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Anti-fibrosis Effect of the Traditional Chinese Medicine Compound *Biejiaruangan* in Patients with Chronic Hepatitis B: A Retrospective Cohort Study

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Background: Liver fibrosis is the intermediate stage of hepatic B virus (HBV) induced-chronic liver disease and a common pathway leading to liver cirrhosis and hepatocellular carcinoma (HCC). It is reversible and can be modified by treatment. Compound *Biejiaruangan* (CBJRG) tablet acts as the first traditional Chinese medicine to treat liver fibrosis and has been widely used in clinical practice. The present study aimed to illustrate the anti-fibrosis effect of CBJRG in patients with chronic hepatitis B (CHB) in West China Hospital.

Methods: All Eligible patients achieved virological response at baseline, and these patients were divided into the Without group and the With CBJGR group based on whether the CBJRG was present in the treatment regimen. The differences of live stiffness measurements (LSM) values, aspartate aminotransferase-to-platelet ratio index (APRI) scores and fibrosis index based on four factors (FIB-4) scores were compared between the baseline and the week 24 in the Without and the With CBJRG groups, and in patients treated with different antiviral drugs, including entecavir (ETV), adefovir dipivoxil (ADV), lamivudine (LAM) and telbivudine (LDT).

Results: Total of 210 patients were enrolled, 90 in the Without CBJRG group and 210 in the With CBJRG group. LSM values ($P < 0.001$) and APRI scores ($P < 0.01$) were significantly decreased in the With CBJRG group after 24-week treatment, while only LSM values ($P < 0.01$) were reduced in the Without group. The improvement of fibrosis stages was only observed in patients receiving 24-week CBJRG in the context of ETV antiviral therapy, not in patients receiving CBJRG plus other antiviral drugs. Moreover, LSM values ($P < 0.001$) at week 24 were decreased as compared to the baseline in the ETV group, whereas no differences of APRI and FIB-4 scores were observed. LSM value ($P < 0.001$), APRI ($P < 0.01$) and FIB-4 score ($P < 0.05$) were all statistically lower in patients treated with ETV plus CBJRG. The percentage of patient with fibrosis F4 were significantly lower in the ETV plus CBJRG group when compared to the ETV group (20% vs 36.67%, $P < 0.05$).

Conclusion: The CBJRG plus ETV combination treatment showed a stronger anti-fibrosis efficacy than ETV alone in patients with CHB.

Keywords: Compound *Biejiaruangan*; Fibrosis; Live stiffness measurement; aspartate aminotransferaseto-platelet ratio index; Fibrosis index based on four factors.

Introduction

Liver fibrosis occurs in response to viral, immunity, toxic-metabolic insults induced-chronic liver disease, and it is caused by excessive accumulation of extracellular matrix (ECM) components[1]. Hepatic B virus (HBV) is one of the main causes of chronic liver disease. Approximate 15-40% patients with chronic hepatitis B (CHB) may die of HBV-related severe consequences, including cirrhosis and hepatocellular carcinoma (HCC)[2]. The courses of disease progression from chronic hepatitis to cirrhosis or even HCC are varied among HBV-infected individuals, which are the consequence of the interaction among virus, host and the environment. And fibrogenesis, a common pathogenic pathway of chronic liver disease, plays a crucial role on the path[3]. Remission or reversal of fibrosis can slow the disease progression in patients with chronic liver disease[4].

In the field of chronic HBV infection, cirrhosis and high viral load are significantly correlated with the development of HBV-related HCC[5,6]. However, about 7.5% HCC may also present in non-cirrhotic patients, and half of these patients have mild fibrosis[7]. In spite of long-term antiviral therapy and sufficient viral suppression, patients with CHB still remain the risk of developing HCC. Cirrhosis and chronically progressive histological fibrosis have been proved to play a core role in the poor prognosis[8,9]. Thus, the degree of liver fibrosis is positively related with hepatocarcinogenesis. Since the early stages of fibrosis may achieve a total curative effect, the early diagnosis and prevention of liver fibrosis is of great importance in the clinical setting.

Methods used to detect liver fibrosis main include liver biopsy, transient elastography (FibroScan), calculation of aspartate aminotransferase-to- platelet ratio index (APRI) and fibrosis in-

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dex based on four factors (FIB-4). Although liver biopsy is the golden standard for the diagnosis and staging of liver fibrosis, it is not generally accepted with the limitation of aggression, risk of serious complications, and sampling errors[10]. Other alternative methods (liver stiffness measurement, APRI and FIB-4) to evaluate fibrosis are widely accepted and used to monitor the disease progression owing to their advantage of non-invasion, convenient operation and high applicability. Liver stiffness measurement is measured using transient elastography, which can accurately detect the early and advanced fibrosis[11,12]. The value for the liver stiffness measurement is one of the significant predictors of HCC occurrence in patients undergoing long-term antiviral therapy[13]. Although APRI and FIB-4 were initially developed and validated in patients with chronic hepatitis C, they also have been established for the assessment of liver fibrosis in patients with CHB[14].

Traditional Chinese medicine (TCM) has unique advantages in alleviating hepatic fibrosis. Compound *Biejiaruangan* (CBJRG) tablet is one of the most common used TCM approved by the China Food and Drug Administration to treat liver fibrosis. CBJRG tablet is comprised by 11 herbs, including turtle shell, radix paeoniae rubra, panax notoginseng, ophiocordyceps sinensis, fructus forsythia and the like. It possesses the potential of dissipating mass, detoxification, invigorating Qi and nourishing blood, enabling itself to be applied to treat liver fibrosis and early cirrhosis[15]. Thus, this drug has been widely used in clinical practice[16,17]. However, few researches focus on the curative effect of the Chinese patent medicine in western China. Thus, in the present study, we aimed to explore the efficacy of CBJRG tablet against liver fibrosis in patients with CHB, particularly in CHB patients treated with entecavir (ETV), as ETV is one of the first-line antiviral oral drugs, and over half of the enrolled patients have been receiving the drug.

Methods

Study design

We performed a retrospective study of 400 patients with CHB in West China hospital from April 2015 to November 2016. CHB was defined as persistent positive of serum hepatitis B surface antigen (HBsAg) for more than 6 months[18]. All eligible patients were treated with at least 1-year antiviral drugs, including entecavir (ETV), adefovir dipivoxil (ADV), lamivudine (LAM) and telbivudine (LDT). The time when they achieved viral response (serum HBV DNA < 100 IU/mL) was considered as baseline, and their laboratory data were recorded. Among these enrolled patients, 90 individuals were only treated with antiviral nucleos(t)ide analogs, while 120 individuals received *traditional Chinese medicine compound Biejiaruangan* (CBJRGT, 2000 mg/time, 3 times per day) on the basis of antiviral therapy.

Exclusion criteria were as follows: (1) co-existence of other liver disease (n = 24), including chronic HCV or HIV infection, alcoholic liver disease and autoimmune liver disease; (2) combined treatment with other hepatoprotective herbs (n = 100); (3) biochemical index alanine transaminase (ALT) > 2 times the upper limit of normal (ULN) (n = 32); (4) body mass index (BMI) > 28 kg/m^2 (n = 14). Our study obtained the approval of Institutional Review Board of Sichuan University.

The degree of liver fibrosis was detected at baseline and at week 24 using non-invasive method transient elastography and serum fibrosis models, and the parameters at baseline and at week 24 were compared to evaluate the efficacy of CBJRG against liver fibrosis.

Live stiffness measurement (LSM)

Liver stiffness value was measured by quantitative assessment of transient elastography. All patients underwent transient elastography at baseline and at week 24 by an experienced technician with an ultrasonic transducer probe mounted on the axis of a vibrator. At least ten valid liver stiffness values were acquired for each patient, and reliable liver stiffness values were defined as > 60% valid measurements[19]. The mean LSM values were calculated and expressed in kPa, and then were used to grade liver fibrosis based on the criteria: < 7.1 kPa no or minimal fibrosis (F0-1); 7.1-9.4 kPa moderate fibrosis (F2); 9.5-12.4 kPa severe fibrosis (F3); ≥ 12.5 kPa cirrhosis (F4).

Serum fibrosis models

The serum fibrosis APRI and FIB-4 were calculated according to the following formulas[12]. APRI = [(AST/ULN)/platelet count (10^9/L)] × 100. Note: ULN of AST = 40 IU/L. FIB-4 = [age (year) × AST (IU/L)]/ [platelet count(10^9/L) × ALT (IU/L)$^{1/2}$]. Routine biochemical tests were performed by standard procedures (Olympus AU5400, Tokyo, Japan).

Statistical analysis

All statistical analyses were performed using SPSS software package version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviation (SD), or medians with interquartile ranges (IQR). Continuous variables with normal or skewed distribution were analyzed using Student's or Mann-Whitney test. Categorical variables were expressed as percentages and analyzed using chi-square test or Fisher exact test, where appropriate. Paired t test (for normal distribution variables) and Wilcoxon test (for non-normal distribution continuous variables) were applied to compare the difference between the results of pre- and post-treatment. A $P < 0.05$ was considered statistically significant.

Results

No statistical differences were observed between the Without CBJRG group and the With CBJRG group at baseline

Excluding unqualified patients, total of 210 patients were finally enrolled, and they were divided into the Without group (n = 90) and the With CBJRG group (n = 120) according to whether CBJRG tablets were present in the treatment regimen (Fig. 1). Demographical, clinical, and biological characteristics of the two groups are shown in Table 1. The median levels of alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin (TBil) showed no significant difference between the two groups at baseline. Fibrosis stages at baseline were graded owing to the LSM values. The percentages of patients with fibrosis stages

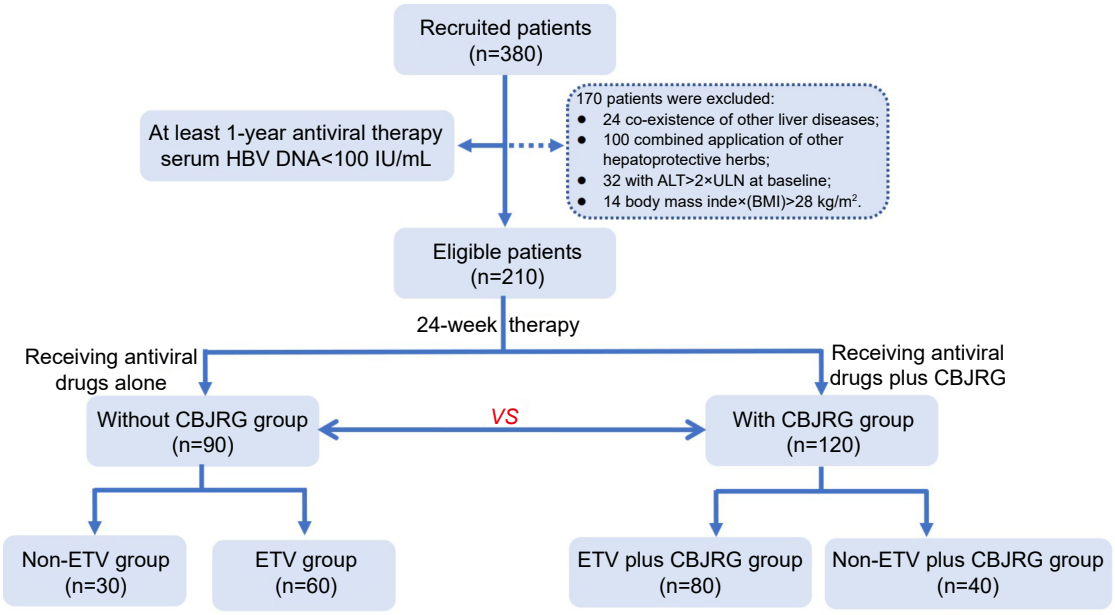

Fig. 1. Flow diagram of the study population.

Table 1. Comparison of the clinical parameters between patients with or without CBJRG on basis of anti-viral treatment at baseline.

Variables	Without CBJRG Group (n = 90)	With CBJRG Group (n = 120)	*P* value
Age (yr)	44.72 ± 8.91	45.53 ± 10.08	0.545
Male	66 (73.33%)	79 (65.83%)	0.245
ALT, IU/L	29.50 (22.00-40.50)	29.00 (21.00-41.50)	0.522
AST, IU/L	31.50 (25.00-40.00)	31.00 (25.00-37.00)	0.413
TBil, umol/L	14.95 (11.65-18.30)	15.95 (12.50-20.98)	0.064
HBeAg negative, (n %)	78 (86.67%)	100 (83.33%)	0.506
Fibrosis Stage Distribution			
F0-1	5 (5.56%)	9 (7.50%)	0.573
F2	20 (22.22%)	25 (20.83 %)	0.808
F3	31 (34.44%)	40 (33.33%)	0.866
F4	34 (37.78%)	46 (38.33%)	0.935

Data are number (%) or medians (interquartile ranges). ALT: alanine aminotransferase; AST: aspartate aminotransferase.

from F0-1 to F4 were similar and were of no difference between the Without group and the With CBJRG group (Table 1). Their APRI and FIB-4 scores were also calculated. No differences of LSM values, APRI and FIB-4 scores were observed between the two groups (Supplementary Fig. S1).

Comparison of the fibrosis improvement between the Without and the With CBJRG groups

Comparison of the fibrosis improvement between the baseline and the week 24 in the two groups is shown in Fig. 2. In the With CBJRG group, both LSM values ($P < 0.001$) and APRI scores ($P < 0.01$) were remarkably decreased in the With CBJRG group after 24-week treatment, while only LSM values were notably lower following 24-week treatment in the Without group (Fig. 2A).

Further comparison revealed that LSM values were significant lower after 24-week treatment both in HBeAg-positive and HBeAg-negative patients only receiving antiviral drugs (Fig. 2B), while APRI and FIB-4 scores were not statistically different in either HBeAg-positive or HBeAg-negative patients. Compared to the results at baseline, LSM values ($P < 0.001$) and APRI scores ($P < 0.01$) were remarkably decreased at week 24 in HBeAg-negative patients treated with antiviral drugs plus CBJRG (Fig. 2C).

Analyses on the improvement of fibrosis stages for patients in the Without and With CBJRG groups are presented in Fig. 3. At the end of our follow up, 39 patients (including 7 patients with F2, 18 patients with F3 and 14 patients with F4 at baseline) got improved in fibrosis stages, 35 patients remained unchanged, and 16 patients (including 5 patients with F0-1, 6 patients with F2 and 5 patients with F3 at baseline) worsened in the Without group. While in the With CBJRG group, 55 patients improved (including 11 patients with F2, 21 patients with F3 and 23 patients with F4 at baseline), and 17 patients (including 9 patients with F0-1, 6

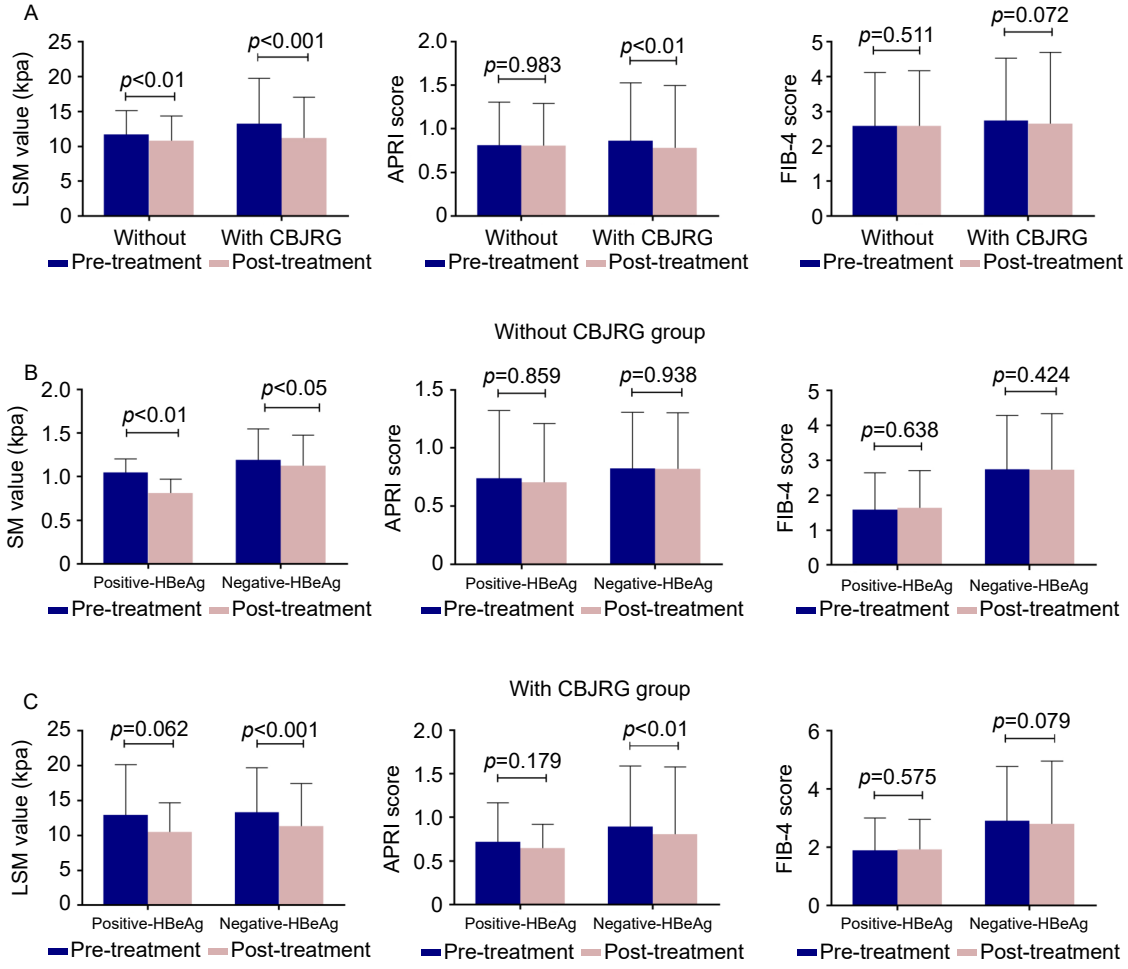

Fig. 2. Comparison of the fibrosis improvement between the Without CBJRG group and the With CBJRG group.
A. LSM values, APRI and FIB-4 scores were compared between the baseline and the week 24 in the two groups.
B. LSM values, APRI and FIB-4 scores were compared in HBeAg-positive and -negative patients among the Without group.
C. LSM values, APRI and FIB-4 scores were compared in HBeAg-positive and -negative patients among the With CBJRG group.
CBJRG: Compound *Biejiaruangan*; LSM: live stiffness measurement; APRI: aspartate aminotransferase-to-platelet ratio index; FIB-4: fibrosis index based on four factors.

Without CBJRG group		At week 24				
		F0-1	F2	F3	F4	Total
At baseline	F0-1	0	3	2	0	5
	F2	7	7	6	0	20
	F3	3	15	8	5	31
	F4	0	4	10	20	34
	Total	10	29	26	25	90

Without CBJRG group		At week 24				
		F0-1	F2	F3	F4	Total
At baseline	F0-1	0	6	2	1	9
	F2	11	8	5	1	25
	F3	5	16	17	2	40
	F4	2	10	11	23	46
	Total	18	40	35	27	120

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Fig. 3. Fibrosis stage was stratified according to the LSM values at week 24 from baseline in the Without and the With CBJRG groups.

patients with F2 and 2 patients with F3 at baseline) worsened in fibrosis stages. No differences about the percentages of patients with fibrosis changes were observed between the two groups (Supplementary Fig. S2).

Evaluation of the fibrosis improvement in patients treated with antiviral drugs plus CBJRG

In the With CBJRG group, all patients received CBJRG on the basis of different antiviral drugs. No severe adverse events were

reported during the 24-week treatment. Among the With CBJRG group, 80 patients were treated with ETV, 22 patients were treated with ADV, 9 patients were treated with LDT, 5 individuals received ETV + ADV, and 4 individuals received ADV + LAM, respectively. Then we compared the fibrosis improvement in patients receiving CBJRG treatment on the basis of different antiviral drugs, and found that LSM values were significantly decreased in ETV-treated patients ($P < 0.001$, Fig. 4A). 38 patients with advance fibrosis and cirrhosis showed improvement in fibrosis stages. The percentage of patients with fibrosis stage F2 was significantly higher (37.50% *vs* 21.25%, $P < 0.05$), and the percentage of patients with F4 was lower after 24-week treatment (20.00% *vs* 42.50%, $P < 0.01$, Fig. 4A).

Although LSM values were not significantly different between the baseline and the week 24 in 5 patients receiving CBJRG tablets based on ETV + ADV antiviral therapy ($P = 0.213$, Fig. 4B), the fibrosis stages got improved with 1 patient from F3 to F0-1 and 1 from F3 to F2.

The mean LSM values were decreased after 24-week treatment in 22 patients receiving ADV plus CBJRG, however, no statistical difference was observed ($P = 0.287$, Fig. 4C). The percentage of patients with F0-1 increased and the percentage of patients with significant fibrosis (F2/F3) and cirrhosis (F4) were decreased, while the differences were all not significant.

For patients receiving 24-week CBJRG in the context of LDT antiviral therapy, 1 patient with F2, 1 patient with F3 and 3 patients with F4 remained unchanged fibrosis stages. 3 patients improved in fibrosis stage, while 1 patient worsened (from F3 to F4). Overall, their mean LSM values were not significant different between the baseline and the week 24 ($P = 0.379$, Fig. 4D).

For patients treated with CBJRG plus ADV + LAM antiviral therapy, 1 patient achieved improvement in fibrosis stage (from F4 to F2) and 3 patients worsened (from F0-1 to F3, from F0-1 to F2 and from F3 to F4, Fig. 4E).

In terms of APRI and FIB-4 scores, patients receiving CBJRG plus ETV showed significant decrease after 24-week treatment ($P < 0.01$, Fig. 5A), whereas, no significant differences were found in APRI and FIB-4 scores in patients receiving CBJRG plus other different antiviral therapies (Fig. 5B-E).

Comparison of the fibrosis improvement between patients treated with ETV and ETV plus CBJRG

Most patients in the two groups were treated with ETV with or without CBJRG, thus we finally compared the fibrosis improvement between patients treated with ETV and treated with ETV plus CBJRG, aiming to further determine the anti-fibrosis effect of CBJRG in patients with CHB.

There were 60 patients in the ETV group and 80 patients in the ETV plus CBJRG group, respectively. The baseline characteristic between the two groups showed no difference in age ($P = 0.295$), gender ($P = 0.355$), ALT ($P = 0.394$), AST ($P = 0.127$), and TBil levels ($P = 0.089$) (Table 2). The percentages of HBeAg-negative patients were not significantly different ($P = 0.300$), about 86.67% (52/60) in the ETV group and 80.00% (64/80) in the ETV plus CBJRG group. Likewise, no statistic differences were observed in the percentages of patients with fibrosis stages from F0-1 to F4. Moreover, there were no differences in LSM values, APRI and FIB-4 scores between the ETV group and the ETV plus CBJRG group at baseline (Supplementary Fig. S3).

After 24-week treatment in the ETV group, LSM values were significantly decreased when compared to the baseline, however, no differences were observed in APRI and FIB-4 scores between the baseline and the week 24 (Fig. 6). The percentage of patients with fibrosis stages from F0-1 to F4 showed no difference between the baseline and the week 24 (Supplementary Fig. S4).

Whereas, among patients treated with ETV plus CBJRG, LSM values, APRI and FIB-4 scores were all statistically lower after 24-week treatment (Fig. 6A-C). Furthermore, the percentage of patient with F4 were significantly lower in the ETV plus CBJRG

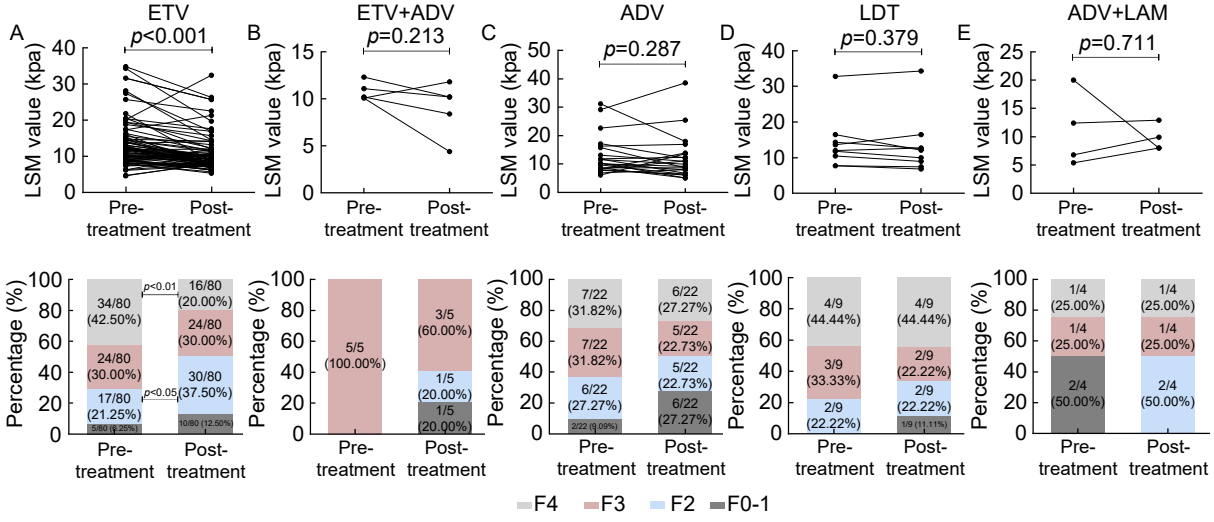

Fig. 4. Improvement of LSM values and fibrosis stages in patients receiving 24-week CBJRG in the context of different anti-HBV drugs.
A. Change of LSM values and fibrosis stages in patients receiving 24-week CBJRG in the context of ETV therapy.
B. Change of LSM values and fibrosis stages in patients receiving 24-week CBJRG in the context of ETV plus ADV therapy.
C. Change of LSM values and fibrosis stages in patients receiving 24-week CBJRG in the context of ADV therapy.
D. Change of LSM values and fibrosis stages in patients receiving 24-week CBJRG in the context of LDT therapy.
E. Change of LSM values and fibrosis stages in patients receiving 24-week CBJRG in the context of ADV+LAM therapy.
LSM: live stiffness measurement; CBJRG: Compound *Biejiaruangan*; ETV: entecavir; ADV: adefovir dipivoxil; LDT: telbivudine; LAM: lamivudine.

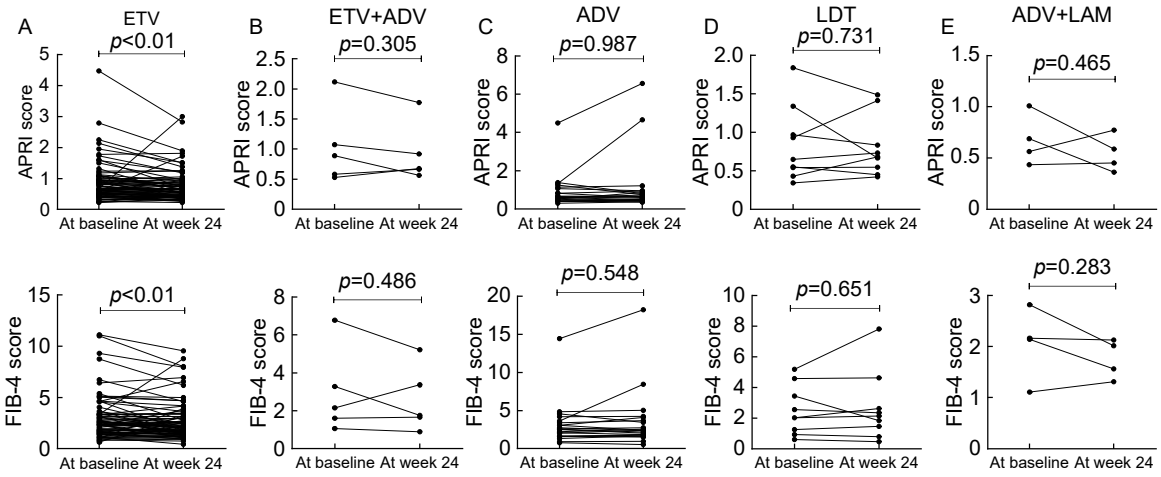

Fig. 5. Measurement of APRI and FIB-4 scores in patients receiving 24-week CBJRG in the context of different anti-HBV drugs.
A. Changes of APRI and FIB-4 scores in patients receiving 24-week CBJRG in the context of ETV therapy.
B. Changes of APRI and FIB-4 scores in patients receiving 24-week CBJRG in the context of ETV plus ADV therapy.
C. Changes of APRI and FIB-4 scores in patients receiving 24-week CBJRG in the context of ADV therapy.
D. Changes of APRI and FIB-4 scores in patients receiving 24-week CBJRG in the context of LDT therapy.
E. Changes of APRI and FIB-4 scores in patients receiving 24-week CBJRG in the context of ADV plus LAM therapy.
APRI: aspartate aminotransferase-to-platelet ratio index; FIB-4: fibrosis index based on four factors; CBJRG: Compound *Biejiaruangan*; ETV: entecavir; ADV: adefovir dipivoxil; LDT: telbivudine; LAM: lamivudine.

Table 2. Comparison of the clinical parameters at baseline between the ETV group and the ETV plus CBJRG group.

Variables	ETV Group (n = 60)	ETV Plus CBJRG Group (n = 80)	*P* Value
Age(yr)	44.55 ± 8.82	46.28 ± 10.16	0.295
Male	42 (70.00%)	50 (62.50%)	0.355
ALT, IU/L	30.00 (23.00-39.75)	29.00 (20.00-41.75)	0.394
AST, IU/L	34.00 (26.00-43.00)	31.50 (25.00-37.00)	0.127
TBil, umol/L	15.25 (11.05-19.20)	15.90 (12.70-21.30)	0.089
HBeAg negative, (n %)	52 (86.67%)	64 (80.00%)	0.300
Fibrosis Stage Distribution			
F0-1	2 (3.33%)	5 (6.25%)	0.435
F2	14 (23.33 %)	17 (21.25%)	0.769
F3	18 (30.00%)	24 (30.00%)	1.000
F4	26 (43.33%)	34 (42.50%)	0.921

Data are number (%) or medians (interquartile ranges). ALT: alanine aminotransferase; AST: aspartate aminotransferase.

group when compared to the ETV group (20.00% *vs* 36.67%, $P < 0.05$, Fig. 6D) at week 24. Together, it suggests that CBJRG plus ETV combination treatment shows a stronger anti-fibrosis effect than ETV alone in patients with CHB, and CBJRG tablet can synergistically alleviate the degree of liver fibrosis on the basis of ETV antiviral therapy.

Discussion

Liver fibrosis and in particular cirrhosis are the major causes of mortality in patients with chronic liver disease. Despite the advent of potent and effective antiviral therapies, fibrosis reversal is slow and the disease may even further progress in some patients with CHB. Anti-fibrotic drugs may help to speed up fibrosis reversal in the context of antiviral therapy[20]. Thus, approaches to relieve or to reverse liver fibrosis can be regarded as a goal of treatment in patients with established fibrosis and cirrhosis. CBJRG tablet is one of the most common used medicines in outpatients, and this study aimed to explore the efficacy of CBJRG against liver fibrosis in patients with CHB.

In the present study, CHB patients received antiviral therapy with or without CBJRG tablet for 24 weeks, and the degree of liver fibrosis was evaluated using LSM, APRI and FIB-4. However, the three non-invasive methods still have some shortcomings[12]. LSM may be influenced by obesity, elevated ALT, ascites and operator experience. Serum biomarkers (APRI and FIB-4) are not liver specific, and they may be influenced by changes in clearance and excretion parameters of each individual. Thus, to guarantee the accuracy of the results, we used the three non-invasive methods together to evaluate the change of liver fibrosis, and strictly screened qualified patients and removed pa-

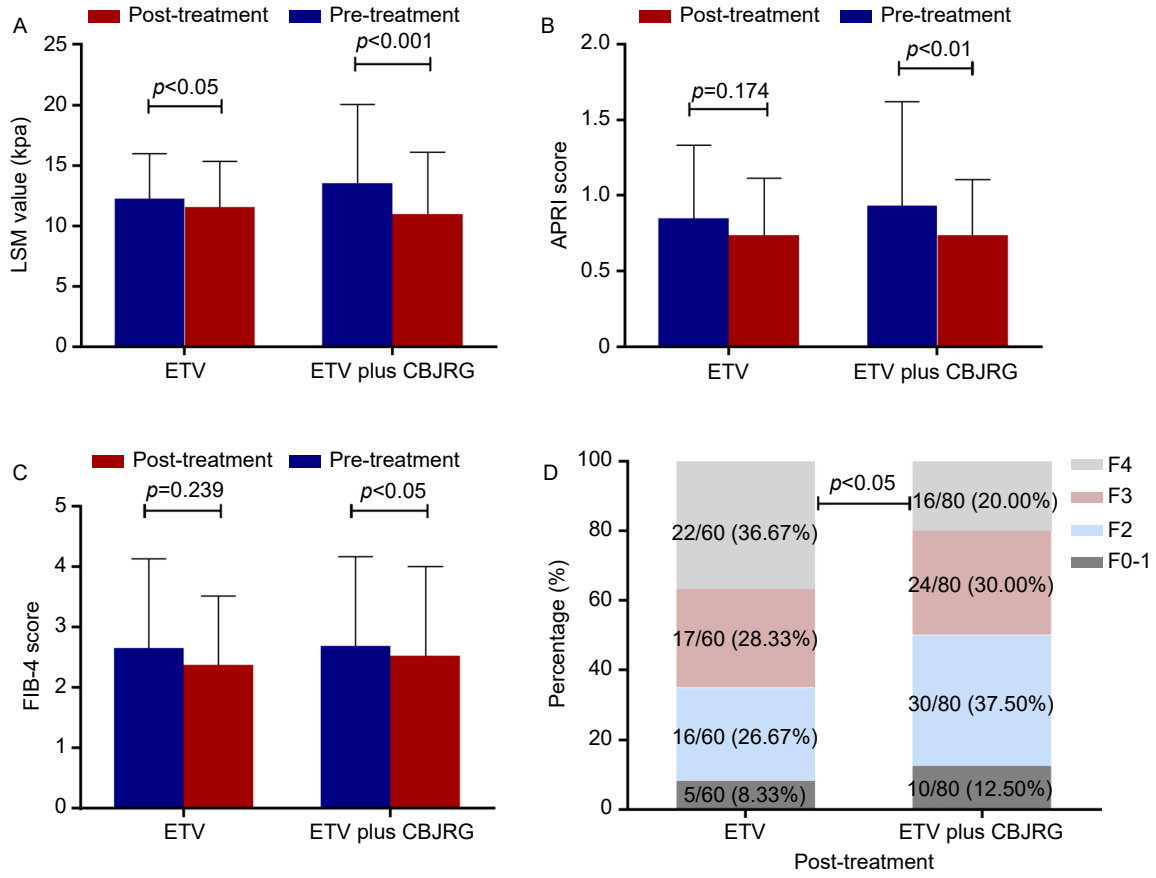

Fig. 6. Comparison of the fibrosis improvement between the ETV group and the ETV plus CBJRG group.
A. LSM values.
B. APRI and FIB-4 scores.
C. Compared between the baseline and the week 24.
D. The changes of fibrosis stages at week 24 between the two groups were also compared.
CBJRG: Compound *Biejiaruangan*; LSM: live stiffness measurement; APRI: aspartate aminotransferase-to-platelet ratio index; FIB-4: fibrosis index based on four factors.

tients with ALT > 2 × ULN and patients with BMI > 28 kg/m^2 at baseline.

Herein, we found that LSM values were remarkably lower after 24-week treatment in the both Without and With CBJRG groups. Whereas, APRI scores were decreased only in the With CBJRG group, not in the Without group. It seemed that antiviral drugs, together with CBJRG, had more powerful anti-fibrosis effect.

For patients in the With CBJRG group, we observed that the regression of liver fibrosis was only present in patients receiving CBJRG plus ETV combination treatment, not in patients receiving CBJRG plus other antiviral drugs (ADV/LDT/ADV + LAM/ETV + ADV). However, ETV is one of the first-line antiviral drugs and shows more potent antiviral efficacy than ADV and LDT monotherapy[5]. ETV itself, to some extent, may improve non-invasive fibrosis markers in some patients[21], thus who on earth shows anti-fibrosis effect in our study, ETV alone or ETV plus CBJRG, deserves consideration. Although previous studies have proved that the combination of CBJRG plus ETV produces a much stronger efficacy than ETV alone in alleviating liver fibrosis[22,23], there are still insufficient data about the efficacy of CBJRG against fibrosis in patients with undetectable serum HBV DNA. Therefore, we subsequently compared the anti-fibrosis effect between the ETV group and the ETV plus CBJRG group.

The baseline characteristics between the ETV group and the ETV plus CBJRG group showed no significant difference. Three non-invasive markers, LSM values, APRI and FIB-4 scores were all significantly decreased in the ETV plus CBJRG group after 24-week treatment, whereas only LSM values were reduced in the ETV group. Additionally, lower percentage of patients with cirrhosis was observed in the ETV plus CBJRG group. Thus, we speculated that CBJRG plus ETV treatment showed a stronger anti-fibrosis efficacy than ETV alone, corresponding to a previous study in which more patients showed fibrosis regression in group receiving CBJRG plus ETV than in group receiving ETV plus placebo[24]. Similarly, Yang et al[23] reported that the mean time to achieve Metavir fibrosis stage improvement was shorter in patients treated with CBJRG plus ETV than in patients treated ETV alone. Moreover, a recent study found that the addition of CBJRG to ETV could also reduce the risk of hepatocellular carcinoma (HCC) in patients with CHB[25].

As for patients receiving ETV plus ADV or ADV plus LAM, the anti-fibrosis effect of CBJRG in these patients needs further investigation since the limited small sample in our study. In addition, it may need a longer follow-up period to investigate the anti-fibrosis effect of CBJRG in patients receiving ADV and LDT, owing to their less potent antiviral efficacy compared with ETV.

Liver fibrosis is the result of excessive ECM deposition secreted by activated hepatic myofibroblasts. Hepatic stellate cells (HSCs) are the major source of myofibroblast. Under condition of chronic liver injury, HSCs are activated and transdifferentiated into myofibroblasts, thereby synthetizing ECM components[1,26]. Several cytokines including platelet derived growth factor (PDGF) and transforming growth factor β1 (TGFβ1), play a key role in the proliferation and activation of HSCs as well as the synthesis of ECM[27]. CBJRG exerts comprehensive anti-fibrotic pharmacological effects of multi-channel, multi-level and multi-target[28]. It can decrease the number of activated HSCs, inhibit the expression of TGFβ1 and PDGF in HSCs, inhibit the fibrogenic signal transduction of TGFβ1/Smad pathway, reduce the production of collagens, promote the degradation of collagen, thereby blocking the process of liver fibrosis[29,30]. Recent study demonstrated that BJRGC could alleviate liver fibrosis through inhibiting the proliferation of HSCs by targeting the PI3K/AKT signaling pathway with its prototype components, such as hyperoside, tumulosic acid, and hederagenin[31].

Besides anti-fibrosis effect, BJRGC also showed potent efficacy in preventing HCC[25,31-33]. However, the real mechanisms of CBJRG in the prevention of HCC remain controversial. It is originally assumed that the addition of CBJRG to ETV therapy exerts a synergistic effect on fibrosis regression, thereby suppressing the development of HBV-induced cirrhosis and even HCC. Multi- pathways, such as PI3K/AKT/NF-κB and the long non-coding RNA TUG1-microRNA-328-3p-SRSF9 mRNA axis, might be involved in the progress[34,35]. However, some researchers recently proved that the underlying mechanism of CBJRG in the contribution of HCC prevention is far more than the assume that cirrhosis is a predisposing factor for hepatocarcinogenesis, since the development of liver fibrosis and of HCC are two independent processes with distinct molecular mechanisms rather than a sequential series of events[32]. Therefore, many unknowns about the mechanism of CBJRG on the development of HCC are worth exploring.

The main limitations of our study are the lack of liver biopsy and the single-center study with small sample size. The outcomes of our study are restricted to observations at treatment week 24. A longer follow-up of observation will allow us to determine the anti-fibrosis effect of CBJRG in patients receiving non-ETV therapies and to explore the risk of HCC development. The retrospective design of this study is another limitation and may cause selective bias.

In summary, the CBJRG plus ETV combination treatment showed a stronger anti-fibrosis efficacy than ETV alone in patients with fibrosis. CBJRG tablet, in addition to ETV, should be considered for CHB patients with advanced fibrosis and cirrhosis.

Abbreviations

ADV, adefovir dipivoxil; ALT, alanine transaminase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate transaminase; CBJRG, compound *Biejiaruangan*; CHB, chronic hepatitis B; ECM, extracellular matrix; ETV, entecavir; FIB-4, fibrosis index based on four factors; HBsAg, hepatitis B surface antigen; HBV, hepatic B virus; HCC, hepatocellular carcinoma; LAM, lamivudine; LDT, telbivudine; LSM, live stiffness measurements; PDGF, platelet derived growth factor; TBil, total bilirubin; TCM, traditional Chinese medicine; TGFβ1, transforming growth factor β1.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest

The authors have no conflict of interests related to this publication.

Data Sharing Statement

The raw data used to support the findings of this study are available from the corresponding author upon request.

Authors' contributions

YCT analyzed data and wrote the paper. MLW, YHW, DMZ and MH contributed to the data collection. EQC corrected the draft and decided the critical revision of the manuscript. All authors approved the final version of the manuscript.

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