Systematic Review and Meta-Analysis

Medicine

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Compound Biejia-Ruangan tablet as an adjunctive therapy to entecavir for chronic hepatitis *B* complicated with hepatic fibrosis

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: The compound *Biejia-Ruangan* tablet (CBRT), as an adjunctive therapy to entecavir, is a potential treatment for hepatic fibrosis (HF) in patients with chronic hepatitis B (HBV). However, the present study yielded inconsistent results. In this systematic review and meta-analysis, we comprehensively investigated the efficacy and safety of CBRT as an adjunctive modality to entecavir for the treatment of HBV infection complicated with HF.

Methods: We searched the Cochrane Library, PubMed, Embase, CNKI, VIP, CBM, and Wangfang databases through April 1, 2022, for randomized controlled trials (RCTs) assessing the effect and safety of CBRT as an adjunctive modality to entecavir for HBV complicated with HF. The primary outcomes were biochemical parameters of serum hyaluronic acid, laminin (LN), pretype-III collagen (PC-III), and type IV collagen (IV-C). The secondary outcomes were liver function indices of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBiL) levels, total effect rate, and occurrence rate of adverse events. Two researchers independently conducted study selection, data extraction, and quality assessment. Statistical analysis was performed using the RevMan 5.3 software.

Results: Eight RCTs involving 747 patients were included. Compared with entecavir monotherapy, CBRT as an adjunctive therapy to entecavir exerted more encouraging effect in serum levels of hyaluronic acid (mean difference [MD] = –28.15; 95% confidence interval [CI]: –43.82 to –12.47; $P < .001$), LN (MD = –29.46; 95% CI: –50.69 to –8.23; $P < .001$), PC-III (MD = –11.83; 95% CI: –19.43 to –4.23; $P < .001$), and IV-C (MD = –19.62; 95% CI: –29.76 to –9.49; $P < .001$); levels of serum ALT (MD = –16.83; 95% CI: –26.30 to –7.36; $P < .001$), AST (MD = –20.52; 95% CI: –33.11 to –7.93; $P < .001$), and TBiL (MD = –7.54; 95% CI: –11.58 to –3.49; $P < .001$); and total effect rate (odds ratio = 3.53; 95% CI: 1.71–7.29; $P < .001$). Meta-analysis results also showed that CBRT as an adjunctive therapy to entecavir had a lower occurrence rate of adverse events (odds ratio = 0.54; 95% CI: 0.22–1.34; $P < .001$) than entecavir alone.

Conclusion: The results of this study showed that CBRT as an adjunctive modality to entecavir may benefit HBV patients complicated with HF. High-quality RCTs are needed to confirm the current findings in the future.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase,CBRT = Biejia-Ruangan tablet, CI = confidence interval, HA = hyaluronic acid,HBV = chronic hepatitis B, HF = hepatic fibrosis, IV-C = type IV collagen, LN = laminin,MD = Mean difference, OR = odds ratio, PC-III = pretype-III collagen, RCTs = randomized controlled trials, TBiL = total bilirubin.

Key words: chronic hepatitis B, compound *Biejia-Ruangan* tablet, Entecavir, hepatic fibrosis, meta-analysis, systematic review

1. Introduction

Hepatic fibrosis (HF) is a pathological condition caused by various chronic liver diseases.[1–3] It is a precursor of cirrhosis in patients with chronic hepatitis B virus (HBV) and affects the physiological function of the liver.[4,5] It is estimated that approximately 400 million people are chronically infected HBV.[6] Moreover, patients with HBV often have different degrees of HF, which greatly impacts their quality of life and survival time.[7–9] Thus, there is an urgent need to explore effective modalities for patients with HBV infection complicated by HF.

Although studies have reported that long-term anti-HBV management can alleviate both replication of HBV virus

All authors stated that they had no competing interests with this study.

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

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How to cite this article: Xu Y-H, Xue C. Compound Biejia-Ruangan tablet as an adjunctive therapy to entecavir for chronic hepatitis B complicated with hepatic fibrosis: A systematic review and meta-analysis of randomized controlled trials. Medicine 2022;101:32(e30020).

Received: 19 April 2022 / Received in final form: 24 June 2022 / Accepted: 24 June 2022

http://dx.doi.org/10.1097/MD.0000000000030020

and HF process, they still suffer from sufficient efficacy.[10–14] Fortunately, traditional Chinese herbal medicine, such as the compound *Biejia-Ruangan* tablet (CBRT) as an adjunctive therapy to entecavir is a promising modality for HBV patients complicated with HF.[15–20] It consists of 11 traditional Chinese herbs, and is the first approved Chinese herbal medicine by the China Food and Drug Administration for anti-HF.[21] Study have reported that it can inhibit the proliferation of fat-storing cells, reduce the synthesis and excessive deposition of collagen.[22] It exerts positive effects in preventing, blocking, and treating HF and early cirrhosis.[22] In this prescription, the turtle shell was the chief Chinese herb. A previous study reported that it has a certain anti-HF effect, and its possible action mechanisms include reducing the contents of human type IV and III collagen, inhibiting lipid peroxidation reaction and activity of hepatic stellate cells, affecting the content of cytokines, and improving the degradability of hyaluronic acid (HA).[23] In addition, other herbs also exert antifibrotic effects in different ways, thereby inhibiting the formation of HF through multiple targets and pathways and exerting synergistic therapeutic effects.[21]

Previous clinical studies investigated the effect and safety of CBRT as an adjunctive therapy to entecavir for the treatment of HBV patients complicated with HF.[24–31] However, there is still insufficient data and evidence to support CBRT as an adjunctive therapy to entecavir for the treatment of HBV patients complicated with HF. Therefore, this systematic review and meta-analysis comprehensively explored the effect and safety of CBRT as an adjunctive therapy to entecavir for the HBV patients complicated with HF.

2. Methods

2.1. Ethical statement

This study does not need ethic approval and patient informed consent because we conduct this study based on the secondary patient data, and no individual data are involved.

2.2. Literature search

A comprehensive search of the Cochrane Library, PubMed, Embase, CNKI, VIP, CBM, and Wangfang was performed on April 1, 2022 for randomized controlled trials (RCTs) investigating the efficacy and safety of CBRT as an adjunctive therapy to entecavir HBV complicated with HF. In addition, we searched other literature sources, such as the reference lists of the associated reviews. The following keywords were used to perform literature sources search, including "hepatitis B virus," "chronic hepatitis B," "liver cirrhosis," "hepatic fibrosis," "compound *Biejia-Ruangan* tablet," "*Biejia-Ruangan* power," "*Biejiaruangan San*," "herbal medicine," "Chinese compound prescription," and "entecavir." The detailed search strategy is presented in Table 1.

Table 1

Detailed search strategy in PUBMED.

Number	Search terms
1	Hepatitis B virus
2	Chronic hepatitis B
3	Liver cirrhosis
4	Hepatic cirrhosis
5	Hepatic fibrosis
6	Liver fibrosis
7	Congenital hepatic fibrosis
8	Or 1–7
9	Compound *Biejia-Ruangan* tablet
10	*Biejia-Ruangan* power
11	*Biejia-Ruangan San*
12	Herbal medicine
13	Chinese compound prescription
14	Or 9–13
15	Entecavir
16	Baraclude
17	Or 15–16
18	Case-control study
19	Observational study
20	Clinical trial
21	Randomized controlled trial
22	Or 18–21
23	8 AND 14 AND 17 AND 22

2.3. Study selection

Two researchers independently selected studies based on the inclusion criteria. This process consists of 3 steps. First, all duplicates were removed after literature search. Second, titles and abstracts of the remaining studies were reviewed to eliminate

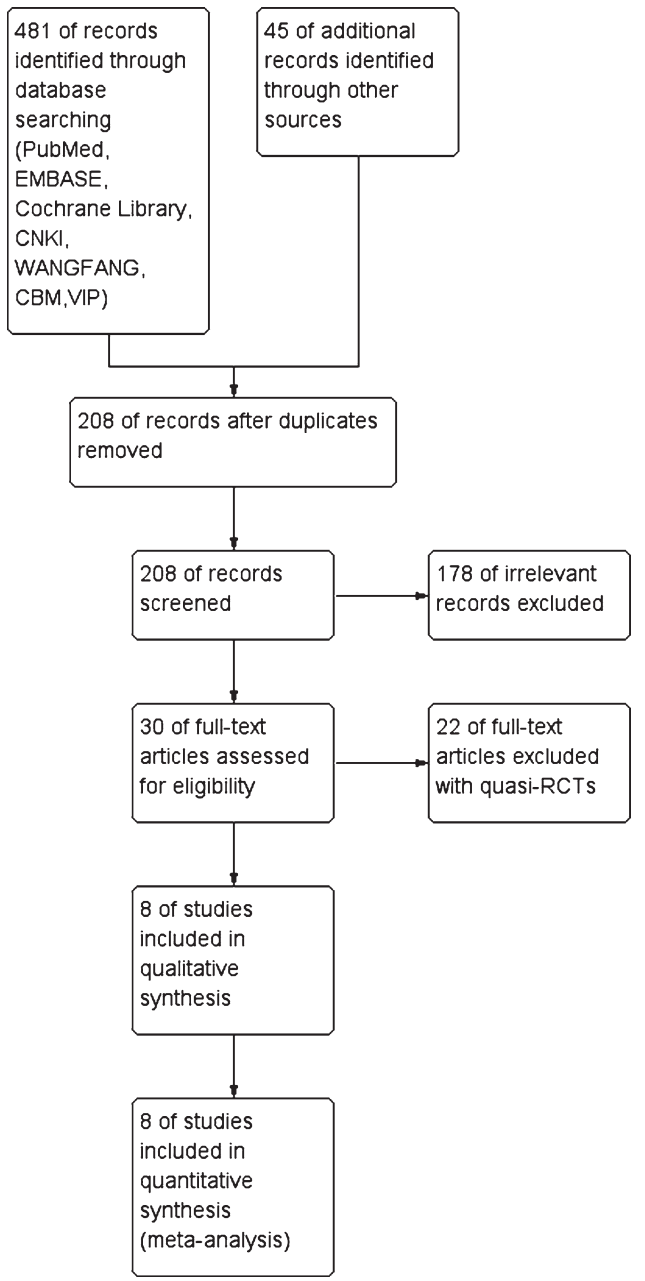

Figure 1. Flow diagram of study selection.

irrelevant studies. Third, the full texts of the potential articles were carefully read, and eligible trials were included. Any conflicts between the 2 researchers were resolved through discussions with an experienced researcher.

2.4. Eligibility criteria

2.4.1. Inclusion criteria. The inclusion criteria were as follows: (1) This study only included RCTs of CBRT as an adjunctive therapy to entecavir for HBV patients complicated with HF. (2) All patients were diagnosed with HBV infection complicated by HF. (3) Patients in the experimental group received CBRT plus entecavir, while those in the control group received entecavir alone.

2.4.2. Exclusion criteria. We excluded studies if they met the following criteria: (1) all irrelevant studies, such as duplicates, reviews, case studies, animal studies, retrospective studies, uncontrolled studies, and quasi-RCTs (defined as using inadequately or no concealed method for different interventions, which is not truly random); (2) studies not related to CBRT plus entecavir, HBV complicated with HF; and (3) studies with insufficient data and information.

2.5. Outcome measurements

The primary outcomes included biochemical parameters of serum HA, laminin (LN), pretype-III collagen (PC-III), and type IV collagen (IV-C). The secondary outcomes included liver function indices of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBiL), total effect rate, and the occurrence rate of adverse events.

2.6. Data collection

Two researchers independently collected data from each trial based on eligibility criteria. Information on title, first author, year of publication, details of study design, intervention, control, primary and secondary outcomes, adverse events, and follow-up. Any differences were resolved through a discussion with a third expert.

2.7. Risk of bias assessment

The Cochrane risk of bias tool was used by 2 independent researchers to assess the methodological quality of all included studies in 7 fields, and each was rated as low, unclear, or high risk of bias. Any divergence was resolved through a discussion with a third experienced expert.

2.8. Statistical Analysis

RevMan 5.3 software was used to perform all statistical analysis. The mean difference (MD) with 95% confidence interval (CI) was used to calculate continuous data, and odds ratio (OR) with 95% CI was utilized to present dichotomous data. Heterogeneity of the pooled data was analyzed using the I^2 test. A fixed-effects model was used if the value of I^2 was < 50% and a random-effects model was used if the value of I^2 was ≥ 50%.

3. Results

3.1. Search results

After a comprehensive literature search, a total of 526 studies were found, 208 of which remained after duplicates were eliminated. After the titles and abstracts were screened, 178 irrelevant studies were removed and 30 potential articles were entered into the next step. After carefully reading the full text, 22 quasi-RCTs were excluded, and 8 eligible RCTs underwent qualitative and quantitative analysis[24–31] (Fig. 1).

3.2. Study characteristics

This study reviewed 8 eligible RCTs involving 747 patients with HF and HBV. All of these studies focused on the comparative outcomes between CBRT plus entecavir and entecavir monotherapy. The general characteristics of the patients with HF and HBV are summarized in Table 2, including the first author, year of publication, age, intervention, control, outcomes, and follow-up.

3.3. Quality assessment

We used the Cochrane Risk of Bias tool to assess the methodological quality of all 8 included RCTs[24–31] (Fig. 2). All trials sufficiently reported random sequence generation, incomplete outcome data, selective reporting, and other bias.[24–31] However, they did not clearly provide details of allocation concealment, blinding of participants, investigators, and outcome assessors.[24–31]

Table 2

General characteristics of included studies.

Study	No. of patients (T/C)	Age (yrs, T/C)	Intervention	Control	Outcomes	Follow-up (mo)
Jiao and Zhang[24]	37/37	T: 45.5 ± 2.0 C: 46.5 ± 1.5	Entecavir 0.5 mg/d plus CBRT 12tablets/d	Entecavir 0.5 mg/d	①②③④⑤⑨	12
Jin[25]	50/50	T: 42.5 ± 8.4 C: 43.2 ± 8.5	Entecavir 0.5 mg/d plus CBRT 6 g/d	Entecavir 0.5 mg/d	①②③④⑤⑦	12
Liu et al[26]	65/64	T: 44.7 ± 2.8 C: 43.9 ± 2.8	Entecavir 0.5 mg/d plus CBRT 6 g/d	Entecavir 0.5 mg/d	①②⑤⑥⑦⑨	12
Mo and Huang[27]	51/51	T: 39.2 ± 5.3 C: 39.0 ± 5.2	Entecavir 0.5 mg/d plus CBRT 6 g/d	Entecavir 0.5 mg/d	①②③④⑤⑥⑧	6
Sun and Zhu[28]	38/38	T: 42.2 ± 2.6 C: 42.3 ± 2.6	Entecavir 0.5 mg/d plus CBRT 6 g/d	Entecavir 0.5 mg/d	①②③④⑧⑨	12
Wang and Li[29]	48/48	T: 44.9 ± 15.2 C: 45.5 ± 15.6	Entecavir 0.5 mg/d plus CBRT 6 g/d	Entecavir 0.5 mg/d	⑤⑥⑦	12
Zhang et al[30]	45/45	T: 42.3 ± 2.7 C: 42.9 ± 2.5	Entecavir 0.5 mg/d plus CBRT 12 tablets/d	Entecavir 0.5 mg/d	①②③④⑦⑧	12
Zhang[31]	40/40	T: 45.6 ± 15.7 C: 45.8 ± 16.1	Entecavir 0.5 mg/d plus CBRT 6 g/d	Entecavir 0.5 mg/d	①②④⑤⑥⑦⑧	6

T, treatment group; C, control group; CBRT, *Biejia-Ruangan* tablet; ① serum HA level; ② serum LN level; ③ serum PC-III level; ④ serum IV-C level; ⑤ serum ALT level; ⑥ serum AST level; ⑦ serum TBiL level; ⑧ total effect ratio; ⑨ adverse events.

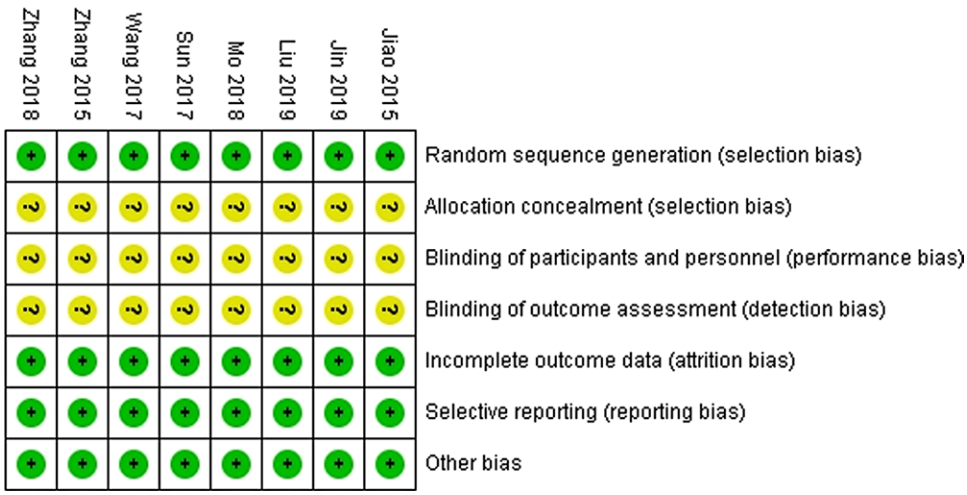

Figure 2. Risk of bias summary.

3.4. Pooled analysis of primary outcomes

Six trials with 577 patients investigated serum levels of HA and LN. Four studies with 368 patients explored the serum levels of PC-III, and 5 studies with 448 patients analyzed the serum levels of IV-C. There were statistically significant difference in the biochemical parameters of serum levels of HA (MD = –28.15; 95% CI: –43.82 to –12.47; $P < .001$; $I^2 = 98\%$; Fig. 3), LN (MD = –29.46; 95% CI: –50.69 to –8.23; $P < .001$; $I^2 = 99\%$; Fig. 4), PC-III (MD = –11.83; 95% CI: –19.43 to –4.23; $P < .001$; $I^2 = 98\%$; Fig. 5), and IV-C (MD = –19.62; 95% CI: –29.76 to –9.49; $P < .001$; $I^2 = 96\%$; Fig. 6).

3.5. Pooled analysis of secondary outcomes

Seven studies (671 subjects), 5 studies (497 participants), and 4 trials (405 patients) examined the levels of serum ALT, AST, and TBiL, respectively. Statistically significant differences were observed between the 2 modalities for serum ALT levels (MD = –16.83; 95% CI: –26.30 to –7.36; $P < .001$; $I^2 = 98\%$; Fig. 7), AST (MD = –20.52; 95% CI: –33.11 to –7.93; $P < .001$; $I^2 = 99\%$; Fig. 8), TBiL (MD = –7.54; 95% CI: –11.58 to –3.49; $P < .001$; $I^2 = 98\%$; Fig. 9); and the total effect rate (OR = 3.53; 95% CI: 1.71–7.29; $P < .001$; $I^2 = 0\%$; Fig. 10). We also found that CBRT plus entecavir treatment was significantly lower for entecavir monotherapy than for the occurrence rate of adverse events (OR = 0.54; 95% CI: 0.22–1.34; $P < .001$; $I^2 = 0\%$; Fig. 11).

4. Discussion

Chronic HBV infection is one of the most common causes of liver-associated diseases such as HF, cirrhosis, and even liver cancer. Thus, proper and timely management of patients with HBV-complicated HF is necessary to prevent them from developing serious conditions of cirrhosis and liver cancer. Entecavir is the first-line drug that effectively blocks HBV replication. However, its efficacy remains unsatisfactory.

Traditional Chinese compound prescriptions, such as CBRT, are widely used for the treatment of patients with HVB and HF. Although various clinical trials regarding entecavir plus CBRT for the treatment of HBV complicated with HF have been conducted, the findings are inconsistent. In this systematic review and meta-analysis, we comprehensively assessed the efficacy and safety of CBRT as an adjunctive therapy to entecavir for the treatment of patients with HBV and HF.

There were statistically significant differences between entecavir plus CBRT and entecavir alone in the biochemical parameters of serum levels of HA, LN, PC-III, and IV-C; liver function indices of levels of serum ALT, AST, and TBiL; total effect rate; and occurrence rate of adverse events. The findings of these pooled data suggest that CBRT as an adjunctive therapy to entecavir is superior to entecavir monotherapy, with fewer adverse events.

This systematic review and meta-analysis had several limitations. First, a limited number of eligible RCTs were included, which may have affected the study findings. Second, none of the trials clearly reported the blinding details of patients, researchers, and outcome assessors, which may have affected the risk of selection, performance, and detection bias in this study. Third, none of the included studies reported drop-off details, which may have affected the reporting bias in this study. Finally, none of the studies reported short-term effects. Therefore, more high-quality multicenter large-sample RCTs are needed to confirm the current findings in the future.

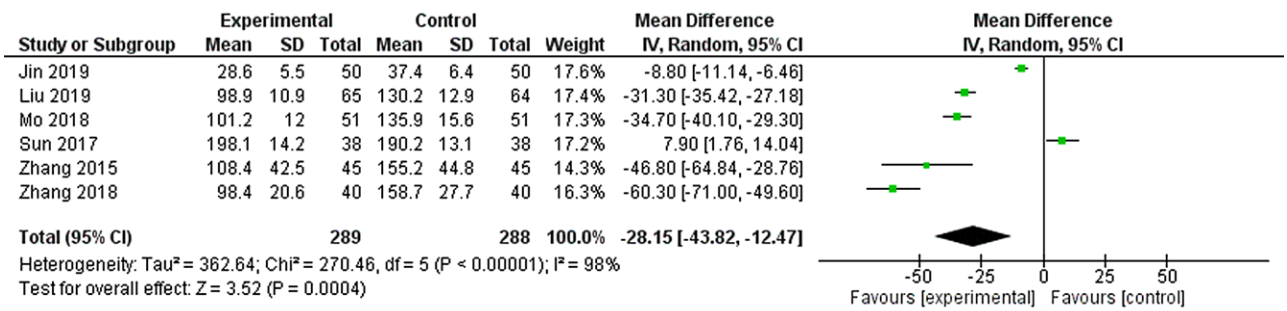

Figure 3. Comparison of serum HA level.

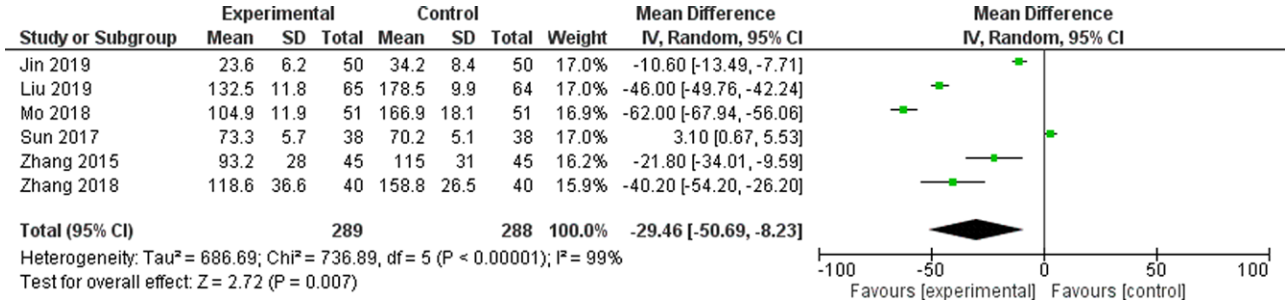

Figure 4. Comparison of serum LN level.

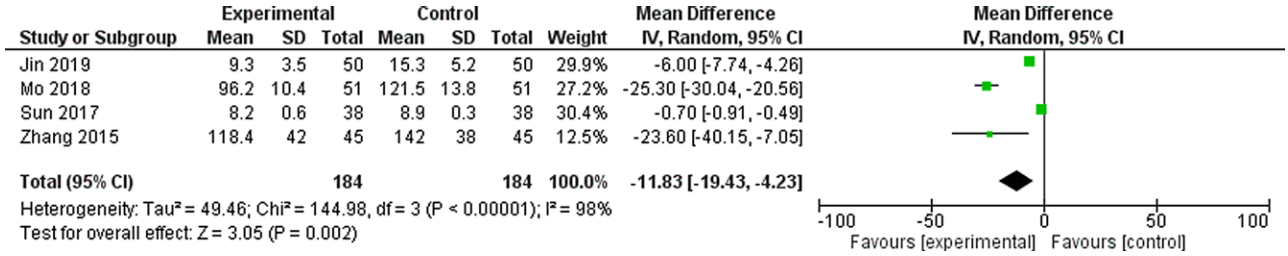

Figure 5. Comparison of serum PC-III level.

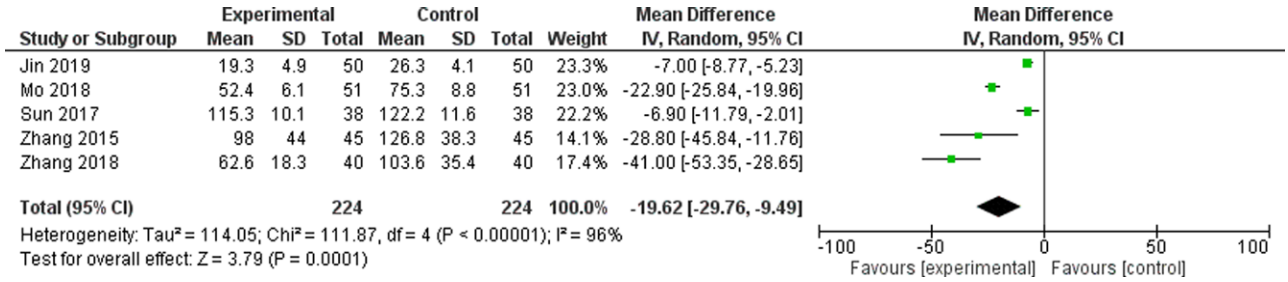

Figure 6. Comparison of serum IV-C level.

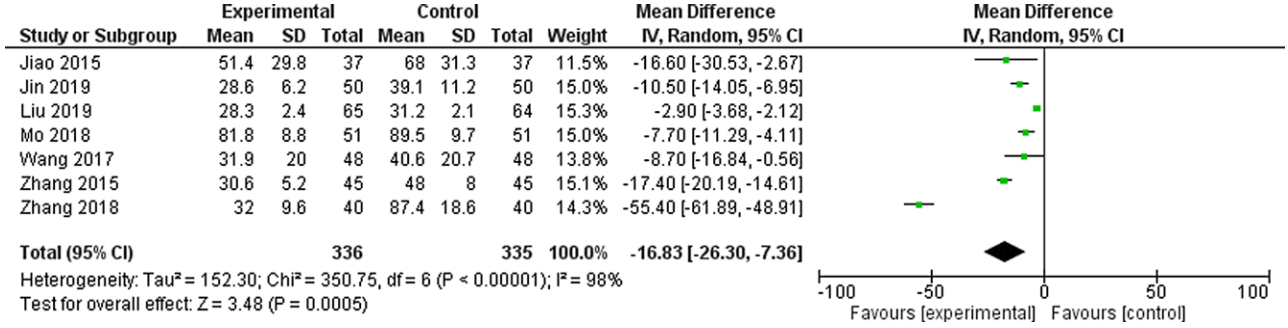

Figure 7. Comparison of serum ALT level.

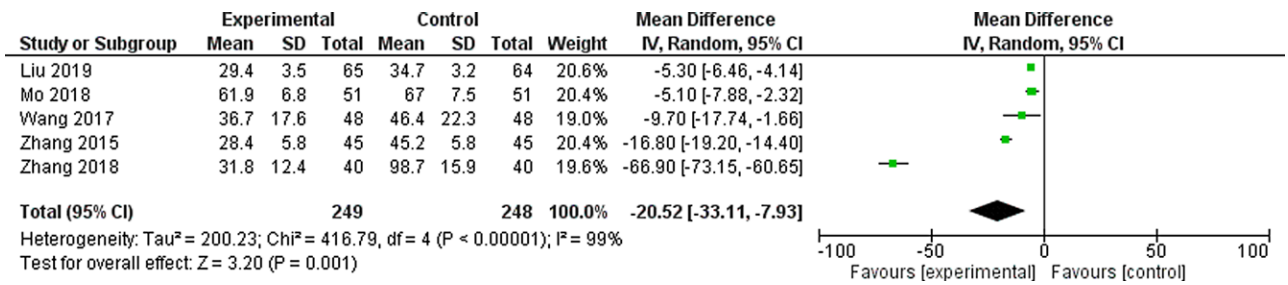

Figure 8. Comparison of serum AST level.

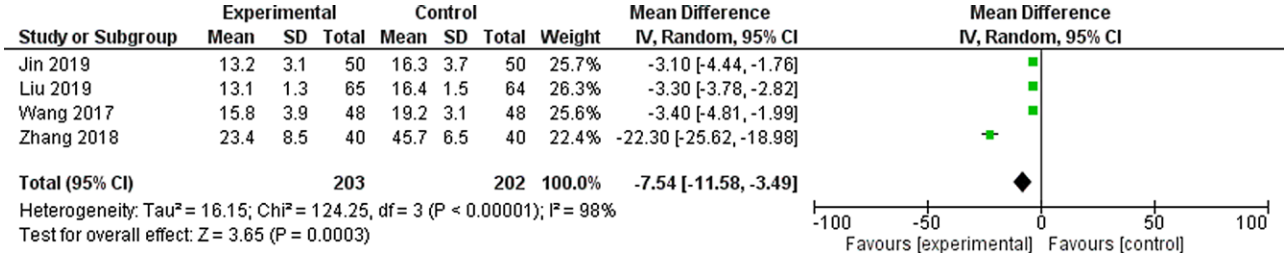

Figure 9. Comparison of serum TBiL level.

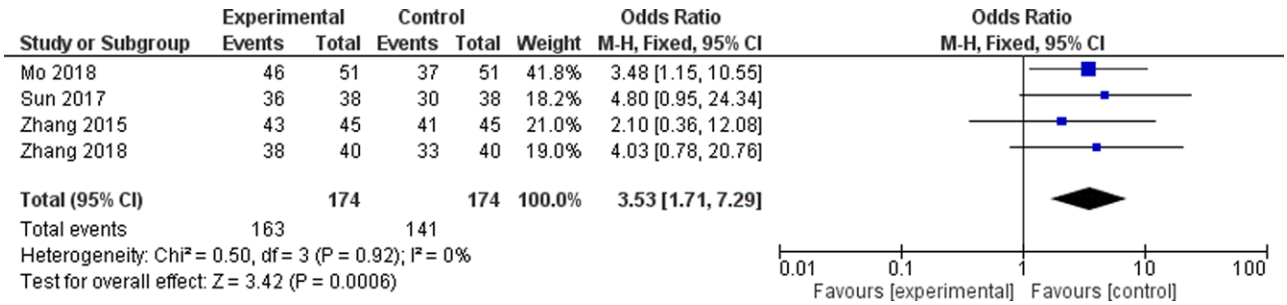

Figure 10. Comparison of total effect rate.

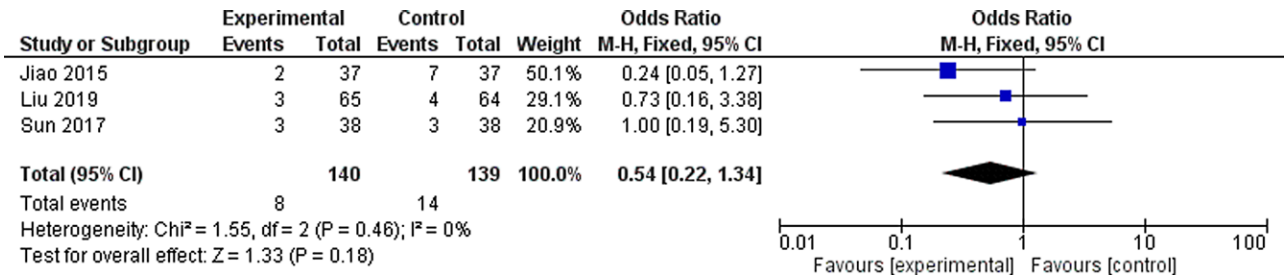

Figure 11. Comparison of occurrence rate of adverse events.

5. Conclusion

This study showed that CBRT, as an adjunctive modality to entecavir, had positive efficacy in patients with HBV and HF. Future studies involving high-quality RCTs are required to validate the present findings.

Author contributions

Conceptualization: Chuan Xue.
Data curation: Yong-hong Xu.
Formal analysis:Yong-hong Xu.
Investigation: Chuan Xue.
Methodology: Yong-hong Xu.
Supervision: Chuan Xue.
Validation: Chuan Xue.
Writing–original draft: Yong-hong Xu.
Writing–review & editing: Chuan Xue.

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