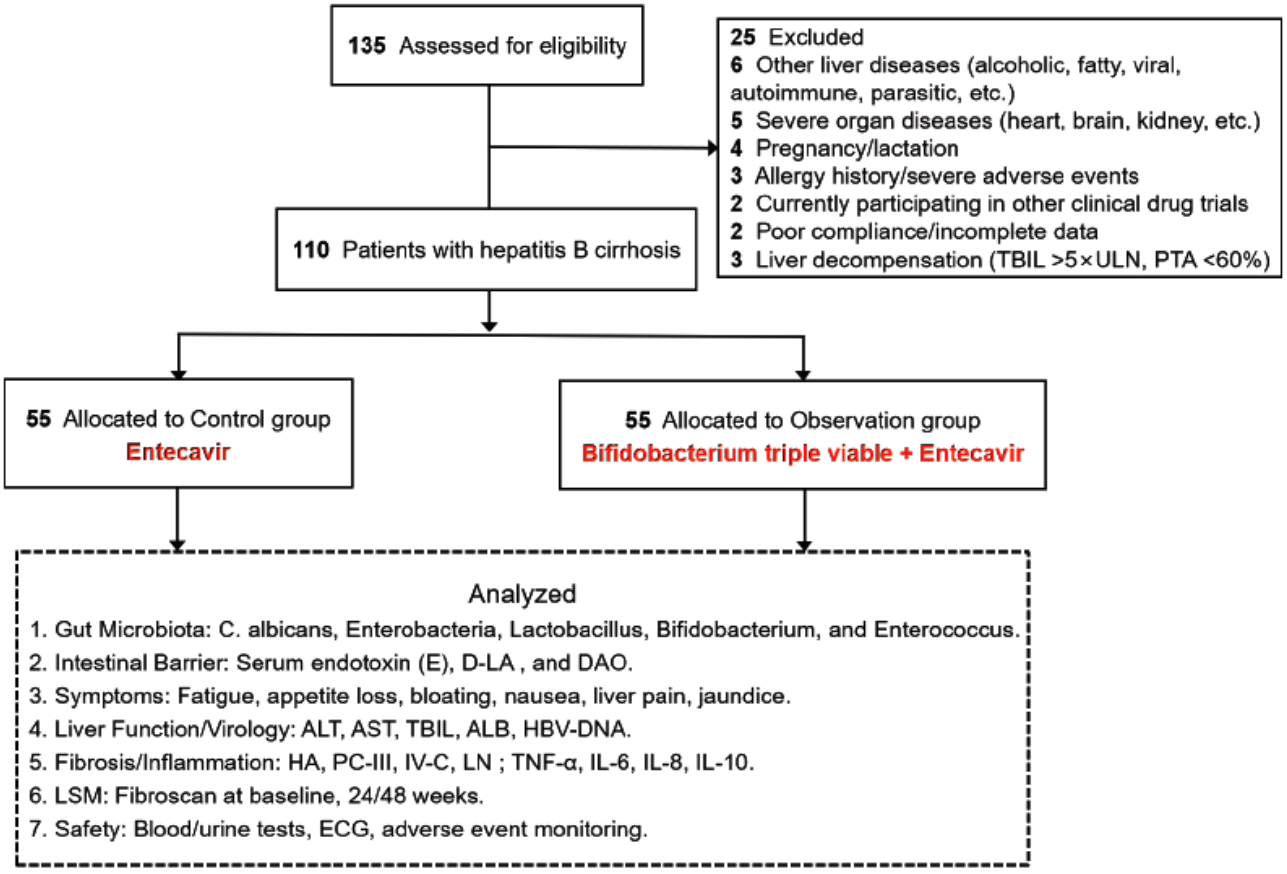

Fig. 1. Flow diagram of the study.

confirmed to have early-stage cirrhosis caused by chronic hepatitis B through liver biopsy. The specific study process is illustrated in Fig. 1.

Inclusion criteria

(1) Meeting the diagnostic criteria for chronic hepatitis B established by the (EASL (ref.[19])); (2) Aged between 18 and 70 years; (3) Positive for HBsAg and HBV-DNA in serum samples, with HBeAg being either positive or negative; (4) Persistent or recurrent elevation of ALT; (5) Degree of hepatic fibrosis: Ishak score ≥ F4.

Exclusion criteria

(1) Concomitant other liver diseases: alcoholic liver disease, non-alcoholic fatty liver disease, other viral hepatitis, autoimmune liver disease, parasitic infections, etc.; (2) Severe diseases of vital organs such as the heart, brain, and kidneys; (3) Pregnant or lactating women; (4) Allergic constitution or history of drug allergy; (5) Currently participating in other clinical drug trials; (6) Poor compliance and incomplete data that affect the judgment of efficacy and safety.

Withdrawal criteria

(1) Liver decompensation, including TBIL > 5 times the ULN or PTA < 60%, with the occurrence of ascites, gastrointestinal bleeding, hepatic encephalopathy, and progression to hepatocellular carcinoma; (2) Special physiological changes, such as pregnancy, rendering the participant unsuitable for continued observation; (3) Allergic reactions or severe adverse events.

Sample size calculation

The case numbers in the observation group and the control group were arranged in a 1:1 ratio. The statistical hypothesis testing formula $n=8Pq/(P1-P2)^2$ was applied, where P1 and P2 represent the clinical effective rates of the observation group and the control group, respectively; P is the combined rate of the two groups = (P1+P2)/2; and q=1−P. According to relevant literature[20], the clinical effective rate (P2) of entecavir monotherapy for Hepatitis B cirrhosis is 0.6, while the assumed clinical effective rate (P1) of entecavir combined with triple-viable bifidobacterium preparation for Hepatitis B cirrhosis is 0.8. After calculation, the sample size was determined to be 42 cases. In this study, 55 cases were included in each group, satisfying the sample size requirement.

Case grouping

Patients were divided into: Observation group: triple-viable bifidobacterium + entecavir; Control group: entecavir alone. The study enrolled a total of 110 participants, with 55 in the observation group (35 males, 20 females; mean age 53.84±11.69 years) and 55 in the control group (38 males, 17 females; mean age 54.24±10.13 years). No significant differences were observed in gender distribution or mean age between the two groups ($P>0.05$), confirming balanced baseline characteristics.

Treatment methods

Both groups received a comprehensive treatment plan, which included ensuring adequate rest and reasonable

dietary adjustments, avoiding alcohol consumption and the use of liver-damaging medications, and promptly supplementing proteins and providing relevant symptomatic treatments. The control group was treated with Entecavir Tablets (manufacturer: Bristol-Myers Squibb (Shanghai) Pharmaceuticals Co., Ltd., National Medicine Approval Number: H20052237, specification: 0.5 mg). The dosage and administration were as follows: 0.5 mg per dose, once daily. The observation group, in addition to the treatment regimen of the control group, was also treated with Triple-Viable Bifidobacterium Capsules (manufacturer: Shanghai Sine Pharmaceutical Co., Ltd., National Medicine Approval Number: S10950032). The dosage and administration were as follows: 420 mg per dose, taken orally, twice daily, after meals. Both groups were treated for 48 weeks.

Observation indicators

(1) Intestinal flora count: Detection was performed before treatment and at 24 weeks and 48 weeks after treatment. Fresh fecal samples (4 g) were collected from patients, and qPCR analyzers were utilized to accurately quantify key intestinal flora such as Candida albicans, Enterobacteriaceae, Lactobacillus, Bifidobacterium, and Enterococcus in the feces. The detection results were expressed as the logarithm of the bacterial gene copies measured per gram of fecal sample, providing a scientific basis for quantitative analysis of the intestinal flora.

(2) Intestinal mucosal barrier function: Detection was performed before treatment and at 24 weeks and 48 weeks after treatment. Morning fasting venous blood was drawn from each group. After centrifugation (3,000 rpm, 10 min) of 5 mL of the sample, the supernatant was frozen at −20°C for future testing. Endotoxin (E) levels were detected using a bacterial endotoxin detector; D-lactic acid (D-LA) levels were detected using fully automatic biochemical analyser; and diamine oxidase (DAO) levels were detected using spectrophotometry. All methods were strictly executed in accordance with the kit instructions.

(3) Clinical manifestations: Including fatigue, susceptibility to fatigue, loss of appetite, abdominal distension, nausea and vomiting, dull pain in the hepatic region, and jaundice.

(4) Liver function indicators: ALT, AST, TBIL, and ALB were detected before treatment and at 24 weeks and 48 weeks after treatment using an automated biochemical analyzer.

(5) Virological indicators: HBV-DNA was detected before treatment and at 24 weeks and 48 weeks after treatment using the Roche LightCycler 480 real-time fluorescence quantitative PCR method, with a detection limit of <15 IU/mL.

(6) Liver fibrosis indicators: HA, PC-III, IV-C, and LN were detected before treatment and at 24 weeks and 48 weeks after treatment using radioimmunoassay.

(7) Liver stiffness measurement (LSM): Detection was performed before treatment and at 24 weeks and 48 weeks after treatment using the transient elastography scanner (Fibroscan) produced by the French company Echosens.

(8) Inflammatory factor indicators: Serum inflammatory factors TNF-α, IL-6, IL-8, and IL-10 were detected using the fully automatic biochemical analyser.

(9) Safety: Routine blood and urine tests, fecal occult blood, renal function, coagulation function, alpha-fetoprotein, myocardial enzymes, and electrocardiogram were regularly monitored during treatment. Any newly emerged adverse reactions, such as allergies, gastrointestinal reactions, palpitations, chest tightness, dizziness, or abnormal urine color, were recorded and analyzed at any time. In the event of severe adverse reactions, the medication was discontinued or treatment was terminated.

Criteria for efficacy evaluation

Efficacy evaluation was conducted for both groups of patients at 24 weeks and 48 weeks after treatment. Total effective rate = (markedly effective cases + effective cases) / Total cases × 100%.

(1) Markedly effective: Patients' clinical symptoms disappeared; serum liver function indicators returned to essentially normal levels; HBV-DNA turned negative; and two or more measurements of liver fibrosis indicators decreased by >50% compared to pre-treatment levels or returned to normal levels.

(2) Effective: Patients' clinical symptoms improved; serum liver function indicators improved; HBV-DNA did not turn negative, but its titer decreased by >2 log10 IU/mL compared to baseline; and two or more measurements of liver fibrosis indicators decreased by >20% compared to pre-treatment levels.

(3) Ineffective: Patients' self-reported symptoms showed no significant improvement or even worsened; serum liver function indicators did not improve or even deteriorated; HBV-DNA did not turn negative, and its titer did not decrease or even increased compared to baseline; and liver fibrosis indicators did not decrease or even increased.

Statistical methods

Statistical analysis was performed with SPSS 25.0. Normally distributed continuous data are presented as mean±SD and compared using t-tests. Categorical data are shown as n (%) and analyzed by χ^2 or Fisher's exact tests, with $P<0.05$ indicating significance.

RESULTS

Comparison of intestinal flora distribution

Post-treatment (24/48 weeks), the observation group showed significantly lower fecal Candida albicans, enterobacteria, and enterococci counts versus baseline and controls ($P<0.05$), but higher lactobacilli and bifidobacteria levels ($P<0.05$). See Table 1.

Comparison of intestinal barrier function indicators

At 24 and 48 weeks post-treatment, E, D-LA, and DAO levels in both groups decreased compared to pre-treatment levels. The observation group had significantly lower levels than the control group ($P<0.05$). See Table 2.

Table 1. Comparison of intestinal flora counts ($\bar{x}$±s).

Group	Time point	Control group (n=55)	Observation group (n=55)	*t*-value	*P*
Candida albicans	Baseline	20.53±2.18	20.44±2.25	0.237	0.813
	24 Weeks	19.86±1.74	18.25±1.66	5.010	0.000
	48 Weeks	18.41±2.08	16.77±1.38	4.870	0.000
Enterobacteriaceae	Baseline	16.38±1.74	16.40±1.85	0.058	0.954
	24 Weeks	15.62±1.87	14.52±1.75	3.193	0.002
	48 Weeks	15.07±1.99	13.27±1.49	5.368	0.000
Lactobacillus	Baseline	19.29±2.44	19.33±2.51	0.105	0.916
	24 Weeks	20.02±2.37	23.45±2.48	7.430	0.000
	48 Weeks	21.40±2.75	25.56±2.15	8.821	0.000
Bifidobacterium	Baseline	23.24±2.79	23.55±2.88	0.573	0.568
	24 Weeks	23.81±2.54	26.60±2.41	5.890	0.000
	48 Weeks	24.22±2.71	28.46±2.69	8.268	0.000
Enterococcus	Baseline	20.23±2.44	20.21±2.27	0.023	0.982
	24 Weeks	19.46±2.15	18.22±2.04	3.079	0.003
	48 Weeks	18.33±2.42	16.75±2.33	3.466	0.001

Table 2. Comparison of intestinal mucosal barrier function levels ($\bar{x}$±s).

Group	Time point	Control group (n=55)	Observation group (n=55)	*t*-value	*P*
E (μg/mL)	Baseline	0.70±0.14	0.72±0.15	0.795	0.428
	24 Weeks	0.63±0.12	0.48±0.15	6.094	0.000
	48 Weeks	0.57±0.13	0.39±0.12	7.849	0.000
D-LA (mg/L)	Baseline	15.46±2.88	15.55±2.46	0.157	0.876
	24 Weeks	14.02±2.54	12.11±2.53	3.972	0.000
	48 Weeks	12.22±2.48	9.33±1.56	7.311	0.000
DAO (U/mL)	Baseline	9.66±2.23	9.49±2.17	0.429	0.669
	24 Weeks	8.28±1.97	6.88±1.36	4.339	0.000
	48 Weeks	6.83±1.49	5.02±1.28	6.857	0.000

Table 3. Comparison of liver function indicators ($\bar{x}$±s).

Group	Time point	Control goup (n=55)	Observation group (n=55)	*t*-value	*P*
ALT (U/L)	Baseline	122.15±12.33	124.66±11.28	1.114	0.268
	24 Weeks	89.66±9.42	68.55±8.12	12.595	0.000
	48 Weeks	50.36±6.88	33.45±6.25	13.499	0.000
AST (U/L)	Baseline	113.55±12.45	116.57±13.48	1.217	0.226
	24 Weeks	80.36±8.58	72.33±7.54	5.211	0.000
	48 Weeks	39.66±8.96	32.44±7.69	4.535	0.000
TBIL (μmol/L)	Baseline	51.88±7.02	52.34±7.56	0.338	0.736
	24 Weeks	36.77±4.31	31.45±5.63	5.559	0.000
	48 Weeks	30.44±5.36	20.17±5.44	9.972	0.000
ALB (g/L)	Baseline	29.56±3.44	29.18±3.25	0.596	0.553
	24 Weeks	32.61±3.17	36.44±4.02	5.564	0.000
	48 Weeks	38.65±5.48	43.86±5.23	5.096	0.000

Comparison of liver function indicators

After treatment intervention, both groups showed a trend of improvement in liver function at 24 weeks and 48 weeks: the levels of ALT, AST, and TBIL significantly decreased compared to baseline (P<0.05), while the level of ALB increased significantly (P<0.05), suggesting that both treatment regimens were effective in improving liver function. Further intergroup comparisons revealed that the observation group had significantly greater reductions in ALT, AST, and TBIL levels at 24 weeks and 48 weeks compared to the control group (P<0.05), as well as significantly greater increases in ALB levels (P<0.05), indicating that the regimen in the observation group had a more pronounced hepatoprotective effect. As the treatment duration extended to 48 weeks, the degree of improvement in liver function in the observation group was more significant compared to that at 24 weeks (P<0.05), revealing a cumulative effect of long-term treatment. See Table 3.

Table 4. Comparison of HBV-DNA negative conversion rates (n, %).

Time point	Control group (n=55)	Observation group (n=55)	χ^2-value	*P*
Baseline	0% (0/55)	0% (0/55)	0.000	0.000
24 Weeks	58.18% (32/55)	67.27% (37/55)	0.972	0.324
48 Weeks	76.36% (42/55)	90.91% (50/55)	4.251	0.039

Table 5. Comparison of liver fibrosis indicators ($\bar{x}$±s, ng/mL).

Group	Time point	Control group (n=55)	Observation group (n=55)	*t*-value	*P*
HA	Baseline	271.66±63.22	279.46±61.73	0.654	0.515
	24 Weeks	146.59±51.56	125.33±42.45	2.361	0.020
	48 Weeks	86.33±21.65	58.66±18.45	7.216	0.000
PC-III	Baseline	186.46±37.45	189.65±40.25	0.432	0.667
	24 Weeks	152.33±40.87	131.22±32.69	2.993	0.003
	48 Weeks	120.45±35.46	79.63±25.66	6.917	0.000
IV-C	Baseline	185.33±38.44	179.65±41.22	0.746	0.457
	24 Weeks	143.66±35.49	126.44±29.46	2.770	0.007
	48 Weeks	97.35±26.88	69.42±22.19	5.943	0.000
LN	Baseline	218.75±38.54	225.33±40.12	0.879	0.382
	24 Weeks	161.45±35.76	141.22±25.87	3.399	0.000
	48 Weeks	99.65±24.38	78.66±21.36	4.800	0.000

Table 6. Comparison of LSM ($\bar{x}$±s, kPa).

Time point	Control group (n=55)	Observation group (n=55)	*t*-value	*P*
Baseline	23.44±4.15	23.61±4.23	0.213	0.832
24 Weeks	20.66±3.12	17.65±3.44	4.814	0.000
48 Weeks	18.65±3.37	14.21±4.19	6.125	0.000

Comparison of HBV-DNA negativization rates

After 24 weeks of treatment, the HBV-DNA negativization rates in the control group and the observation group were 58.18% and 67.27%, respectively (χ^2=0.972, *P*=0.324), with no statistically significant difference. However, at 48 weeks of treatment, the HBV-DNA negativization rates in the two groups increased to 76.36% and 90.91%, respectively, and the intergroup comparison showed a significant statistical difference (χ^2=4.251, *P*=0.039). The results of this study indicate that both treatment regimens can effectively inhibit HBV replication, but after long-term treatment (48 weeks), the virological response rate in the observation group is significantly superior to that in the control group (*P*<0.05). In the case of extended treatment duration, the antiviral effect of the observation group may be more advantageous. See Table 4.

Comparison of liver fibrosis indicators

At 24 and 48 weeks post-treatment, HA, PC-III, IV-C, and LN levels decreased significantly in both groups compared to baseline (*P*<0.05). The observation group showed greater reductions than the control group (*P*<0.05), with further declines at 48 vs. 24 weeks (*P*<0.05). See Table 5.

Comparison of LSM

At 24 and 48 weeks post-treatment, LSM values in both groups decreased significantly from baseline (*P*<0.05). The observation group showed a greater reduction in LSM than the control group at both time points (*P*<0.05). The continuous decrease in LSM suggests that the observation group had a better effect in inhibiting fibrosis progression. As the treatment duration extended, the improvement in LSM at 48 weeks was more pronounced than that at 24 weeks (*P*<0.05), indicating that liver fibrosis reversal may require a longer treatment period, and long-term intervention may bring further benefits. See Table 6.

Comparison of serum inflammatory factor indicators

At 24 and 48 weeks post-treatment, both groups showed significant reductions in pro-inflammatory factors (TNF-α, IL-6, IL-8) and a rise in anti-inflammatory IL-10 compared to baseline (*P*<0.05), indicating effective inflammation suppression and a potential anti-inflammatory microenvironment. The observation group demonstrated greater reductions in pro-inflammatory markers and a higher increase in IL-10 than the control group (*P*<0.05), suggesting superior inflammatory regulation. Additionally, as the treatment duration extended to 48 weeks, the improvements in inflammatory factors were more pronounced than those at 24 weeks (*P*<0.05), indicating that longer-term treatment may bring greater anti-inflammatory effects. See Table 7.

Table 7. Comparison of serum inflammatory factor indicators ($\bar{x}$±s, pg/mL).

Group	Time point	Control group (n=55)	Observation group (n=55)	*t*-value	*P*
TNF-α	Baseline	59.67±5.44	58.48±5.69	1.130	0.261
	24 Weeks	35.96±3.66	30.22±2.54	9.554	0.000
	48 Weeks	28.46±2.48	19.23±3.03	17.452	0.000
IL-6	Baseline	46.22±4.13	45.66±4.18	0.707	0.481
	24 Weeks	34.66±2.44	25.74±2.19	20.180	0.000
	48 Weeks	22.78±2.01	17.08±3.43	10.647	0.000
IL-8	Baseline	39.44±2.88	39.76±2.87	0.603	0.548
	24 Weeks	31.38±2.46	26.86±2.26	10.012	0.000
	48 Weeks	25.58±1.75	19.44±2.15	16.457	0.000
IL-10	Baseline	5.99±1.23	6.02±1.34	0.122	0.903
	24 Weeks	11.66±1.45	14.78±1.16	12.415	0.000
	48 Weeks	14.38±3.12	20.44±4.13	8.670	0.000

Table 8. Comparison of the comprehensive clinical efficacy (*n*, %).

Time point	Control group (n=55)	Observation group (n=55)	χ^2-value	*P*
Baseline	0% (0/55)	0% (0/55)	0.000	0.000
24 Weeks	54.55% (30/55)	69.09% (38/55)	2.465	0.116
48 Weeks	65.45% (36/55)	83.64% (46/55)	4.791	0.029

Comparison of clinical comprehensive efficacy

Based on a comprehensive assessment of various outcomes, including improvement in clinical symptoms, recovery of liver function, HBV-DNA negativity rate, reduction in liver fibrosis indicators, and improvement in LSM indicators, clinical efficacy was categorized into three levels: marked effectiveness, effectiveness, and ineffectiveness. By the end of the 48-week treatment period, the total effective rate reached 83.64% (46/55) in the observation group, compared to only 65.45% (36/55) in the control group, with a statistically significant disparity (χ^2=4.791, *P*=0.029). See Table 8.

Safety observation

During the clinical observation period, general vital signs (respiration, body temperature, pulse, blood pressure) as well as routine blood, urine, and stool tests, renal function, routine twelve-lead electrocardiogram, and abdominal color Doppler ultrasound were monitored in both groups of patients. The results showed no significant abnormalities. The observation group reported adverse events including headache (1 case), fatigue (2 cases), and dizziness (1 case), showing an overall adverse reaction rate of 7.27%. Conversely, the control group exhibited headache (2 cases), fatigue (1 case), dizziness (1 case), and nausea (2 cases), totaling a 10.91% incidence rate. All symptoms subsided naturally within five days without treatment. The intergroup difference in adverse event frequency was not statistically significant (χ^2=0.440, *P*=0.507).

DISCUSSION

Currently, antiviral drugs serve as the primary means of clinical treatment for Hepatitis B cirrhosis, effectively inhibiting HBV replication and delaying disease progression[21]. Entecavir, as a potent NAs, selectively inhibits HBV-DNA polymerase, significantly reducing serum HBV-DNA load, and is characterized by high efficacy and low resistance. However, its role in reversing liver fibrosis remains limited[22, 23]. As research on the microbiome progresses, scientists are paying more attention to how gut bacteria influence viral hepatitis progression. Studies have shown that the liver and intestine are not only anatomically closely connected but also functionally intertwined through the "gut-liver axis" forming a bidirectional regulatory mechanism[24]. Disruption of the gut microbiome can cause deterioration in the function of the intestinal barrier, facilitating the translocation of endotoxins and bacterial metabolites to the liver, activating immune-inflammatory responses, and subsequently accelerating the process of liver fibrosis[25]. Therefore, modulating the gut microbiota may represent a novel strategy for improving the prognosis of patients with Hepatitis B cirrhosis. Our prior work showed that adding Bifidobacterium to entecavir improves liver and inflammatory indices in HBV-cirrhosis, but left the microbiota, barrier function and long-term virology unexplored[26]. This study tracked these parameters for 48 weeks, demonstrating sustained HBV-DNA suppression, reduced endotoxin and specific gut-flora shifts, thereby validating the gut–liver axis as a therapeutic target.

Hepatitis B cirrhosis represents the pathological process in which chronic hepatitis B progresses from hepatic fibrosis to cirrhosis step by step in its natural course[27]. It is

noteworthy that the stages of hepatic fibrosis and early cirrhosis remain reversible. During this progression, serum markers of hepatic fibrosis often exhibit characteristic elevations. Among them, PC-III, an important extracellular matrix component synthesized by hepatic stellate cells, demonstrates a strong positive association with the severity of hepatic fibrosis as serum levels increase. IV-C is a sensitive indicator reflecting fibrotic tissue proliferation, with marked extracellular matrix deposition observed in hepatic fibrosis, particularly a notable increase in IV-C. LN is primarily produced by endothelial cells and serves as a key mediator in cell-matrix adhesion. HA, a glycosaminoglycan synthesized by mesenchymal cells, demonstrates characteristic changes of increased synthesis and reduced degradation during liver injury[28]. This study demonstrated that serum hepatic fibrosis marker levels in both groups decreased significantly after 24 and 48 weeks of treatment compared to baseline. Notably, the observation group showed more substantial reductions in HA, PC-III, IV-C, and LN at both time points than the control group, with greater improvements at 48 weeks, indicating a duration-dependent therapeutic effect. Additionally, dynamic monitoring of LSM showed that the reduction in LSM in the observation group was significantly superior to that in the control group, with further improvement in LSM at 48 weeks compared to 24 weeks. This trend indicates that the anti-fibrotic efficacy is better in the observation group, and long-term intervention may yield more significant clinical benefits.

Entecavir reduces viral replication by inhibiting HBV-DNA polymerase, indirectly decreasing the activation level of hepatic stellate cells and reducing the abnormal deposition of PC-III and IV-C in the extracellular matrix[29]. However, monotherapy with antiviral agents has limited regulatory effects on intestinal microecological balance and systemic inflammatory responses, which may, to some extent, restrict their anti-fibrotic efficacy[30]. Previous studies have found that chronic HBV infection and cirrhosis patients commonly exhibit intestinal dysbiosis, marked by a decline in helpful microorganisms and excessive proliferation of potentially harmful bacteria[31]. This microecological imbalance can lead to impaired intestinal barrier function, facilitating endotoxin translocation to the liver, activating inflammatory responses, and exacerbating the hepatic fibrosis process[32]. Our research yields comparable results to these previous findings. The combination therapy group significantly reduced pathogenic bacteria counts and increased probiotic counts by regulating intestinal microecological balance, thereby improving intestinal mucosal barrier function, reducing endotoxin translocation, and providing a foundation for the improvement of hepatic fibrosis. Additionally, inflammation is an initiating factor in hepatic fibrosis, capable of not only releasing various pro-fibrotic mediators, including reactive oxygen species, osteopontin, and transforming growth factor-β1, but also activating hepatic stellate cells or myofibroblasts, promoting increased cytokine secretion, and initiating excessive extracellular matrix deposition[33-35]. This research demonstrated that combination therapy synergistically regulated inflammation, with significantly decreased pro-inflammatory markers (TNF-α, IL-6, IL-8) and increased anti-inflammatory IL-10 levels, highlighting its superior anti-inflammatory potential. Entecavir significantly reduces viral load and alleviates hepatic inflammation and fibrosis progression by strongly inhibiting HBV-DNA polymerase. After viral replication is suppressed, hepatocyte necrosis and inflammatory responses are reduced, thereby decreasing hepatic stellate cell activation and reducing the production of fibrosis markers[36]. Cirrhosis patients often exhibit intestinal dysbiosis and intestinal mucosal barrier damage, leading to bacterial translocation and endotoxin entry into the bloodstream[37]. Probiotics such as Bifidobacterium can enhance intestinal tight junctions, reduce endotoxemia, and decrease lipopolysaccharide-induced activation of pro-fibrotic signals in intrahepatic Kupffer cells and hepatic stellate cells[38]. Additionally, probiotics inhibit hepatic stellate cell activation and collagen deposition indirectly by regulating Th1/Th2 balance, increasing anti-inflammatory factor secretion, and suppressing pro-inflammatory factors. They can also reduce the entry of ammonia, endotoxin, and other substances into the liver via the portal vein, alleviating hepatocyte damage and fibrosis stimulation[39]. These mechanisms collectively create a microenvironment conducive to reducing hepatic inflammatory responses, providing a theoretical basis for the advantages of combination therapy in anti-fibrosis. Since the reversal of hepatic fibrosis involves multiple complex biological processes, such as the inhibition and apoptosis of activated hepatic stellate cells, this pathophysiological change typically requires a relatively long period of treatment to manifest significant effects[40, 41]. Therefore, the intervention effect of probiotics is time-dependent, with continuous treatment gradually optimizing the intestinal flora structure, and its anti-inflammatory and immunomodulatory effects enhancing with prolonged treatment duration.

Patients with Hepatitis B cirrhosis often exhibit liver function impairment, with liver cell damage primarily manifested as elevated ALT and AST levels. Dysfunction in liver synthesis and metabolism is mainly characterized by increased TBIL and decreased ALB. In the compensated stage of Hepatitis B cirrhosis, TBIL and ALB levels are mostly within the normal range, whereas patients in the decompensated stage show varying degrees of elevated TBIL and reduced ALB, with the extent of these changes positively correlated with disease severity[42, 43]. HBV infection of hepatocytes, coupled with the body's efforts to clear the virus, results in hepatocyte damage and the release of inflammatory and fibrogenic mediators that stimulate fibrous tissue proliferation. Therefore, inhibiting viral replication, promoting hepatocyte repair, and reducing fibrous tissue proliferation contribute to improving the degree of cirrhosis[44]. In this study, the observational group received a treatment regimen combining entecavir with bifidobacterium triple viable bacteria, which more effectively reduced viral replication levels and promoted hepatocyte repair. Entecavir, as a potent antiviral agent, significantly lowers viral load by selectively inhibiting HBV-DNA polymerase, while bifidobacterium triple viable bacteria regulate intestinal microecological balance,

reduce endotoxin translocation, lower serum endotoxin levels, alleviate hepatic inflammatory responses, and simultaneously improve hepatic microcirculation and nutrient supply[45, 46]. This multi-targeted therapeutic strategy not only more effectively controls viral replication but also creates a favorable microenvironment for hepatocyte repair, thereby demonstrating significant advantages in improving the degree of cirrhosis.

CONCLUSION

This study provides a more effective combined therapeutic regimen for the treatment of Hepatitis B cirrhosis. Entecavir combined with bifidobacterium triple viable bacteria therapy demonstrates superiority over entecavir alone in improving intestinal flora, repairing intestinal mucosal barriers, promoting liver function recovery, alleviating hepatic fibrosis, and enhancing antiviral efficacy. By delaying the worsening of the disease, preventing additional complications, and promoting better living standards, it benefits patients significantly. Additionally, this study reveals the close association between intestinal flora and liver diseases, enhancing our comprehension of Hepatitis B cirrhosis pathogenesis and offering a theoretical foundation for novel treatment approaches through the lens of intestinal microecology, thereby advancing research in the field of liver disease treatment. It is worth noting that this study is a retrospective case-control study. Although some confounding factors were controlled, there is still a risk of selection bias and information bias. Due to limitations in the completeness and accuracy of medical records, some data may be biased. Furthermore, the small sample size may affect subgroup analysis of different clinical characteristics, limiting the generalizability of the results. Moreover, the brief observation period limits the evaluation of long-term efficacy and its effect on hepatocellular carcinoma risk. Future research should include large-scale, multi-center, prospective randomized controlled trials with longer follow-up to confirm the long-term benefits of combination therapy.

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Data availability statement: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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