Am J Transl Res 2024;16(8):4163-4173
www.ajtr.org /ISSN:1943-8141/AJTR0156562

Original Article

Effects of Bushen Huayu Decoction combined with entecavir on liver function and hepatic fibrosis in patients with compensated cirrhosis

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Received March 14, 2024; Accepted July 17, 2024; Epub August 15, 2024; Published August 30, 2024

Abstract: Objective: To analyze the effect of Bushen Huayu Decoction combined with entecavir on alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil) and albumin (Alb) in patients with hepatitis cirrhosis. Methods: A retrospective study was conducted on 102 patients with compensated hepatitis cirrhosis treated at the No. 2 Hospital of Baoding from February 2020 to April 2023. These patients were divided into two groups based on different treatment modalities: a control group treated with entecavir (n=51) and an observation group treated with Bushen Huayu decoction plus entecavir (n=51). The Traditional Chinese Medicine (TCM) syndrome scores, level of liver function indicators, and liver fibrosis symptoms were compared between the two groups before treatment and after 2 weeks and 4 weeks of treatment. Results: Before treatment, the two groups differed insignificantly in liver fibrosis indicators (HA, IV-C, and PCIII), liver function indices (ALT, AST, TBil, and Alb) and TCM syndrome scores (all P>0.05). After 2 weeks and 4 weeks of treatment, HA, IV-C, and PCIII in both groups decreased. Those in the observation group were significantly lower than those in the control group (P<0.05). The levels ALT, AST, and TBil decreased significantly in both groups. The level of Alb increased significantly, and the alterations in the observation group was more prominent compared with those in the control group (all P<0.05). The scores of TCM syndromes across various aspects all decreased significantly. The scores in the observation group were significantly lower than those of control group (P<0.05). Conclusion: The combined treatment of Bushen Huayu Decoction and entecavir is helpful to improve the TCM symptoms, reduce the levels of ALT, AST, and TBil, increase the level of Alb, improve the state of liver fibrosis, and promote the recovery of liver function in patients with compensatory hepatitis cirrhosis.

Keywords: Bushen Huayu Decoction, entecavir, compensated hepatitis cirrhosis, liver function indicators

Introduction

Alanine aminotransferase (ALT) [1], aspartate aminotransferase (AST) [2], total bilirubin (TBil) [3], and albumin (Alb) [4] are crucial indicators of liver function. Changes in these indicators reflect the disease status of hepatitis cirrhosis. As these indicators worsen, the patient's condition deteriorates, impacting prognosis and increasing mortality [5]. Improving these liver function indicators is critical for assessing the disease severity of hepatitis cirrhosis [6]. Hepatitis cirrhosis is characterized by chronic, diffuse, and progressive liver damage caused by hepatitis viruses, involving extensive hepatic cell necrosis [7], significant hyperplasia of hepatic fibrous tissue [8], formation of regenerative nodules and pseudolobules [9], and disruption of normal blood vessel and hepatic lobule structures [10]. These pathological changes are fundamental to the disease. With the rising prevalence of hepatitis B, the incidence of Hepatitis cirrhosis is increasing annually [11]. Most patients with compensatory cirrhosis lack significant clinical symptoms or signs initially. As the disease progresses to a decompensated stage, damaged hepatocytes undergo necrosis, and persistent liver fibrosis impairs normal liver blood flow, causing portal hypertension, complications, and cancer [12].

In western medicine, the primary treatment methods for hepatitis cirrhosis emphasize comprehensive strategies such as anti-inflammation [13], antivirus [14], anti-fibrosis [15], and prevention of complications [16]. Entecavir, a

https://doi.org/10.62347/QDXJ3369

Table 1. Comparison of baseline data between the two groups ($\bar{x}\pm s$, %)

Group		Control group	Observation group	X^2/t	*P*
Sex	Male	29	30	0.040	0.841
	Female	22	21		
Age (years)		47.59±10.29	47.83±10.15	0.165	0.869
Course of disease (years)		4.68±1.15	4.83±1.07	0.682	0.497
Portal vein width (mm)		14.13±0.57	14.22±0.49	0.794	0.429
Spleen thickness (mm)		45.48±0.73	45.26±0.91	1.347	0.181

guanine nucleoside analogue, exerts its therapeutic effect by inhibiting polymerase activity, suppressing hepatitis virus proliferation and replication [17]. Despite these treatments, some patients exhibit low HBV-DNA replication, indicating ongoing inflammatory responses and fibrosis progression [18], which adversely impact disease prognosis and patient safety. Combining traditional Chinese medicine with western medicine in treating compensated hepatitis cirrhosis can comprehensively alleviate clinical symptoms and signs, enhance treatment efficacy, improve disease prognosis, and enhance overall quality of life [19].

According to Traditional Chinese Medicine (TCM) theory, liver cirrhosis is caused by deficiency of healthy Qi in the body, emotional disturbances, and irregularities in daily habits, resulting in Qi stagnation, impaired blood circulation, and disrupted liver function. Factors such as Qi deficiency and blood stasis play crucial roles in liver fibrosis [20]. TCM herbal formulas tailored to individual syndrome patterns can effectively alleviate the clinical symptoms of liver cirrhosis and delay fibrosis progression, optimizing disease management and prognosis [21]. Bushen Huayu Decoction is a TCM formula known for its ability to nourish blood, resolve stasis, tonify yang, support kidney function, and alleviate pain [22]. It has shown significant efficacy in improving symptoms of compensated cirrhosis and reducing adverse reactions associated with western medicine treatments. Previous studies on the combined use of entecavir and Bushen Huayu Decoction in patients with compensated hepatitis cirrhosis are sparse. This study investigated 102 patients with compensated hepatitis cirrhosis treated with Bushen Huayu Decoction combined with entecavir.

Materials and methods

Study subjects

The clinical data from 102 patients with compensated hepatitis cirrhosis hospitalized in the No. 2 Hospital of Baoding from February 2020 to April 2023 were retrospectively analyzed in this study. According to different treatment methods, the patients were divided into a control group that treated with entecavir alone and an experimental group that treated with Bushen Huayu Decoction combined with entecavir, with 51 in each group. There was no significant difference in gender, age, course of disease, portal vein width, and spleen thickness between the two groups (all P>0.05). Details are shown in **Table 1**.

Inclusion and exclusion criteria

Inclusion criteria: 1) Confirmed diagnosis of compensated hepatitis cirrhosis by CT imaging, meeting the diagnostic criteria outlined in the Guidelines for Diagnosis and Treatment of Hepatic Fibrosis with Integrated Traditional Chinese and western Medicine (2019 Edition) [23]; 2) Meeting the standards of traditional Chinese medicine formula syndrome differentiation [24]; 3) Presence of evident symptoms and manifestations of compensatory cirrhosis, such as anorexia, abdominal distension, right upper quadrant dull pain, aversion to greasy food, and signs of portal hypertension; 4) Previous history of hepatitis B with a positive serum HBV DNA result; 5) Normal cognition and spirit, capable of cooperating with the treatment regimen. The study was conducted with the approval of the Ethics Committee of No. 2 Hospital of Baoding.

Exclusion criteria: 1) Cirrhosis due to drugs, hepatitis C virus (HCV) infection, alcohol abuse,

cholestasis, autoimmune conditions, or identifiable causes; 2) Presence of human immunodeficiency virus (HIV) infection; 3) Renal dysfunction defined by a measured creatinine level 1.5 times above normal; 4) Complications with severe organic diseases such as heart, blood vessel, or lung conditions; 5) Patients who are pregnant or breastfeeding.

Treatment method

Control group: Entecavir capsules (Suzhou Dongrui Pharmaceutical Co., Ltd.; GYZZ: H20100129; 0.5 mg × 21 tablets/box) were administered at 0.5 mg once daily.

Observation group: Based on treatment regimen in control group, patients in the observation group received an additional Bushen Huayu Decoction. The composition of Bushen Huayu Decoction: 40 g prepared rehmannia root, 20 g Chinese yam, 20 g vinegar-processed trionycis carapax, 20 g cornelia officinalis, 15 g cortex moutan, 15 g tuckahoe, 15 g rhizoma alismatis, 5 g processed aconite radix et rhizoma, 5 g cinnamon, 10 g achyranthes bidentata, 10 g plantain seed, and 2 g panax notoginseng powder (taken alone). The above herbs were mixed and decocted into 400 mL. After residue filter, the decoction was orally taken twice/day before breakfast and 1 h after dinner. Treatment was continued for 4 weeks in both groups.

Observation indicators

The following indicators were assessed before treatment, at 2 weeks and 4 weeks after treatment.

Liver fibrosis indicators: Serum hyaluronic acid (HA), type IV collagen (IV-C) and N-terminal peptide of type III collagen (PCIII) were measured using automatic biochemical analyzers.

Liver function indicators: A 5 ml sample of fasting venous blood was collected from each patient, the serum levels of aspartate aminotransferase (AST), total bilirubin (TBil), and albumin (Alb) were determined using an automated biochemical analyzer.

TCM syndrome score: Based on the Guidelines for Clinical Research of Chinese Medicine [10], supplemented by the patient's specific condition, a total of 8 symptom indicators were assessed: epigastric stuffiness and abdominal distension, poor appetite, lassitude, soreness and weakness of waist and knees, deep pulse, bitter taste in the mouth, pale purple dark tongue, and dull complexion. Each symptom was scored by a 4-level scoring method: 0: none; 1: mild; 2: moderate; 3: severe. The higher the score, the more serious the patient's symptoms.

Treatment response rate: The effectiveness of liver treatment was evaluated and judged by clinicians through B-ultrasonography and liver function tests. Markedly effective: B-ultrasound showed normal liver morphology, significant improvement of systemic symptoms and normal liver function; Effective: B-ultrasound showed improvement of liver morphology, systemic symptoms, and liver function; Ineffective: Liver Morphology: Systemic symptoms and liver function are in an abnormal state, failing to meet the above criteria or even deteriorating. Total response rate = (markedly effective cases + effective cases)/total cases × 100%.

Statistical analysis of data

Statistical analysis was conducted using the SPSS25.0. Measured data in normal distribution were described as mean ± standard deviation ($\overline{X}\pm S$). An independent samples t-test was utilized for inter-group comparison. A paired t-test was applied for intra-group comparisons. Categorical data were expressed as the number of cases (n) and percentages (%). Chi-square (χ^2) test was used for comparisons between groups. A *P*-value <0.05 was considered with significant difference.

Results

Comparison of baseline data between the two groups

There was no significant difference in gender, age, course of disease, portal vein width, or spleen thickness between the two groups (all *P*>0.05). See **Table 1** for details.

Comparison of liver fibrosis indicators between the two groups before, 2 weeks and 4 weeks after treatment

Before treatment, there was no significant difference in hepatic fibrosis indexes between the two groups (all *P*>0.05). After 2 weeks and 4 weeks of treatment, HA, IV-C, and PCIII in both groups decreased. Those in the observation group were significantly lower than those in

Table 2. Comparison of liver fibrosis indicators before, 2 weeks and 4 weeks after treatment between the two groups ($\bar{x}\pm s$)

Group	Time	Control group	Observation group	*t*	*P*
HA (ng/mL)	Before treatment	122.34±10.36	122.59±10.17	0.123	0.902
	2 weeks after treatment	100.55±9.48#	93.47±8.19#	4.036	0.001
	4 weeks after treatment	84.36±7.89#,*	72.06±6.27#,*	8.716	0.000
IV-C (ng/mL)	Before treatment	113.69±20.09	113.27±20.74	0.104	0.918
	2 weeks after treatment	98.37±17.34#	91.07±16.27#	2.192	0.031
	4 weeks after treatment	88.47±15.19#,*	81.69±14.21#,*	2.328	0.022
PCIII (ng/mL)	Before treatment	194.26±23.10	194.07±23.67	0.041	0.967
	2 weeks after treatment	155.69±22.35#	129.78±21.48#	5.969	0.000
	4 weeks after treatment	112.15±22.07#,*	98.67±20.37#,*	3.205	0.002

Note: #P<0.05, compare with before treatment; *P<0.05, compare with 2 weeks after treatment. HA: hyaluronic acid; IV-C: type IV collagen; PCIII: type III procollagen.

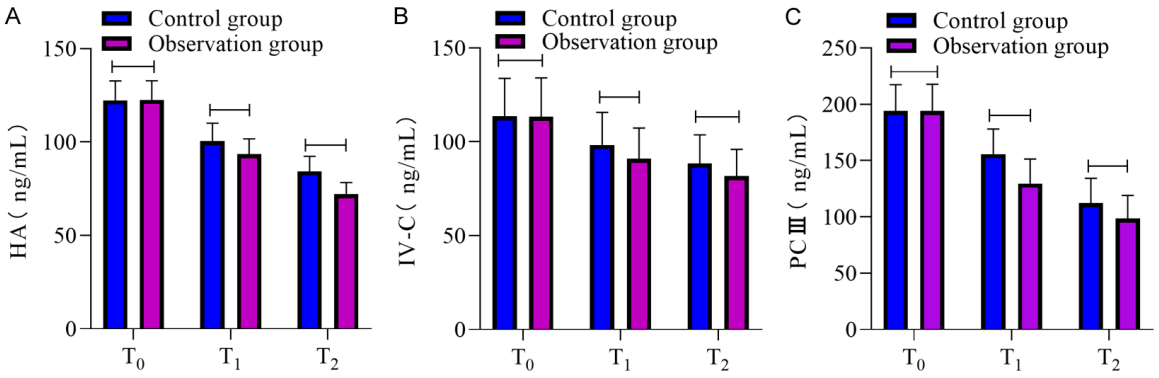

Figure 1. Bar chart comparison of hepatic fibrosis indexes in different time periods between the two groups. A. HA index; B. IV-C index; C. PCIII index. T0: before treatment; T1: 2 weeks after treatment; T2: 4 weeks after treatment.

the control group (all *P*<0.05, **Table 2**; **Figure 1**).

Comparison of liver function indicators between the two groups before, 2 weeks, and 4 weeks after treatment

Before treatment, there was no significant difference in the levels of ALT, AST, TBil, and Alb between the two groups (all *P*>0.05). After 2 weeks and 4 weeks of treatment, ALT, AST, and TBil decreased significantly in both groups, and were significantly lower in the observation group than those in the control group (all *P*<0.05); Alb showed an opposite trend (*P*< 0.05), as shown in **Table 3** and **Figure 2**.

Comparison of TCM syndrome scores between the two groups before, 2 weeks, and 4 weeks after treatment

Before treatment, there was no significant difference in the scores of each TCM syndrome between the two groups (all *P*>0.05). After 2 weeks and 4 weeks of treatment, the scores of abdominal distension, poor appetite, lassitude and asthenia, soreness and weakness of waist and knees, thready deep pulse, bitter taste, pale-purple dark tongue, and dull complexion all decreased in both groups, and the scores of the observation group were lower than those of the control group (all *P*<0.05, **Table 4** and **Figure 3**).

Comparison of prognosis between the two groups

The effective rate of the observation group was higher than that of the control group, and the difference was statistically significant (*P*<0.05, **Table 5**).

Discussion

Hepatitis virus infection and replication are monitored through HBV DNA levels [25, 26],

Table 3. Comparison of liver function indexes before, 2 weeks and 4 weeks after treatment between the two groups ($\bar{x}\pm s$)

Group	Time	Control group	Observation group	*t*	*P*
ALT (U/L)	Before treatment	110.26±16.37	110.16±16.25	0.031	0.975
	2 weeks after treatment	61.22±14.09#	43.11±13.00#	6.746	0.000
	4 weeks after treatment	36.48±12.66#,*	28.06±10.09#,*	3.714	0.003
AST (U/L)	Before treatment	97.68±10.28	97.54±10.07	0.069	0.945
	2 weeks after treatment	58.74±9.66#	46.07±7.36#	7.451	0.000
	4 weeks after treatment	37.29±8.11#,*	27.06±7.35#,*	6.675	0.000
TBil (U/L)	Before treatment	28.89±3.47	28.57±3.61	0.456	0.649
	2 weeks after treatment	22.15±2.74#	18.34±2.08#	7.909	0.000
	4 weeks after treatment	16.37±1.98#,*	12.07±1.31#,*	12.934	0.000
Alb (g/L)	Before treatment	25.69±1.15	25.88±1.36	0.762	0.448
	2 weeks after treatment	27.69±2.81#	29.71±3.15#	3.417	0.001
	4 weeks after treatment	30.11±3.00#,*	33.16±3.27#,*	4.908	0.000

Note: #P<0.05, compare with before treatment; *P<0.05, compare with 2 weeks after treatment. ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBil: total bilirubin; Alb: albumin.

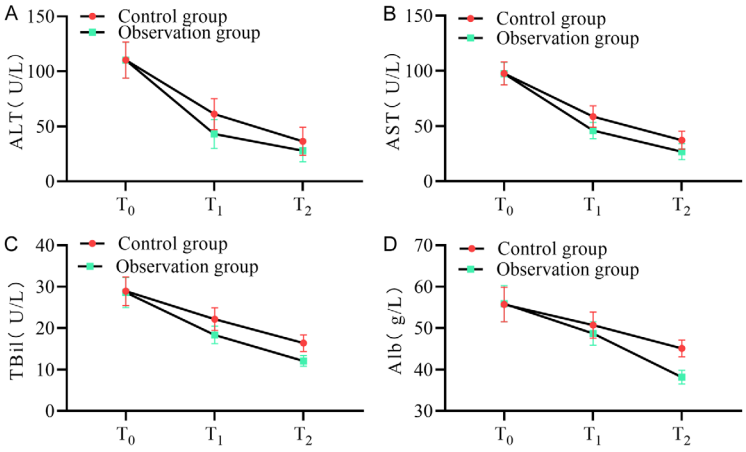

Figure 2. Comparison of liver function indicators between the two groups in different time periods. A. ALT; B. AST; C. TBil; D. Alb. T0: before treatment; T1: 2 weeks after treatment; T2: 4 weeks after treatment. ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBil: total bilirubin; Alb: albumin.

crucial for assessing disease progression and treatment efficacy. There is not a cure that exists for liver cirrhosis, but, there is a combination of antiviral, anti-fibrotic, and liver protective drugs that may be helpful [27-29]. Western medicine ~~nor~~ and traditional Chinese medicine are not stand alone medicines that can achieve ideal therapeutic effect in improving the symptoms of liver cirrhosis. For patients with compensated cirrhosis, long-term antiviral therapy is essential, focusing on drugs with potent antiviral effects and minimal resistance [30]. In the treatment of compensatory cirrhosis, selecting effective drugs plays a vital role in disease rehabilitation. The application of entecavir in patients with compensated cirrhosis can effectively improve their histological, serological, virological abnormalities, promote the recovery of liver function, and prolong the survival time of patients [31]. Entecavir, a deoxyguanosine analogue, functions by selectively inhibiting HBV replication. Upon entering the body, it undergoes conversion into its triphosphate active form [32], which effectively inhibits the activity of viral polymerase [33]. This inhibition occurs through competitive binding with deoxyguanosine triphosphate [34], leading to rapid suppression of HBV-DNA replication. It reduces the viral load in serum, targets antigens present on hepatocyte surfaces, alleviates liver inflammation, prevents disease progression, and provides hepatic protection [35]. According to TCM theory, liver cirrhosis and fibrosis are attributed to liver-kidney yin deficiency and blood stasis obstructing the Luo vessels. Bushen Huayu Decoction addresses these underlying TCM principles by nourishing the kidney and liver, promoting fluid balance, and resolving blood stasis [36]. It enhances immune function, promotes lymphocyte activity, and inhibits HBV replication, sup-

Table 4. Comparison of TCM syndrome scores before treatment, 2 weeks after treatment and 4 weeks after treatment between the two groups ($\bar{x}\pm s$, points)

Group	Time	Control group	Observation group	*t*	*P*
Abdominal distension	Before treatment	2.57±0.21	2.51±0.28	1.224	0.224
	2 weeks after treatment	1.34±0.19#	1.26±0.17#	2.241	0.027
	4 weeks after treatment	1.02±0.11#,*	0.97±0.09#,*	2.512	0.014
Poor appetite	Before treatment	2.47±0.31	2.55±0.43	1.078	0.284
	2 weeks after treatment	1.54±0.23#	1.13±0.20#	9.606	0.000
	4 weeks after treatment	1.12±0.17#,*	0.98±0.12#,*	4.805	0.000
Burnout and fatigue	Before treatment	2.41±0.42	2.53±0.34	1.586	0.116
	2 weeks after treatment	1.97±0.31#	1.43±0.24#	9.837	0.000
	4 weeks after treatment	1.16±0.29#,*	1.01±0.18#,*	3.138	0.002
Soreness and weakness of waist and knees	Before treatment	2.31±0.30	2.38±0.41	0.984	0.328
	2 weeks after treatment	2.08±0.24#	1.76±0.16#	5.948	0.000
	4 weeks after treatment	1.80±0.21#,*	1.23±0.14#,*	16.128	0.000
Fine and deep pulse	Before treatment	2.39±0.61	2.40±0.58	0.085	0.933
	2 weeks after treatment	1.85±0.56#	1.43±0.31#	4.686	0.000
	4 weeks after treatment	1.22±0.35#,*	0.87±0.20#,*	6.200	6.200
Bitter taste	Before treatment	2.27±0.62	2.43±0.58	1.346	0.181
	2 weeks after treatment	1.67±0.55#	1.30±0.41#	3.852	0.000
	4 weeks after treatment	1.29±0.25#,*	1.02±0.19#,*	6.141	0.000
Purple and dark tongue	Before treatment	2.81±0.14	2.74±0.23	1.857	0.066
	2 weeks after treatment	1.82±0.13#	1.22±0.10#	26.125	0.000
	4 weeks after treatment	1.56±0.12#,*	0.98±0.09#,*	27.614	0.000
Dark complexion	Before treatment	2.67±0.16	2.69±0.20	0.558	0.578
	2 weeks after treatment	1.87±0.14#	1.56±0.10#	12.868	0.000
	4 weeks after treatment	1.48±0.11#,*	0.91±0.03#,*	35.702	0.000

Note: #P<0.05, compare with before treatment; *P<0.05, compare with 2 weeks after treatment.

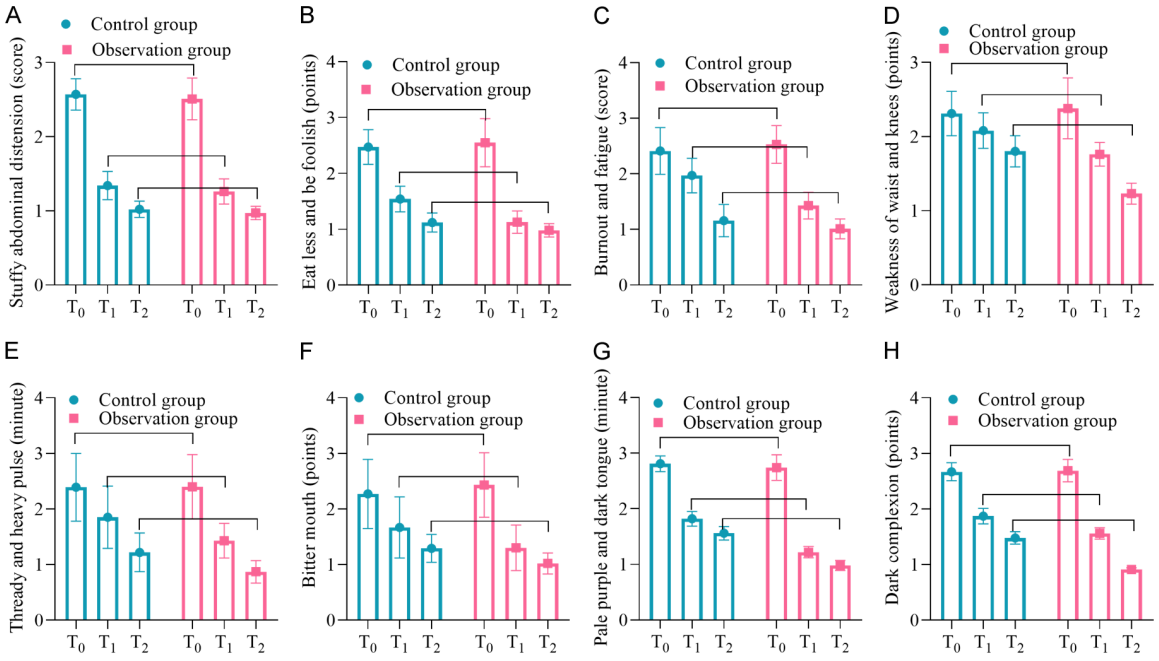

Figure 3. Comparison of TCM syndrome scores between the two groups at different times. A. Abdominal distension; B. Poor appetite and anorexia; C. Fatigue; D. Soreness and weakness of waist and knees; E. Thready deep pulse; F. Bitter taste in mouth; G. Dark pale purple tongue; H. Dark complexion. T0: before treatment; T1: 2 weeks of treatment; T2: 4 weeks of treatment.

Table 5. Comparison of prognosis outcomes between the two groups (n, %)

Group	Control group	Observation group	χ^2	P
Effective rate of treatment	43	49	3.991	0.046

porting liver function recovery [37]. Combining Chinese and western medicines optimize treatment outcomes for compensated liver cirrhosis. Integrating Bushen Huayu Decoction with entecavir enhances therapeutic effects, highlighting the importance of a comprehensive approach in managing this complex condition.

HA (hyaluronic acid) is a macromolecular glucosamine polysaccharide in the body, which is synthesized by interstitial cells and metabolized in the liver. It exists in synovial fluid, connective tissue, and cartilage serving as an important matrix for tissue composition [38]. Its level can reflect the function of hepatic endothelial cells and fibrosis, which is a good indicator to predict the condition of liver cirrhosis [39]. IV-C (type IV collagen) is an important collagen component of the basement membrane, predominantly composed of one α2(IV) chain and two α1(IV). Its fragments in serum are indicative of liver fibrosis and hepatocyte damage, assessed through immunological detection [40]. PCIII (N-terminal peptide of type III collagen) is another marker reflecting collagen over-synthesis, sensitive in detecting liver fibrosis [41]. Compared with the control group treated with entecavir alone, the liver fibrosis indexes (HA, IV-C, and PCIII) in the observation group treated with Bushen Huayu Decoction and entecavir were significantly decreased. ALT (alanine aminotransferase) and AST (aspartate aminotransferase) are enzymes predominantly found in hepatocytes, with elevated levels indicating liver cell damage [42, 43]. TBil (total bilirubin) and Alb (albumin) are crucial in assessing liver function, with TBil reflecting liver metabolic function and Alb indicating hepatic synthesis capability [44, 45]. The liver function indexes of ALT, AST and TBilAlb were lower. The level of Alb was higher in the observation group than those in the control group.

Bushen Huayu Decoction comprises a diverse array of traditional Chinese medicine (TCM) herbs, each with specific therapeutic properties: prepared rehmannia root replenishes essence and nourishes the kidneys while promoting blood circulation and dredging meridians [46]; Cornus officinalis tonifies the liver and kidneys, and protects against oxidation and inflammation [47]; yam nourishes the spleen and stomach, tonifies the kidneys, and strengthens essence [48]; Achyranthes bidentata promotes blood circulation to remove stasis, nourishes Yin, benefits the kidneys, and enhances liver function and immune response [49]; Alismatis rhizoma and Poria cocos invigorate the spleen, promote diuresis, and resolve dampness, effectively preventing greasiness caused by Rehmannia glutinosa and yam [50]; Plantain seed clears heat and promotes diuresis; Cortex moutan clears deficiency heat, promotes blood circulation without causing stagnation, and has significant anti-fibrotic and liver protective effects [51]; Vinegar-treated Trionycis Carapax softens masses, nourishes Yin, suppresses Yang, and nourishes liver blood and Yin [52]; Pharmacological studies suggest oligopeptides in Acetonia trionycis Carapax inhibit hepatocyte proliferation and activation, reducing liver fibrosis [53]; Panax notoginseng powder disperses stagnation, relieves pain, dissipates blood stasis, and stops bleeding, contributing to liver health in TCM [54]. These TCM combinations collectively strengthen the spleen, tonify Qi and kidneys, promote blood circulation to remove stasis, soften and soothe the liver, detoxify, and protect liver function. When combined with the antiviral effects of entecavir, this treatment regimen enhances drug efficacy, promoting improvements in various indicators of hepatic fibrosis and facilitating liver function recovery [55]. Studies on Zhenggan Huayu Decoction combined with entecavir have shown improved liver function in patients with chronic hepatitis B fibrosis [56]. Severe hepatitis and liver cirrhosis cases may have limitations when treated solely with traditional Chinese medicine, as treatment duration tends to be longer and recovery effects slower [57].

Compared to the control group treated solely with entecavir, the observation group receiving Bushen Huayu Decoction showed reduced scores in each TCM syndrome. This indicated that combined therapy can significantly improve TCM syndrome scores in patients with compen-

sated hepatitis cirrhosis. The main rationale lies in the synergistic effect of Bushen Huayu Decoction and entecavir. Entecavir significantly eliminates the virus. Bushen Huayu Decoction mitigates the overall adverse bodily conditions through traditional Chinese medicine principles. This combined approach delays liver fibrosis progression and enhances patients' autoimmune capacity, facilitates liver function recovery, and improves disease prognosis. It contributes to alleviating various clinical symptoms observed in TCM [58]. Similar findings were noted in a study by Wang Y, 52 patients with significant fibrosis/cirrhosis due to chronic Hepatitis B showed significant improvement in TCM syndrome with combined Fuzheng Huayu and entecavir treatment. This integration of traditional Chinese medicine bolstered treatment safety and maximized therapeutic efficacy, enhancing improvements in TCM syndromes [59]. Lim S's study highlighted challenges in directly correlating antiviral drugs with improvements in traditional Chinese medicine symptoms among patients with chronic Hepatitis B. The treatment significantly reduced the risk of hepatocellular carcinoma in individuals with indeterminate chronic Hepatitis B infection [60]. Despite achieving significant effects, some patients did not achieve ideal outcomes due to factors such as age, weight, overall health, and drug tolerance. Clinical practice should account for individual differences among patients with compensated cirrhosis when implementing combined treatment of entecavir and Bushen Huayu Decoction, adjusting treatment plans to maximize drug efficacy.

In conclusion, the combination of Bushen Huayu Decoction and entecavir improves the therapeutic effectiveness, reverses liver fibrosis, enhances liver function, and alleviates TCM syndromes and signs in patients with compensated cirrhosis. This research had limitations. The study was conducted at a single center with a small sample size, impacting result variability. Long-term efficacy and quality of life post-treatment were not evaluated, resulting in incomplete research outcomes and a lack of understanding of treatment's long-term effects. Future studies should involve larger sample sizes from multiple centers and include assessments of long-term treatment effects and quality of life to enhance research comprehensiveness.

Disclosure of conflict of interest

None.

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References

[1] Kim MN, Lee JS, Lee HW, Kim BK, Park JY, Kim DY, Ahn SH, Jang SY, Tak WY, Kweon YO, Park SY and Kim SU. ALT is not associated with achieving subcirrhotic liver stiffness and HCC during entecavir therapy in HBV-related cirrhosis. Clin Gastroenterol Hepatol 2023; 21: 2278-2287, e5.

[2] Niu A and Qi T. Diagnostic significance of serum type IV collagen (IVC) combined with aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio in liver fibrosis. Ann Transl Med 2022; 10: 1310.

[3] Lee HA, Jung JY, Lee YS, Jung YK, Kim JH, An H, Yim HJ, Jeen YT, Yeon JE, Byun KS, Um SH and Seo YS. Direct bilirubin is more valuable than total bilirubin for predicting prognosis in patients with liver cirrhosis. Gut Liver 2021; 15: 599-605.

[4] Zhang J, Shen H, Xu J, Liu L, Tan J, Li M, Xu N, Luo S, Wang J, Yang F, Tang J, Li Q, Wang Y, Yu L and Yan Z. Liver-targeted siRNA lipid nanoparticles treat hepatic cirrhosis by dual antifibrotic and anti-inflammatory activities. ACS Nano 2020; 14: 6305-6322.

[5] Zanetto A, Campello E, Bulato C, Gavasso S, Farinati F, Russo FP, Tormene D, Burra P, Senzolo M and Simioni P. Increased platelet aggregation in patients with decompensated cirrhosis indicates higher risk of further decompensation and death. J Hepatol 2022; 77: 660-669.

[6] Wijayasiri P, Astbury S, Kaye P, Oakley F, Alexander GJ, Kendall TJ and Aravinthan AD. Role of hepatocyte senescence in the activation of hepatic stellate cells and liver fibrosis progression. Cells 2022; 11: 2221.

[7] Kotani K, Enomoto M, Uchida-Kobayashi S, Tamori A, Yukawa-Muto Y, Odagiri N, Motoyama H, Kozuka R, Kawamura E, Hagihara A, Fujii H, Kageyama K, Yamamoto A, Yoshida A, Higashiyama S, Kawabe J and Kawada N. Short-term hepatocyte function and portal hypertension outcomes of sofosbuvir/velpatasvir for decompensated hepatitis C-related cirrhosis. J Gastroenterol 2023; 58: 394-404.

[8] Chen Q, Mei L, Zhong R, Han P, Wen J, Han X, Zhai L, Zhao L and Li J. Serum liver fibrosis

markers predict hepatic decompensation in compensated cirrhosis. BMC Gastroenterol 2023; 23: 317.
[9] Navin PJ, Hilscher MB, Welle CL, Mounajjed T, Torbenson MS, Kamath PS and Venkatesh SK. The utility of MR elastography to differentiate nodular regenerative hyperplasia from cirrhosis. Hepatology 2019; 69: 452-454.
[10] Hsu WF, Tsai PC, Chen CY, Tseng KC, Lai HC, Kuo HT, Hung CH, Tung SY, Wang JH, Chen JJ, Lee PL, Chien RN, Lin CY, Yang CC, Lo GH, Tai CM, Lin CW, Kao JH, Liu CJ, Liu CH, Yan SL, Bair MJ, Su WW, Chu CH, Chen CJ, Lo CC, Cheng PN, Chiu YC, Wang CC, Cheng JS, Tsai WL, Lin HC, Huang YH, Huang JF, Dai CY, Chuang WL, Yu ML and Peng CY. Hepatitis C virus eradication decreases the risks of liver cirrhosis and cirrhosis-related complications (Taiwanese chronic hepatitis C cohort). J Gastroenterol Hepatol 2021; 36: 2884-2892.
[11] Nii M, Inuzuka R, Inai K, Shimada E, Shinohara T, Kogiso T, Ono H, Ootsuki S, Kurita Y, Takeda A, Hirono K, Takei K, Yasukochi S, Yoshikawa T, Furutani Y, Shinozaki T, Matsuyama Y, Senzaki H, Tokushige K and Nakanishi T. Incidence and expected probability of liver cirrhosis and hepatocellular carcinoma after fontan operation. Circulation 2021; 144: 2043-2045.
[12] Yanagaki M, Shirai Y, Hamura R, Taniai T, Tanji Y, Haruki K, Furukawa K, Onda S, Shiba H and Ikegami T. Novel combined fibrosis-based index predicts the long-term outcomes of hepatocellular carcinoma after hepatic resection. Int J Clin Oncol 2022; 27: 717-728.
[13] Zhang T, Ye B and Shen J. Prognostic value of albumin-related ratios in HBV-associated decompensated cirrhosis. J Clin Lab Anal 2022; 36: 24338.
[14] Jeng WJ and Liaw YF. Finite antiviral therapy in chronic hepatitis B patients with cirrhosis. Semin Liver Dis 2021; 41: 349-357.
[15] Li W, Yu X, Chen X, Wang Z, Yin M, Zhao Z and Zhu C. HBV induces liver fibrosis via the TGF-β1/miR-21-5p pathway. Exp Ther Med 2021; 21: 169.
[16] Huang DQ, Tamaki N, Lee HW, Park SY, Lee YR, Lee HW, Lim SG, Lim TS, Kurosaki M, Marusawa H, Mashiba T, Kondo M, Uchida Y, Kobashi H, Furuta K, Izumi N, Kim BK and Sinn DH. Outcome of untreated low-level viremia versus antiviral therapy-induced or spontaneous undetectable HBV-DNA in compensated cirrhosis. Hepatology 2023; 77: 1746-1756.
[17] Wang Q, Zhao H, Deng Y, Zheng H, Xiang H, Nan Y, Hu J, Meng Q, Xu X, Fang J, Xu J, Wang X, You H, Pan CQ, Xie W and Jia J. Validation of Baveno VII criteria for recompensation in entecavir-treated patients with hepatitis B-related decompensated cirrhosis. J Hepatol 2022; 77: 1564-1572.
[18] Friedman SL and Pinzani M. Hepatic fibrosis 2022: unmet needs and a blueprint for the future. Hepatology 2022; 75: 473-488.
[19] Wang YL, Zhang HX, Chen YQ, Yang LL, Li ZJ, Zhao M, Li WL, Bian YY and Zeng L. Research on mechanisms of Chinese medicines in prevention and treatment of postoperative adhesion. Chin J Integr Med 2023; 29: 556-565.
[20] Song YN, Chen J, Cai FF, Lu YY, Chen QL, Zhang YY, Liu P and Su SB. A metabolic mechanism analysis of Fuzheng-Huayu formula for improving liver cirrhosis with traditional Chinese medicine syndromes. Acta Pharmacol Sin 2018; 39: 942-951.
[21] Wang S, Chen G, Chen K and Kan J. Bioavailability and prebiotic potential of Carapax Trionycis, a waste from soft-shelled turtle processing. J Sci Food Agric 2020; 100: 2554-2567.
[22] Zhao D, Yu S, Guo P, Zhang X, Tang Y, Dong C, Zhao S, Li L, Al-Dhamin Z, Ai R, Xue N, Dong S and Nan Y. Identification of potential plasma markers for hepatitis B virus-related chronic hepatitis and liver fibrosis/cirrhosis. J Med Virol 2022; 94: 3900-3910.
[23] Xu LM and Liu P; Hepatology Committee of Chinese Association of Integrative Medicine, China. Guidelines for diagnosis and treatment of hepatic fibrosis with integrated traditional Chinese and Western medicine (2019 edition). J Integr Med 2020; 18: 203-213.
[24] Li YN, Cheng XP and Geng MX. Treatment of renal edema based on TCM syndrome differentiation. Int J Clin Exp Med 2023; 7: 482-486.
[25] Hofmann E, Surial B, Boillat-Blanco N, Günthard HF, Stöckle M, Bernasconi E, Schmid P, Calmy A, Suter-Riniker F, Rauch A, Wandeler G and Béguelin C; Swiss HIV Cohort Study. Hepatitis B virus (HBV) replication during tenofovir therapy is frequent in human immunodeficiency virus/HBV coinfection. Clin Infect Dis 2023; 76: 730-733.
[26] Zi J, Li YH, Wang XM, Xu HQ, Liu WH, Cui JY, Niu JQ and Chi XM. Hepatitis D virus dual-infection among Chinese hepatitis B patient related to hepatitis B surface antigen, hepatitis B virus DNA and age. World J Gastroenterol 2023; 29: 5395-5405.
[27] McDaniel K, Utz AE, Akbashev M, Fuller KG, Boyle A, Davidson K, Marra F, Shah S, Cartwright EJ, Arora AA, DuPont S and Miller LS. Safe co-administration of direct-acting antivirals and direct oral anticoagulants among patients with hepatitis C virus infection: an international multicenter retrospective cohort study. J Viral Hepat 2022; 29: 1073-1078.
[28] Lopez-Lopez L, Cabrera Cesar E, Lara E, Hidalgo-San Juan MV, Parrado C, Martín-Montañez E and Garcia-Fernandez M. Pro-

fibrotic factors as potential biomarkers of antifibrotic drug therapy in patients with idiopathic pulmonary fibrosis. Arch Bronconeumol (Engl Ed) 2021; 57: 231-233.
[29] El-Khateeb E, Achour B, Al-Majdoub ZM, Barber J and Rostami-Hodjegan A. Non-uniformity of changes in drug-metabolizing enzymes and transporters in liver cirrhosis: implications for drug dosage adjustment. Mol Pharm 2021; 18: 3563-3577.
[30] Huang DQ, Tran A, Yeh ML, Yasuda S, Tsai PC, Huang CF, Dai CY, Ogawa E, Ishigami M, Ito T, Kozuka R, Enomoto M, Suzuki T, Yoshimaru Y, Preda CM, Marin RI, Sandra I, Tran S, Quek SXZ, Khine HHTW, Itokawa N, Atsukawa M, Uojima H, Watanabe T, Takahashi H, Inoue K, Maeda M, Hoang JK, Trinh L, Barnett S, Cheung R, Lim SG, Trinh HN, Chuang WL, Tanaka Y, Toyoda H, Yu ML and Nguyen MH. Antiviral therapy substantially reduces HCC risk in patients with chronic hepatitis B infection in the indeterminate phase. Hepatology 2023; 78: 1558-1568.
[31] Wu X, Hong J, Zhou J, Sun Y, Li L, Xie W, Piao H, Xu X, Jiang W, Feng B, Chen Y, Xu M, Cheng J, Meng T, Wang B, Chen S, Kong Y, Ou X, You H and Jia J. Health-related quality of life improves after entecavir treatment in patients with compensated HBV cirrhosis. Hepatol Int 2021; 15: 1318-1327.
[32] Li P, Wang Y, Yu J, Yu J, Tao Q, Zhang J, Lau WY, Zhou W and Huang G. Tenofovir vs entecavir among patients with HBV-related HCC after resection. JAMA Netw Open 2023; 6: e2340353.
[33] Kazmi SS, Naz Awan A, Khan A, Muhammad G, Kanwal A and Haneef M. Molecular dynamics simulation of entecavir-silver nanoparticles at different biological pH. Pak J Pharm Sci 2022; 35: 973-983.
[34] Wu Y, Wen J, Tang G, Zhang J and Xin J. On-treatment HBV RNA dynamic predicts entecavir-induced HBeAg seroconversion in children with chronic hepatitis B. J Infect 2021; 83: 594-600.
[35] Chen S, Lu Z, Jia H, Yang B, Liu C, Yang Y, Zhang S, Wang Z, Yang L, Li S, Li J and Yang C. Hepatocyte-specific Mas activation enhances lipophagy and fatty acid oxidation to protect against acetaminophen-induced hepatotoxicity in mice. J Hepatol 2023; 78: 543-557.
[36] Hindson J. Investigating two versus three doses of mRNA vaccine in patients with cirrhosis. Nat Rev Gastroenterol Hepatol 2022; 19: 752.
[37] Liu J, Ma J, Yang C, Chen M, Shi Q, Zhou C, Huang S, Chen Y, Wang Y, Li T and Xiong B. Sarcopenia in patients with cirrhosis after transjugular intrahepatic portosystemic shunt placement. Radiology 2022; 303: 711-719.
[38] Grecian SM, McLachlan S, Fallowfield JA, Hayes PC, Guha IN, Morling JR, Glancy S, Williamson RM, Reynolds RM, Frier BM, Zammitt NN, Price JF and Strachan MWJ. Addition of hyaluronic acid to the FIB-4 liver fibrosis score improves prediction of incident cirrhosis and hepatocellular carcinoma in type 2 diabetes: the edinburgh type 2 diabetes study. Obes Sci Pract 2021; 7: 497-508.
[39] Aleknaviciute-Valiene G and Banys V. Clinical importance of laboratory biomarkers in liver fibrosis. Biochem Med (Zagreb) 2022; 32: 030501.
[40] Lehmann J, Praktiknjo M, Nielsen MJ, Schierwagen R, Meyer C, Thomas D, Violi F, Strassburg CP, Bendtsen F, Møller S, Krag A, Karsdal MA, Leeming DJ and Trebicka J. Collagen type IV remodelling gender-specifically predicts mortality in decompensated cirrhosis. Liver Int 2019; 39: 885-893.
[41] Martlı HF, Saylam B, Er S, Yücel Ç and Tez M. Evaluation of preoperative procollagen type 1 N-terminal peptide and collagen type 1 C-telopeptide levels in the prediction of postoperative hypocalcemia in patients undergoing parathyroidectomy due to primary hyperparathyroidism. Langenbecks Arch Surg 2023; 408: 71.
[42] Ma HY, Dong L, Quan SZ, Li RY and Wang XR. Comparison of four markers of hepatic fibrosis and hepatic function indices in patients with liver cirrhosis and hepatoma. Ann Palliat Med 2021; 10: 4108-4121.
[43] Chen YP, Huang LW, Lin XY, Hu XM, Liang XE and Jiang RL. Alanine aminotransferase influencing performances of routine available tests detecting hepatitis B-related cirrhosis. J Viral Hepat 2020; 27: 826-836.
[44] Pieters A, Gijbels E, Cogliati B, Annaert P, Devisscher L and Vinken M. Biomarkers of cholestasis. Biomark Med 2021; 15: 437-454.
[45] Luo S, Yang Y, Zhao T, Zhang R, Fang C, Li Y, Zhang Z and Gong T. Albumin-based silibinin nanocrystals targeting activated hepatic stellate cells for liver fibrosis therapy. ACS Appl Mater Interfaces 2023; 15: 7747-7758.
[46] Yang B, Li X, Badran AMM and Abdel-Moneim AE. Effects of dietary incorporation of Radix rehmanniae praeparata polysaccharide on growth performance, digestive physiology, blood metabolites, meat quality, and tibia characteristics in broiler chickens. Poult Sci 2023; 102: 103150.
[47] Zheng C, Yang C, Gao D, Zhang L, Li Y, Li L and Zhang L. Cornel iridoid glycoside alleviates microglia-mediated inflammatory response via the NLRP3/calpain pathway. J Agric Food Chem 2022; 70: 11967-11980.

[48] Enghard P, Hardenberg JH, Stockmann H, Hinze C, Eckardt KU and Schmidt-Ott KM. Long-term effects of COVID-19 on kidney function. Lancet 2021; 397: 1806-1807.
[49] Li Z, Ma D, Peng L, Li Y, Liao Z and Yu T. Compatibility of achyranthes bidentata components in reducing inflammatory response through arachidonic acid pathway for treatment of osteoarthritis. Bioengineered 2022; 13: 1746-1757.
[50] Min F, Ziming J, Ming W, Bolin F, Xiaoqiao T, Wenhua C and Fanzhong S. Effectiveness of Fuling () and its extracts against spleen deficiency in rats tonifying spleen. J Tradit Chin Med 2023; 43: 501-506.
[51] Zhao H, Xu J, Wang R, Tang W, Kong L, Wang W, Wang L, Zhang Y and Ma W. Plantaginis Semen polysaccharides ameliorate renal damage through regulating NLRP3 inflammasome in gouty nephropathy rats. Food Funct 2021; 12: 2543-2553.
[52] Yang C, Cheng J, Zhu Q, Pan Q, Ji K and Li J. Review of the protective mechanism of paeonol on cardiovascular disease. Drug Des Devel Ther 2023; 17: 2193-2208.
[53] Wang Z, Chen Z, Fan Z and Jiang Y. Traditional Chinese medicine on treating splenomegaly due to portal hypertension in cirrhosis: a protocol for systematic review and meta-analysis. Medicine (Baltimore) 2021; 100: 24081.
[54] Liao H, Ran Y, Zhong J, Li J, Li M and Yang H. Panax notoginseng powder -assisted preparation of carbon-quantum-dots/BiOCl with enriched oxygen vacancies and boosted photocatalytic performance. Environ Res 2022; 215: 114366.
[55] Chang TS, Yang YH, Chen WM, Shen CH, Tung SY, Yen CW, Hsieh YY, Lee CP, Tsai ML, Hung CH and Lu SN. Long-term risk of primary liver cancers in entecavir versus tenofovir treatment for chronic hepatitis B. Sci Rep 2021; 11: 1365.
[56] Wenlin C, Fang L, Yuncheng Z, Jinzhen LV and Daguo Y. Effects of Zhenggan Huayu decoction combined with entecavir on gut microbiota in patients with chronic hepatitis B fibrosis. J Tradit Chin Med 2023; 43: 559-567.
[57] Chu J, Yang Y, Liu Y, Pei L, Zhou Y, Lu T, Zhang Y, Hu H, Li Y, Yang F and Lin S. Bacterial infections confer a risk of progression to acute-on-chronic liver failure in patients with HBV-related compensated cirrhosis during severe hepatitis flares. Infect Dis Ther 2022; 11: 1839-1851.
[58] Gui HL, Zhao CQ, Wang Y, Gu HT, Wang WJ, Cai W, Guo Q, Bao SS, Xu LM and Xie Q. Histological outcome of Fuzheng Huayu plus entecavir combination therapy in chronic hepatitis B patients with significant liver fibrosis. J Clin Transl Hepatol 2020; 8: 277-284.
[59] Wang Y and Liu Y. Gut-liver-axis: barrier function of liver sinusoidal endothelial cell. J Gastroenterol Hepatol 2021; 36: 2706-2714.
[60] Lim SG, Baumert TF, Boni C, Gane E, Levrero M, Lok AS, Maini MK, Terrault NA and Zoulim F. The scientific basis of combination therapy for chronic hepatitis B functional cure. Nat Rev Gastroenterol Hepatol 2023; 20: 238-253.