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**Original Research Article**

# Clinical effectiveness of combined Bifidobacterium live bacteria preparation and entecavir therapy in the management of Hepatitis B cirrhosis

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## Abstract

***Purpose:*** *To investigate the efficacy of combining Bifidobacterium live bacteria preparation with entecavir in the treatment of hepatitis B cirrhosis and its effect on cytokines and liver function.*
***Methods:*** *88 patients with HBV-induced cirrhosis admitted to Qinzhou People's Hospital, Qinzhou, China between January 2021 and January 2023 were divided into control and study groups with 44 patients each. Control group received entecavir, while study group received Bifidobacterium live bacteria preparation in addition to entecavir. Clinical treatment outcomes, liver function, liver fibrosis, immune function, and inflammatory cytokine indices were compared between the two groups.*
***Results:*** *There was a significant increase in total effective rate of treatment in study group (95.45 %) compared to control group (79.55 %; $p < 0.05$). After treatment, the study group showed significantly lower levels of alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), total bilirubin (TBIL), hyaluronic acid (HA), laminin (LN), N-terminal propeptide of type III procollagen (PIIINP), and type IV collagen (IV-C), and higher levels of CD4+ and CD4+/CD8+ compared to control group ($p < 0.05$). Furthermore, study group exhibited significantly lower levels of IL-6, TNF-α, and HS-CRP after treatment compared to control group ($p < 0.05$).*
***Conclusion:*** *The combined use of Bifidobacterium live bacteria preparation and entecavir in treating HBV-induced cirrhosis demonstrates significant clinical improvement. This combined approach effectively enhances liver function, improves immune response reduces inflammation and liver fibrosis. Hence, in future studies, efforts will be directed towards improving absorption and reducing the metabolism/excretion of the drug to validate these findings.*

***Keywords:*** *Bifidobacterium live bacteria preparation, Entecavir, HBV-induced cirrhosis, Clinical efficacy, Cytokines, Liver function*



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## INTRODUCTION

Hepatitis B Virus (HBV) is a highly prevalent viral infection worldwide, and its associated condition, hepatitis B, may lead to cirrhosis, resulting in severe consequences such as impaired liver function and liver cancer [1]. Although antiviral drugs like entecavir have achieved some success in HBV treatment, effective methods for treating cirrhosis, particularly interventions

targeting its causes and mechanisms, are still lacking [2]. In recent years, research on gut microbiota has emerged significantly, revealing close connection between gut microbiota and host health [3]. The role of gut microbiota in immune regulation, nutritional metabolism, and other aspects has been extensively studied, and its potential impact on the progression of HBV-induced cirrhosis has attracted attention within the medical community [4].

Bifidobacterium, as a beneficial gut microorganism, is thought to have positive effects on immune function, inflammatory responses, and liver fibrosis, making it a potential component of therapeutic strategies for HBV-induced cirrhosis [5]. However, specific effects and mechanisms of Bifidobacterium live bacteria preparation in the treatment of HBV-induced cirrhosis remain inadequately understood. Therefore, this study was aimed at investigating the clinical efficacy of combining bifidobacterium live bacteria preparation with entecavir in the management of hepatitis B virus-induced cirrhosis, as well as its effect on cytokine and liver function markers. Ultimately, findings from this research aim to furnish a scientific basis and serve as a reference for enhancing therapeutic strategies for HBV-induced cirrhosis.

## METHODS

### Subjects

A total of 88 patients with HBV-induced cirrhosis admitted to Qinzhou People's Hospital, Qinzhou, China were enrolled. These patients were randomly and equally divided into control (received entecavir monotherapy) and study groups (received combined treatment). Clinical outcomes, liver function, immune function, and inflammatory responses were monitored. Comprehensive demographic data, including gender, age, duration of hepatitis B infection, duration of cirrhosis, family history, prior treatment history, and comorbidities, were documented. This study was conducted following the principles in the Helsinki Declaration [6] and approved by the Ethics Committee of Qinzhou People's Hospital, Qinzhou, China (approval no. JY 202-092-002). All patients and their families provided informed consent for participation.

#### *Inclusion criteria*

Patients who met the clinical diagnostic criteria for hepatitis B and were confirmed to have HBV-induced cirrhosis through liver and gallbladder ultrasound, CT scans, and laboratory tests; individuals aged between 18 and 65 years, disease duration exceeding 6 months, presence of bacterial flora in fecal culture results regularly, gastroscopy showing esophageal and gastric varices, no antibiotic intervention within 14 days before enrollment.

#### *Exclusion criteria*

Pregnant or lactating females, individuals with severe immune system disorders, such as autoimmune diseases, patients with severe organ diseases affecting the heart, lungs, kidneys, etc; individuals with a history of liver transplantation or current liver transplant recipients, previous or current use of other immunomodulatory drugs, previous severe allergic reactions to Bifidobacterium preparations or entecavir, participation in other clinical trials or treatment programs, and patients with other diseases or factors that may affect the study results.

### Treatments

Both groups of patients received routine treatment interventions upon admission, including diuretics, liver protection, and symptomatic supportive care measures. All patients required a treatment period of 6 months before efficacy assessment. In addition to routine treatment interventions, control group received entecavir treatment. Entecavir tablets (Shanghai Sino-American Pharmaceutical Co., Ltd., National Medical Products Administration approval no. H20052237) were administered orally at 5 mg/day.

The study group received an additional intervention with Bifidobacterium live bacteria preparation in conjunction with treatments administered to control group. During the initial period, intervention methods for the study group, including routine treatment and entecavir treatment, remained consistent with those of control group. Furthermore, Bifidobacterium live bacteria preparation, specifically Bifidobacterium triple live bacteria enteric-coated capsules (Jincheng Haisi Pharmaceutical Co., Ltd., National Medical Products Administration approval no. S19993065), was orally administered at 0.63 g per dose, three times a day.

### Evaluation of parameters/indices

#### *Treatment efficacy*

Treatment efficacy was classified as significant improvement, effective, and ineffective. Significant improvement was defined as the

disappearance of main clinical symptoms, normalization of liver function, and negative qualitative HBV-DNA test results. Effective was defined as significant improvement in main clinical symptoms, liver function improvement of more than 50 % compared to before treatment, and a decrease in HBV-DNA viral load by ≥ 2 × $10^5$ cps/mL. Ineffective was defined as no significant improvement or worsening of main clinical symptoms and positive HBV-DNA qualitative test results.

### *Liver function*

Liver function markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (TBIL), were measured using a fully automated biochemical analyzer before and after treatment.

### *Liver fibrosis*

Liver fibrosis markers such as layered adhesion protein (LN), hyaluronic acid (HA), N-terminal propeptide of type III collagen (PIIINP), and type IV collagen (IV-C), were measured using the FibroScan non-invasive liver fibrosis diagnostic instrument before and after treatment.

### *Immune function indicators*

Immune function indicators, specifically T-lymphocyte subsets (CD4+, CD8+, CD4+/CD8+), were measured using flow cytometry before and after treatment.

### *Inflammatory cytokine indicators*

Fasting venous blood samples (5 mL) were collected before and after treatment, and centrifuged to obtain serum. The serum was tested using enzyme-linked immunosorbent assay (ELISA) for serum interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Furthermore, high-sensitivity C-reactive protein (hs-CRP) was measured using latex-enhanced immunoturbidimetric assay.

### Statistical analysis

GraphPad Prism 8 was used for graphical presentation, and Statistical Packages for Social Sciences (SPSS version 22.0) was used for data analysis. For continuous data, descriptive statistics including mean and standard deviation were used to describe the distribution, and statistical analysis was performed using methods of t-tests and analysis of variance (ANOVA). For categorical data, distribution was described using frequency and percentage, and statistical analysis was conducted using as chi-square test and Fisher's exact tests. $P < 0.05$ was considered statistically significant.

## RESULTS

### Baseline characteristics

Control group consisted of 44 patients, including 24 males and 20 females. Mean age of the patients was 47.27 ± 6.62 years, the average duration of hepatitis B was 7.12 ± 1.76 years, and the duration of cirrhosis was 2.31 ± 0.56 years. Similarly, study group comprised 44 patients, with 25 males and 19 females. Mean age was 47.16 ± 6.75 years, the mean duration of hepatitis B was 7.09 ± 1.81 years, and the duration of cirrhosis was 2.29 ± 0.54 years. There was no statistical difference in baseline characteristics between the two groups ($p > 0.05$; Table 1).

**Table 1:** Comparison of baseline characteristics (N = 44 in each group)

| Parameter | Control | Study | t/x² | *P*-value |
|---|---|---|---|---|
| Gender | | | 0.046 | 0.830 |
| Male | 24 | 25 | | |
| Female | 20 | 19 | | |
| Average age (years) | 47.27±6.62 | 47.16±6.75 | 0.077 | 0.938 |
| Hepatitis B course (years) | 7.12±1.76 | 7.09±1.81 | 0.078 | 0.937 |
| Liver cirrhosis duration (years) | 2.31±0.56 | 2.29±0.54 | 0.170 | 0.865 |
| Family history | | | 0.046 | 0.830 |
| Have | 26 | 25 | | |
| None | 18 | 19 | | |
| Previous treatment history | | | 0.045 | 0.830 |
| Have | 24 | 23 | | |
| None | 20 | 21 | | |
| Comorbidities | | | | |
| Hypertension | 22 | 20 | 0.182 | 0.669 |
| Diabetes | 19 | 18 | 0.046 | 0.829 |
| Coronary heart disease | 16 | 15 | 0.049 | 0.823 |

**Table 2:** Comparison of clinical treatment efficacy (N = 44 in each group)

| Group | Markedly effective | Efficient | Invalid | Total effective rate (%) |
|---|---|---|---|---|
| Control | 12 | 23 | 9 | 79.55% |
| Study | 17 | 25 | 2 | 95.45% |
| $\chi^2$ | - | - | - | 5.090 |
| *P*-value | - | - | - | 0.024 |

## Clinical treatment efficacy

Study group showed a significantly higher total effective rate compared to control group ($p < 0.05$) (Table 2).

## Liver function indices (ALT, AST, and TBIL)

Levels of alanine aminotransferase (ALT), aspartate aminotransaminase (AST), and total bilirubin (TBIL) in control group were higher compared to study group before treatment. However, levels of ALT, AST, and TBIL showed a significant decrease in study group compared to control group after treatment ($p < 0.05$) (Figure 1 A to C).

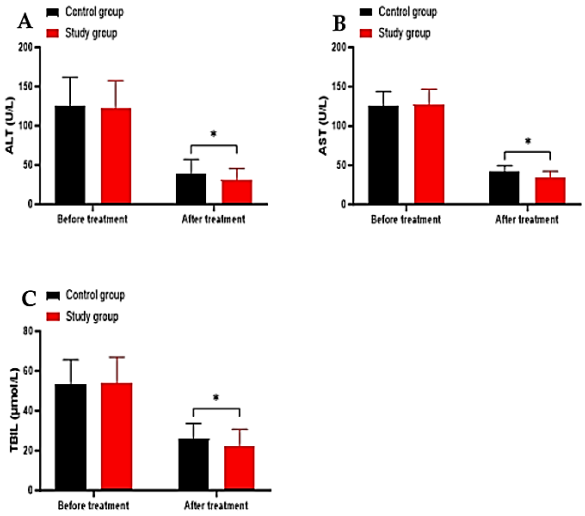


**Figure 1:** Comparison of ALT, AST, and TBIL. A: Levels of ALT were significantly lower in study group after treatment compared to control group *$p < 0.05$. B: Levels of AST were significantly lower in study group after treatment compared to control group *$p < 0.05$. C: Levels of TBIL were significantly lower in study group after treatment compared to control group *$p < 0.05$

## Liver fibrosis indices

Control group exhibited higher levels of liver fibrosis indices such as hyaluronic acid (HA), laminin (LN), N-terminal propeptide of type III procollagen (PIIINP), and type IV collagen (IV-C), before treatment compared to the study group. However, after treatment, the levels of these fibrosis indices significantly decreased in study group compared to control group ($p < 0.05$).

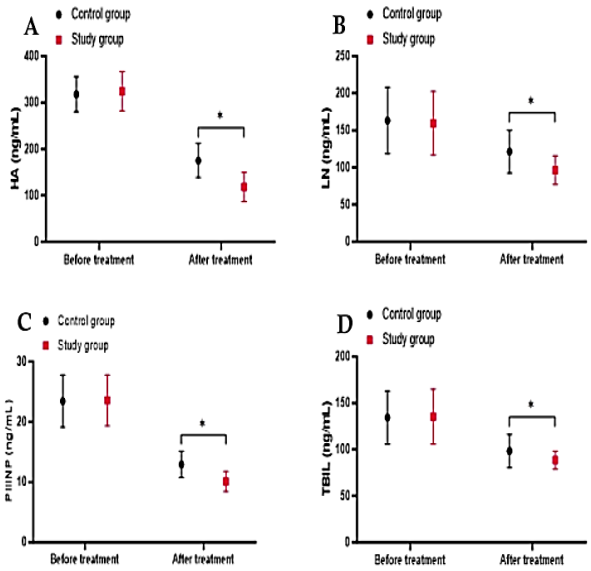


**Figure 2:** Comparison of liver fibrosis indices. A: Hyaluronic acid (HA) significantly reduced in study group after treatment *$p < 0.05$. B: Laminin (LN) significantly reduced in study group after treatment *$p < 0.05$. C: N-terminal propeptide of type III procollagen (PIIINP) significantly reduced in study group after treatment, *$p < 0.05$. D: type IV collagen (IV-C) significantly reduced in study group after treatment, *$p < 0.05$

## Immune function indices

Control group showed lower levels of CD4+ lymphocytes and higher levels of CD8+ lymphocytes before treatment compared to the study group. However, after treatment, the study group showed significantly higher counts of CD4+ and CD8+ compared to control group ($p < 0.05$).

## Inflammatory factors

There was no significant difference in levels of IL-6, TNF-α, and hs-CRP between the two groups ($p > 0.05$) before treatment. After treatment, the levels of IL-6, TNF-α, and hs-CRP in study group were significantly lower compared to control group ($p < 0.05$).

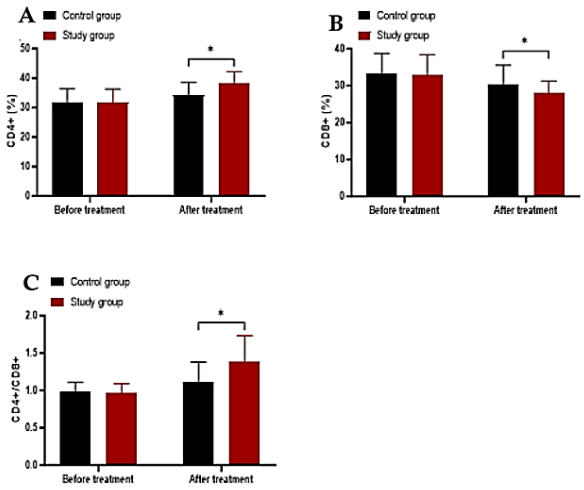


**Figure 3:** Comparison of immune function indices. A: Study group showed significantly higher CD4+ counts compared to control *$p < 0.05$. B: Study group showed significantly higher CD8+ counts compared to control *$p < 0.05$. C: Study group showed significantly higher CD4+/CD8+ counts compared to control *$p < 0.05$

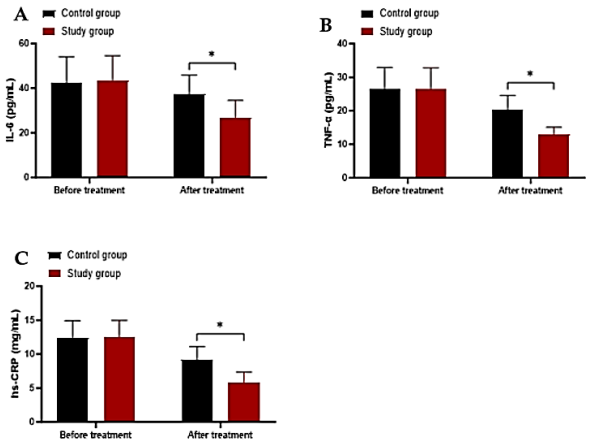


**Figure 4:** Comparison of inflammatory factors. A: Levels of interleukin-6 (IL-6) significantly reduced in study group after treatment *$p < 0.05$. B: Levels of tumor necrosis factor-alpha (TNF-α) significantly reduced in study group after treatment *$p < 0.05$. C: Levels of high-sensitivity C-reactive protein (hs-CRP) significantly reduced in study group after treatment *$p < 0.05$

## DISCUSSION

Hepatitis B virus (HBV) induced cirrhosis is a diffuse parenchymal liver disease caused by repeated interactions of one or multiple factors with the liver [7]. A study [8] has revealed that sustained HBV replication and intra-hepatic inflammation are decisive factors in the progression of cirrhosis, making inhibition of HBV replication, reduction of intra-hepatic inflammation, and improvement of liver function crucial in the treatment of HBV-induced cirrhosis. Currently, antiviral drugs are the mainstay of therapy for HBV-induced cirrhosis, including interferon and nucleoside analogs [9].

Prior studies [10] have shown that interferon, as a broad-spectrum antiviral drug, exhibits significant individual variability in treatment response and is associated with various adverse reactions, thereby limiting its clinical importance. Consequently, nucleoside analog of antiviral drugs has become the preferred choice for treating HBV-induced cirrhosis. Entecavir, a broad-spectrum antiviral drug targeting HBV, is a nucleoside reverse transcriptase inhibitor. It is frequently employed in clinical practice to manage HBV infection, particularly among chronic carriers and cirrhosis patients [11]. Entecavir exerts its pharmacological effects by interfering with the activity of the reverse transcriptase enzyme of the hepatitis B virus, thereby inhibiting viral DNA synthesis and impeding viral replication and proliferation. As a result, viral load is reduced, leading to decrease in liver inflammation and damage. This mechanism ultimately contributes to improved liver function and deceleration of disease progression [12].

However, utilization of entecavir monotherapy for HBV-induced cirrhosis is challenging. The challenges stem from the prolonged half-life of HBV-DNA and the inhibitory mechanism of antiviral drugs, which make complete viral clearance difficult. Furthermore, the emergence of drug-resistant mutations in the virus impedes the efficacy of antiviral medications. Additionally, patients with HBV-induced cirrhosis often experience compromised immune function and diminished immunotolerance, further hindering viral clearance.

Previous studies [13,14] have elucidated the connection between hepatic blood supply and the intestinal tract through the portal vein system. Both the liver and intestines play pivotal roles in the digestive system. Under normal physiological conditions, the liver possesses an inherent immune tolerance mechanism that enables it to withstand attacks from intestinal antigens, thereby maintaining immune homeostasis within the body. Disruption of the physiological structure of the liver exacerbates dysregulation of intestinal homeostasis.

Research has found that the occurrence and progression of chronic liver diseases are closely associated with factors such as intestinal dysbiosis and microbial imbalance [15]. In clinical practice, patients with HBV-induced cirrhosis often experience disruptions in gut microbiota,

which result in the continuous accumulation and absorption of endotoxins, forming a vicious cycle that worsens the condition. Thus, restoring intestinal homeostasis holds significant importance in the prevention and treatment of liver diseases. Probiotic preparations, categorized as microbiota-based interventions, contain beneficial bacterial strains such as probiotics and bifidobacteria.

These preparations provide specific live strains of bacteria that aid in restoring microbial diversity within the intestines. They positively influence immune regulation, enhance nutrient absorption, and inhibit the proliferation of harmful microbes [16]. Bifidobacterium triple live bacteria preparation is a commonly used microbiota-based intervention in clinical settings. It promotes the growth of beneficial bacteria in the intestines, suppresses replication of pathogenic bacteria, rectifies imbalances in gut microbiota, improves intestinal inflammation, maintains and restores intestinal mucosal barrier function, aids in the recovery of intestinal epithelial tissue, and consequently improves liver diseases [17].

The findings of this study revealed that the total effective rate of treatment was significantly higher in study group compared to control group. Following treatment, the study group showed significantly lower levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL) compared to control group. Additionally, post-treatment levels of hyaluronic acid (HA), laminin (LN), N-terminal propeptide of type III procollagen (PIIINP), and type IV collagen (IV-C) were significantly lower in study group compared to control group. These findings are in tandem with prior investigations [18], collectively asserting that the combined approach of microbiota-based interventions and antiviral drugs enhances treatment efficacy in patients with HBV-induced cirrhosis. This treatment approach improves liver function and reduces liver fibrosis. Study [19] has shown that the human body primarily clears the HBV virus through T cell-mediated immune responses after infection. However, these responses also induce liver cell damage.

Study has indicated a close relationship between disrupted gut microbiota and the body's immune response [20]. For patients with chronic HBV-induced cirrhosis, the presence of HBV triggers immune responses, which in turn affects the dynamic balance of gut microbiota, further exacerbating immune response reactions. The findings of this study revealed that the study group showed significant increase in CD4+ T lymphocytes and CD4+/CD8+ ratio compared to control group after treatment. Conversely, the level of CD8+ T lymphocytes was significantly lower in study group. These results suggest a strong association between the combined administration of Bifidobacterium live bacteria preparation and entecavir and the modulation of peripheral blood T cell subsets, thereby enhancing immune responses.

Furthermore, previous research [21] has demonstrated a clear link between dysbiosis of the gut microbiota and the release of endotoxins into the liver. This release triggers upregulation of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and protein high-sensitivity C-reactive protein (hs-CRP) within the systemic circulation, thereby initiating a cascading inflammatory response. Additionally, activation of the transforming growth factor-beta (TGF-β) signaling pathway through the lipopolysaccharide (LPS)/Toll-like receptor 4 (TLR4) pathway and sensitized dendritic cells further amplifies the inflammatory responses [22]. Results of this present study revealed that the study group showed significantly lower levels of IL-6, TNF-α, and hs-CRP compared to control group. These findings establish a direct correlation between the combined administration of Bifidobacterium live bacteria preparation and entecavir, and the effective attenuation of the inflammatory responses in patients with HBV-induced cirrhosis.

### Limitations of this study

The study included a relatively small sample size which might negatively impact on the reliability of the results. Also, the study focused solely on short-term treatment outcomes and did not cover long-term effects and follow-up. Hence, in future studies, efforts will be directed towards addressing these limitations to improve the credibility of these findings.

## CONCLUSION

Combined administration of Bifidobacterium live bacteria preparation and entecavir is clinically efficacious, enhances liver function, improves immune status, inflammatory responses and reduces liver fibrosis. These findings highlight the significant clinical relevance of this combined approach as a valuable therapeutic strategy for patients with HBV-induced cirrhosis. Hence, in future studies, efforts will be directed towards addressing these limitations to improve the credibility of these findings.

## DECLARATIONS


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### *Funding*

None provided.


### *Ethical approval*

None provided.

### *Availability of data and materials*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.



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