Journal of Traditional Chinese Medical Sciences (2015) 2, 11–24

HOSTED BY

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/jtcms

Chinese herbal medicine combined with nucleotide analogues for compensated HBV-related cirrhosis: a systematic review of randomized controlled trials

Tingting Li [a], Tianfang Wang [a,*], Yutong Fei [b,*], Xiaolin Xue [a], Xiuyan Wu [a]

[a] *Department of Chinese Medicine Diagnosis, School of Basic Medical Science, Beijing University of Chinese Medicine, Beijing 100029, China*
[b] *Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China*

Received 20 November 2014; accepted 15 December 2014

Available online 30 January 2016

KEYWORDS
Liver cirrhosis;
Traditional Chinese medicine;
Systematic review

Abstract *Objective:* To systematically evaluate the effectiveness and safety of Chinese herbal medicine (CHM) plus nucleotide analogues (NAs) for treating compensated HBV-related cirrhosis, the early stage of cirrhosis.
Methods: PubMed, Cochrane library, China Network Knowledge Infrastructure Database (CNKI), Chinese Scientific Journals Database (VIP), Wan Fang Database and Sino-Med Database were searched. Randomized controlled trials (RCTs) and quasi-RCTs comparing NAs and NAs plus CHM therapy on patients with compensated HBV-related cirrhosis were included. Two reviewers independently extracted information and assessed the methodological quality of the trials. Different CHM herbal formulas used in the trials were considered. Primary meta-analysis was conducted when there were at least two trials comparing the same CHM formula.
Results: Forty-five trials comprising 3497 participants were included. The quality of most of the trials was moderate or low. Twenty-six herbal formulations were identified. A meta-analysis was conducted for compound Biejia Ruangan (FFBJ), Dahuang Zhechong (DHZC), and Fuzheng Huayu (FZHY). The results of the subgroup analysis showed a beneficial effect of FFBJ plus entecavir (ETV), and DHZC plus adefovir dipivoxil (ADV) on hyaluronic acid (HA); FFBJ plus ADV on laminin (LN); and FZHY plus ADV on HA, LN, and precollagen type III (PC-III). The results from other studies suggested significant benefits of CHM plus NAs compared with NAs alone, except those on albumin (ALB). None of the trials evaluated the quality of life

* Corresponding authors.
E-mail addresses: tianfangwang2000@163.com (T. Wang), yutong_fei@163.com (Y. Fei).
Peer review under responsibility of Beijing University of Chinese Medicine.

http://dx.doi.org/10.1016/j.jtcms.2014.12.006

or reported severe adverse events.
Conclusions: A positive effect was found for FFBJ plus ETV, DHZC plus ADV, and FZHY plus ADV on HA; FZHY plus ADV and FFBJ plus ADV on LN; and FZHY plus ADV on PCIII compared with the effects of NAs used alone.

Introduction

Cirrhosis is regarded as the result of chronic liver disease and is characterized by the replacement of liver tissue with fibrous scar tissue as well as the histological development of regenerative nodules leading to portal hypertension and end-stage liver disease.[1] Approximately 350 million people worldwide are chronically infected with hepatitis B virus (HBV)[2] and $>$ 82% of the Chinese population suffering from cirrhosis have had a history of HBV infection.[3] The natural incidence of cirrhosis ranges from 8% to 20% at 5 years in patients with hepatitis B e antigen (HBeAg)—positive chronic hepatitis B.[4,5] The 5-year cumulative incidence of hepatic cell carcinoma is ~20% in patients with compensated cirrhosis[6,7] and their 5-year survival rate is ~80%—85%.[8]

The mainstream medications for treating compensated HBV-related cirrhosis are interferons (IFNs) and nucleotide analogues (NAs). However, the practice guidelines of the American Association for the Study of Liver Diseases suggest that patients with compensated cirrhosis should receive long-term treatment with NAs because of the risk of hepatic decompensation associated with IFN-α-related flares of hepatitis,[9] even if IFNs can reduce liver fibrosis by lowering hepatic stellate cells (HSC)[5] and even though NAs have some side effects, such as fatigue, anorexia, an initial influenza-like illness, and even serious renal toxicity.[9,10]

Together with the use of antiviral drugs, many traditional Chinese physicians and those who integrate Chinese and western medicine have combined CHM with NAs in treating cirrhosis,[11—13] especially in treating compensated HBV-related cirrhosis.[14—16] However, there has been no relevant systematic review to assess the effectiveness and safety of CHM plus NAs in treating the disease.

Methods

Search strategy

PubMed, Cochrane Library, and four major Chinese electronic databases (China Network Knowledge Infrastructure Database, CNKI; Chinese Scientific Journals Database, VIP; Wan Fang Database and Sino-Med Database) were searched from their inception to October 9, 2014. Unpublished postgraduate theses listed in Chinese databases and trials in Clinicaltrials (www.clinicaltrials.gov) and the Chinese clinical trial registry (www.chictr.org/cn/) were also searched.

The search terms were used individually or in combination, and comprised "cirrhosis", "hepatitis B", "compensat*", "traditional Chinese medicine", "TCM", "Chinese herbal medicine", "herbal medicine", "herb*", and "random*" in English or Chinese. We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, or in progress).

Selection criteria

The inclusion criteria for the study were as follows:

1) RCTs and quasi-RCTs, regardless of blinding.
2) Participants with compensated HBV-related cirrhosis as diagnosed by validated diagnostic criteria.
3) Therapy with CHM plus NAs versus NAs alone. Conventional treatments were allowed as long as they were used in both groups. Neither group who used other complementary and alternative medicine treatments, such as acupuncture or moxibustion were allowed regardless of the method of administration. There were no restrictions on frequency, dose, or duration.
4) The primary outcome was liver biopsy. The secondary outcomes were liver fibrosis biomarkers [hyaluronic acid (HA), laminin (LN), precollagen type III (PC-III), and type-IV collagen (IV-C)], liver function biomarkers [alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), and total bilirubin (TBiL)], liver stiffness, quality of life, and adverse events.

Study selection and data extraction

Two reviewers (TTL, XYW) independently assessed all potentially relevant studies for inclusion using a screening criteria table. The reasons for excluding studies were stated and any disagreements were resolved through discussion. The data on basic participant information, interventions, duration, outcomes, and adverse events were extracted.

Trial quality assessment

Two reviewers (TTL, XLX) independently assessed the risk of bias according to the following seven points: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome report, and other bias. For each of these components, a judgment was made regarding the risk of bias as being high, low, or

unclear based on guidance from the "Cochrane Handbook for Systematic Reviews of Interventions".[17] Any disagreements were resolved through discussion.

Data analyses

Data were analyzed using RevMan 5.3 (Cochrane Informatics & Knowledge Management Department, London, UK). Dichotomous data were expressed as a risk ratio (RR) and continuous outcomes as the weighted mean difference (WMD) and included their 95% confidence intervals (CI). If the data required were not reported, the corresponding author was contacted for the absent data. Because of the unavoidable intervention heterogeneity, the random effects model was used to pool data in this systematic review when $I^2 < 75\%$. When $I^2 \geq 75\%$, data were not pooled. Subgroup analysis was conducted under the following conditions:

1) studies used the same CHM and NAs;
2) the estimated effects of trials with low risk and high risk of bias needed to be compared.

Results

Forty-five trials with 3497 participants were included in the study. All trials were conducted in China and published in Chinese. The detailed characteristics of the included trials are provided in Table 1. The mean sample size was 78 (range: 38–320) and the mean duration of treatment was 10 months (range: 3.0–24 months). CHM was classified into 26 major types according to the formula composition, and three major types of NAs, lamivudine (LAM), entecavir (ETV), and adefovir dipivoxil (ADV), were identified. Apart from these NAs, conventional drugs used were glutathione, polyene phosphatidylcholine, creatinine, and vitamins. There were four comparisons made among the drugs as follows: CHM plus LAM versus LAM,[20,23,31,32,41,42] CHM plus ETV versus ETV,[14,16,25,27,33,35,36,41,45,47,48,50,52,54–56] CHM plus ADV versus ADV,[15,18,19,21,22,24,26,28–30,34,37,38,40,44,46,49,51,58,59] and CHM plus multiple NAs versus multiple NAs.[43,53,57] Fig. 1 shows the search process.

Assessment of methodological quality

Among the 45 trials, six[25,26,45,55–57] used the random number table, one[33] used SPSS 20.0 (IBM Corporation, Armonk, NY, USA), and eight[20–22,27,34,35,49,53] generated the random sequence using a rule based on date of admission or on hospital or clinic record number. The remaining trials simply mentioned "randomization" and did not provide the specific method of random sequence generation. Two trials[33,57] used sequentially numbered opaque sealed envelopes; 12 trials[18,20–22,25,27,34,35,45,49,53,55] used non-random allocation schedule. The methods of concealment used in the remaining trials were not described. None of the trials reported any information on drop-out cases; however, according to the number of participants randomized and analyzed, 12 trials[14,15,23,25,27,31,39,41,46,47,50,55] had no missing outcome data. The study protocols were not available. Apart from the three trials[41,43,56] that reported a liver biopsy, none mentioned biopsy or any other information on the quality of life, clinical symptoms, or the progression of the disease (Fig. 2 and Additional File 1).

Effects of the interventions

Liver biopsy

Three studies reported the results of a liver biopsy.[41,43,56] Data could not be pooled because different measures were used to assess the outcomes. From Table 2, we find that the intervention group treated with the combined treatment showed better effects in terms of controlling inflammation, Knodell HAI score, and HSC counts.

Biomarkers for liver fibrosis

As shown in Table 3, three trials[23,31,41] with 282 participants compared CHM plus LAM with LAM alone and all showed that the combined treatment significantly reduced the levels of HA, LN, PC-III, and IV-C.

Fourteen trials[14,16,25,27,33,35,36,45,47,48,50,54–56] compared CHM plus ETV with ETV alone and showed that the combined treatment reduced the levels of HA,[16,25,27,33,35,45,47,54,56] LN,[14,16,25,27,33,35,45,48,54–56] and IV-C.[14,25,35,36,45,48,50,54,56] Ten trials[14,16,25,27,36,48,50,54–56] suggested that the combined treatment had obvious advantages in reducing the levels of PC-III. Two trials showed no statistical differences in reducing the levels of HA,[36,50] LN,[36,47] or IV-C[33,47] and four trials[33,35,45,47] showed no statistical difference in reducing the levels of PC-III. For IV-C, one trial[27] suggested that ETV alone was better than ETV plus CHM. The meta-analysis was done because the three studies[14,48,55] used the same CHM and NAs and the results supported that FFBJ plus ETV had a significant advantage in reducing the levels of HA (WMD −30.76; 95% CI, −39.04, −22.47; $P < .00001$; $I^2 = 9\%$) (Fig. 3 and Table 4).

As shown in Figs. 4–6 and Table 5, 16 trials[15,19,21,22,24,26,30,34,37,38,40,46,49,51,58,59] that compared CHM plus ADV versus ADV alone were included in this study. Eleven trials suggested that there was no statistical difference between the two groups in reducing HA,[37] LN,[38,40,51] PC-III,[15,24,38,46,58] or IV-C.[22,34,51] One trial[21] showed that ADV alone could be more effective in reducing the levels of LN. A meta-analysis was performed according to CHM classifications and the methodological quality of the trials. DHZC plus ADV versus ADV alone[19,51] (pooled WMD −22.11; 95% CI, −42.99, −1.24; $P = .04$; $I^2 = 0\%$) and FZHY plus ADV versus ADV alone[30,34] (pooled WMD-89.03; 95% CI, −112.18, −65.88; $P < .00001$; $I^2 = 33\%$) suggested that the combined treatment had more advantages in reducing HA. FFBJ plus ADV versus ADV alone[15,22,24,46] (pooled WMD-12.22; 95% CI, −19.84, −4.61; $P = .002$; $I^2 = 0\%$) and FZHY plus ADV versus ADV alone[30,34] (pooled WMD-20.54; 95% CI, −35.62, −5.47; $P = .008$; $I^2 = 56\%$) showed that the combined treatment was better than ADV alone in reducing the levels of LN. FZHY plus ADV versus ADV alone[30,34] (pooled WMD-37.76; 95% CI, −47.47, −28.06; $P < .00001$; $I^2 = 0\%$) showed that the combined treatment had an obvious advantage in reducing the levels of PC-III. As for comparing CHM plus multiple NAs versus multiple NAs alone, two trials[43,53] showed that the combined treatment could reduce the levels of HA, PC-III, and IV-C, while one trial[53] gave the same results as the above,

Table 1 Characteristics of the included trials.

Study ID	Sample size (I:C)	Age	Intervention group; Disease course (years)	Control group; Disease course (years)	Course of treatment (months)	Outcomes	Adverse events
Dai, 2011[14]	68 (34:34)	Avg 46.2 (32—66)	FFBJ+ETV NR	ETV NR	12	ALT/AST/TBiL; HA/LN/IV-C/PCIII	NR
Dai, 2013[15]	66 (33:33)	NR	FFBJ+ADV NR	ADV NR	12	ALT/AST/TBiL; HA/LN/IV-C/PCIII	N
Ding, 2012[16]	50 (26:24)	NR	BSHY+ETV NR	ETV NR	3	ALT/AST; HA/LN/PCIII	N
Fu, 2008[18]	68 (37:31)	NR	HLSG+ADV NR	ADV NR	6	ALT/AST/TBiL	NR
Gui, 2012[19]	71 (37:34)	NR	DHZC+ADV NR	ADV NR	6	ALT/AST/TBiL; HA/LN/PCIII	NR
Hao, 2008[20]	55 (28:27)	Avg 41.4 ± 6.2 (30—48)	DHZC+LAM 2—10	LAM 3—10	12	ALT/ALB/TBiL	Y, Stools frequency increased
Hu, 2011[21]	70 (35:35)	Avg 42.4 ± 10.2 (18—56)	HLSG+ADV NR	ADV NR	12	HA/LN/IV-C	Y, nausea and vomiting caused by ADV
Hu, 2012[22]	50 (25:25)	Avg 46 (30—62)	FFBJ+ADV NR	ADV NR	12	ALT/ALB/TBiL; HA/LN/IV-C/PCIII	NR
HuZB, 2011[23]	120 (60:60)	42.5	FFBJ+LAM 11.5	LAM 11.8	6	ALT/AST/TBiL; HA/LN/IV-C/PCIII	NR
Jin, 2010[24]	60 (30:30)	25—59	FFBJ+ADV 2—20	ADV 3—23	12	ALT/AST; HA/LN/IV-C/PCIII	N
Lang, 2013[25]	152 (76:76)	Avg 46 ± 10 (41—59)	FFDS+ETV 2—17	ETV 3—16	6	ALT/AST/TBiL; HA/LN/IV-C/PCIII	NR
Li, 2012[26]	48 (25:23)	Avg 40.53 ± 6.54 (21—62)	YiGJ+ADV Avg 6.8 ± 2.32 (0.5—18)	ADV Avg 6.92 ± 2.45 (0.5—18)	12	HA/LN/IV-C/PCIII	NR
Li, 2013[27]	65 (33:32)	46.75 ± 9.83	XiXS+ETV 9.31 ± 7.85	ETV 10.12 ± 7.37	6	HA/LN/IV-C/PCIII	NR
Liao, 2009[28]	53 (28:25)	28—49	FFBJ+ADV 2—9	ADV 3—10	12	ALT/ALB/TBiL	NR
Liu, 2013[29]	128 (66:62)	31—58	DHZC+ADV 2—15	ADV 2—13a	12	ALT/AST/ALB/TBiL	Y, diarrhea and epigastric discomfort
LiuMD, 2013[30]	80 (40:40)	31.2 ± 9.7	FZHY+ADV 5.7 ± 2.6	ADV 5.6 ± 2.5	6.5	ALT/AST/TBiL; HA/LN/IV-C/PCIII	NR
LiuYJ, 2013[31]	97 (52:45)	NR	QiGa+LAM NR	LAM NR	12	ALT/AST/ALB/TBiL; HA/LN/IV-C/PCIII	NR
Lu, 2007[32]	53 (28:25)	26—47	QiGa+LAM 2—10	LAM 3—10	12	ALT/ALB/TBiL	NR
Lv, 2012[33]	40 (20:20)	43.7 ± 8.52	RJHY+ETV 9.24 ± 2.38	ETV 9.84 ± 1.75	6	ALT/AST/ALB/TBiL; HA/LN/IV-C/PCIII	N
Pan, 2009[34]	93 (48:45)	41 ± 1.58	FZHY+ADV 11 ± 1.2	ADV 11.3 ± 2.3	6	HA/LN/IV-C/PCIII	NR
Pei, 2012[35]	58 (29:29)	43.3 ± 11.7	FZHY+ETV NR	ETV NR	12	ALT/AST/ALB/TBiL; HA/LN/IV-C/PCIII	Y, Mild epigastric discomfort
Peng, 2014[36]	50 (25:25)	42.3 ± 11.3	GLXD+ETV NR	ETV NR	12	ALT/AST/ALB/TBiL; HA/LN/IV-C/PCIII	NR

Table 1 (*continued*)

Study ID	Sample size (I:C)	Age	Intervention group; Disease course (years)	Control group; Disease course (years)	Course of treatment (months)	Outcomes	Adverse events
Qian, 2011[37]	89 (46:43)	25–61	YQHYRJ+ADV 8–19	ADV 9–20	18	ALT/AST; HA/LN/IV-C/PCIII	NR
Qin, 2012[38]	60 (30:30)	25–59	FZRG+ADV 2–20	ADV 3–23	12	ALT/AST/TBiL; HA/LN/IV-C/PCIII	N
Shen, 2014[39]	72 (42:30)	Avg 39.2 (19–58)	LWWL+ETV Avg 9.8 (4–16)	ETV Avg 10.1 (4–15)	12	ALT/AST	N
Si, 2009[40]	58 (28:30)	34–56	RuGa+ADV 2–9	ADV 3–7	12	ALT/ALB/TBiL; HA/LN/IV-C/PCIII	Y, Upper abdominal discomfort, nausea and vomiting caused by ADV
Song, 2008[41]	65 (33:32)	Avg 42.5 ± 12.6 (28–51)	Marine Capsules +LAM NR	LAM NR	12	Liver biopsy; ALT/ALB/TBiL; HA/LN/IV-C/PCIII	N
Su, 2009[42]	53 (28:25)	26–47	HLSG+LAM 2–10	LAM 3–10	12	ALT/ALB/TBiL	NR
Wang, 2009[43]	97 (49:48)	NR	ALHX+LAM +ADV+ETV NR	LAM +ADV+ETV NR	24	Liver biopsy; ALT/ALB/TBiL; HA/LN/IV-C/PCIII	NR
Wang, 2010[44]	132 (67:65)	24–51	DHZC+ADV 2–12	ADV 2–11	12	ALT/AST/ALB/TBiL	NR
Wang, 2012[45]	60 (30:30)	NR	YQPXXQ+ETV NR	ETV NR	6	HA/LN/IV-C/PCIII; liver stiffness	NR
Wei, 2010[46]	44 (22:22)	NR	FFBJ+ADV NR	ADV NR	12	ALT/AST/TBiL; HA/LN/IV-C/PCIII	NR
Xiao, 2014[47]	60 (30:30)	28–70	RGWJ+ETV NR	ETV NR	6	HA/LN/IV-C/PCIII	N
Xie, 2010[46]	80 (40:40)	Avg 41.8 (24–60)	HYYG+ADV Avg 12.5 (5–18)	ADV Avg 12.1 (4–17)	6	ALT/AST/TBiL; HA/LN/IV-C	NR
Yan, 2014[48]	56 (29:27)	Avg 44.5 (27–64)	FFBJ+ETV Avg 16.9 (3–32)	ETV Avg 17.8 (2–30)	12	ALT/ALB/TBiL; HA/LN/IV-C/PCIII; liver stiffness	N
Yang, 2011[49]	63 (33:30)	NR	JWXY+ADV NR	ADV NR	12	ALT/AST/TBiL; HA/LN/PCIII	NR
Yuan, 2013[50]	50 (25:25)	NR	SGJPHX+ETV NR	ETV NR	6	ALT/AST/TBiL; HA/PCIII/IV-C	N
Zhang, 2008[51]	45 (23:22)	Avg 35.6 (28–47)	DHZC+ADV NR	ADV NR	12	HA/LN/IV-C/PCIII	Y, mild diarrhea, headache
Zhang, 2012[52]	220 (112:108)	Avg 41.46 (30–48)	FFBJ+ETV 2–10	ETV 3–10	6	ALT/ALB/TBiL	NR
Zhang, 2013[53]	60 (30:30)	Avg 45 (29–61)	DaYe+LAM+ADV Avg 4.5 (0.5–10)	LAM+ADV Avg 4.6 (0.5–11)	12	HA/LN/IV-C/PCIII	NR
ZhangFM, 2012[54]	38 (20:18)	43 ± 8	CHM Decoction +ETV 3.1 ± 2.3	ETV 2.9 ± 2	6	ALT/AST/ALB/TBiL; HA/LN/IV-C/PCIII	N
ZhangW, 2013[55]	64 (32:32)	Avg 45.5 (42–70)	FFBJ+ETV Avg 15(10–18)	ETV Avg 16 (8–20)	6	ALT/AST/TBiL; HA/LN/PCIII	NR

(*continued on next page*)

Table 1 (*continued*)

Study ID	Sample size (I:C)	Age	Intervention group; Disease course (years)	Control group; Disease course (years)	Course of treatment (months)	Outcomes	Adverse events
Zheng, 2012[56]	320 (160:160)	17–56	RGHX+ETV 0.6–22	ETV 0.6–24	12	Liver biopsy; ALT/ALB/TBiL; HA/LN/IV-C/PCIII	N
Zhou, 2013[57]	56 (28:28)	40.96 ± 9.53	FFBJ+ADV/ETV /ADV+ETV 5.12 ± 2.23	ADV/ETV /ADV+ETV 5.37 ± 2.08	3	Liver stiffness	NR
Zhu, 2012[58]	60 (30:30)	35.2 ± 9.6	WJBF+DHZC +ADV 4.5	ADV 5.2	12	ALT/AST/TBiL; HA/LN/IV-C/PCIII	NR

I: Intervention group; G: Control group; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; TBiL: Total bilirubin; HA: Hyaluronic acid; LN: Laminin; PC-III: Precollagen type III; IV-C: Type IV collagen; LAM: Lamivudine; ADV: Adefovir dipivoxil; ETV: Entecavir; FFBJ: Compound Biejia Ruangan Tablets; BSHY: Bushen Huayu Decoction; HLSG: Heluo Shugan Capsule; DHZC: Dahuangzhechong Pill; FFDS: Compound Danshen Dripping Pills; YiGJ: Yiguanjian Decoction; XiXS: Xiaoxian Pulvis; FZHY: Fuzheng Huayu Capsule; QiGa: Qianggan Capsule; RJHY: Ruanjian Huayu Decoction; GLXD: Ganlu Xiaodu Pill; YQHYRJ: Yiqi Huayu Ruanjian Decoction; FZRG: Fuzheng Ruangan Pill; LWWL: Liuwei Wuling tablets; RuGa: Ruangan pill; ALHX: Anluo Huaxian Pill; YQPXXQ: Yiqi Poxue Xingqi Decoction; RGWJ: Ruangan Wenjing Paste; HYYG: Huayu Yigan Capsule; JWXY: Jiawei Xiaoyao Capsule; SGJPHX: Shugan Jianpi Huoxue Decoction; DaYe: Danye Capsule; RGHX: Ruangan Huaxian Capsule; WJBF: Wuji Baifen Wan; NR: No report; N: No; Y: Yes.

and the other showed no statistical difference in reducing the levels of LN.

Biomarkers for liver function

Thirty-three trials reported the outcome of identifying liver function biomarkers. Compared to NAs alone, ALT,[16,18–20,22,25,28,31–33,35,36,39–43,46,48–50,52,54–56,58,59] AST,[16,18,19,25,29,31,33,35,37,39,44,49,50,54,55,58,59] and TBiL[18,20,22,28,29,31,32,35,36,41,42,44,48–50,52,54–56,58,59] could be significantly reduced by treating with CHM plus NAs; however, for ALB, only seven trials[31,40,41,43,52,54,56] suggested that the combined treatment was better than NAs alone, while the others showed no statistical difference between the two groups in increasing the levels of ALB (Additional File 2).

Liver stiffness

Three trials[45,48,57] reported liver stiffness. Although these trials used different drugs and treatment courses, a meta-analysis was done to determine the difference between CHM plus NAs and NAs alone in decreasing liver stiffness, which is a new index by which to assess liver fibrosis in patients with cirrhosis. Finally, the results showed that the combined group had more significantly statistical differences than the group with NA treatment alone (random, pooled WMD −2.85; 95% CI, −3.91, −1.79; $P < .00001$; $I^2 = 0\%$).

Quality of life

None of the trials reported on the quality of life of the participants.

Adverse events

Six trials[20,21,29,35,40,51] described the adverse effects of the treatments in detail. Among them, two[21,40] trials reported upper abdominal discomfort, nausea, and vomiting and suggested that they were related to NAs, and four[20,29,35,51] trials reported mild epigastric discomfort, mild diarrhea, and headache. Twelve trials[15,16,24,33,38,39,41,47,48,50,54,56] reported no adverse effects; 27 trials[14,18,19,22,23,25–28,30–32,34,36,37,42–46,49,52,53,55,57–59] had no information on adverse events.

Publication bias

We did not conduct funnel plots because there were less than 10 studies in each and every meta-analysis.

Discussion

Summary of the main results

From the results of the meta-analysis, FFBJ plus ETV, DHZC plus ADV, and FZHY plus ADV were more effective on HA than ETV or ADV alone. FZHY plus ADV and FFBJ plus ADV had obvious advantages in reducing LN. FZHY plus ADV was superior to ADV alone on PC-III. The results from the other single trials showed potential benefits of CHM plus LAM, CHM plus ETV, CHM plus ADV, and CHM plus multiple NAs to improving HA, LN, PC-III, IV-C, ALT, AST, TBiL, and liver stiffness; improvement in ALB level was the only exception. The quality of life of the participants and severe adverse events were not reported.

Quality of the evidence

There is most likely performance bias because none of the 45 trials included those of blinded participants and personnel. Considering this, all trials were defined as "high risk of bias". For detection bias, the overall quality of the 45 included trials was defined as "low risk of bias" because

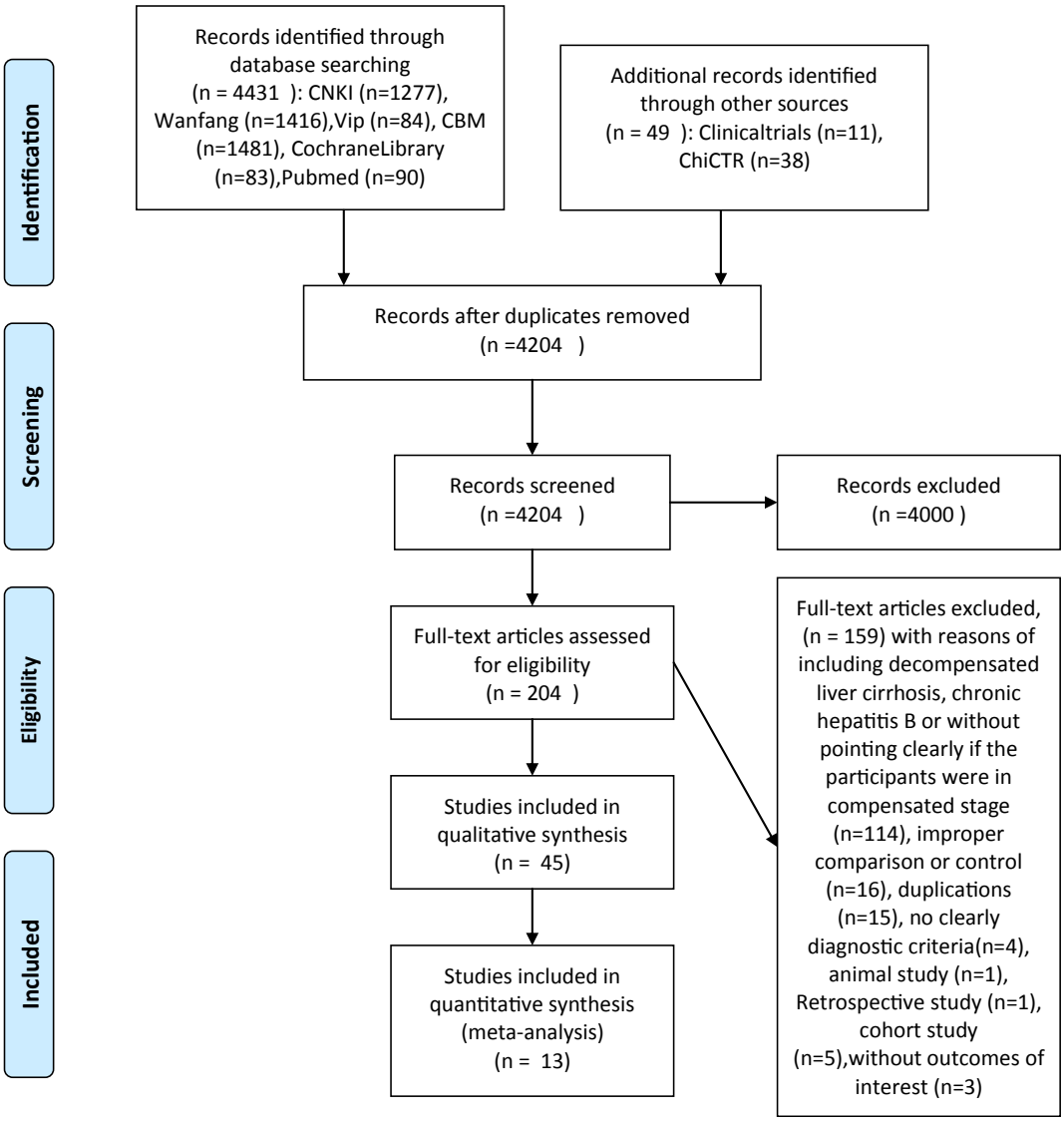

Figure 1 Procedure for searching, screening, and selecting literature with the numbers of articles at each stage.
Notes: CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific Journal Database; CBM, Chinese Biomedical database; ChiCTR, Chinese Clinical Trial Registry.

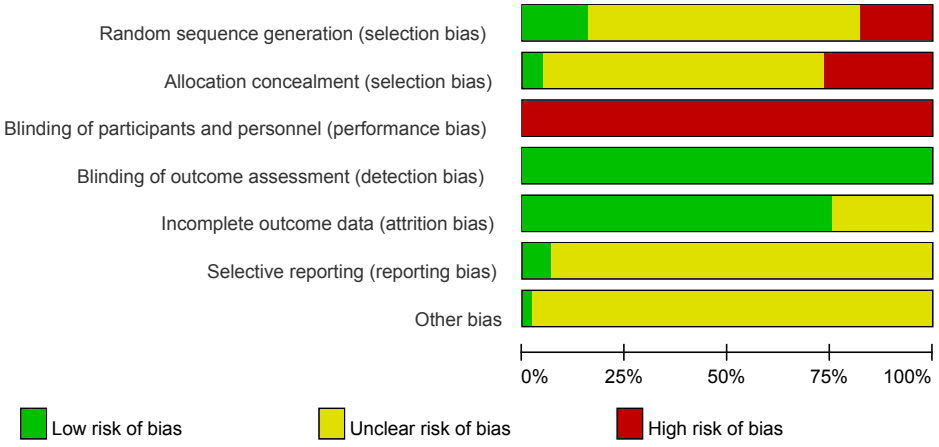

Figure 2 Risk of bias graph.
Author judgments on each risk-of-bias item presented as percentages across all included studies.

Table 2 Qualitative synthesis of liver biopsy.

Study ID	Group	n	Results	RR (95%CI) or MD (95%CI)
Song, 2008[41]	Intervention group	10	G3(n = 0), G2(n = 1), G1(n = 4), G0(n = 5)	4.00 [0.55, 29.10]
	Control group	10	G3(n = 0), G2(n = 2), G1(n = 6), G0(n = 2)	
Wang, 2009[43]	Intervention group	14	Knodell HAI reduced 3–4 scores;	
	Control group	12	Knodell HAI reduced 2 scores;	
Zheng, 2012[56]	Intervention group	56	Activated HSC 16.95 ± 11.59	−3.53 [−8.51, 1.45]
	Control group	44	Activated HSC 20.48 ± 13.35	
	Intervention group	56	Apoptotic activated HSC 10.78 ± 5.72	2.66 [0.95, 4.37]
	Control group	44	Apoptotic activated HSC 8.12 ± 2.78	

G: Grade; HAI: Histological activity index; HSC: Hepatic stellate cell.

Table 3 The original data and mean difference of the comparison, CHM plus LAM versus LAM, examining the effect on HA, LN, PC-III, IV-C.

Study or Subgroup	CHM+LAM			LAM			Mean Difference [95%CI]
	Mean	SD	Total	Mean	SD	Total	
HA							
HuZB, 2011[23]	115.6	79.5	60	198.7	78.6	60	−83.10 [−111.39, −54.81]
LiuYJ, 2013[31]	185.3	21.35	52	245.6	39.78	45	−60.30 [−73.29, −47.31]
Song, 2008[41]	112.8	46.5	33	186.5	56.5	32	−73.70 [−98.90, −48.50]
LN							
HuZB, 2011[23]	86.6	33.1	60	159.3	32.3	60	−72.70 [−84.40, −61.00]
LiuYJ, 2013[31]	109.9	23.86	52	158	29.78	45	−48.10 [−58.95, −37.25]
Song, 2008[41]	107.5	45.7	33	142.7	65.6	32	−35.20 [−62.76, −7.64]
PC-III							
HuZB, 2011[23]	110.6	28.8	60	186.3	30.5	60	−75.70 [−86.31, −65.09]
LiuYJ, 2013[31]	110.5	12.94	52	167.4	18.97	45	−56.90 [−63.46, −50.34]
Song, 2008[41]	105.6	53.8	33	163	76.6	32	−57.40 [−89.67, −25.13]
IV-C							
HuZB, 2011[23]	72.5	25.8	60	165.7	26.6	60	−93.20 [−102.58, −83.82]
LiuYJ, 2013[31]	75.39	29.67	52	112.5	19.78	45	−37.11 [−47.03, −27.19]
Song, 2008[41]	86.5	45.7	33	126.7	56.6	32	−40.20 [−65.25, −15.15]

HA: Hyaluronic acid; LN: Laminin; PC-III: Precollagen type III; IV-C: Type IV collagen; LAM: Lamivudine; CHM: Chinese herbal medicine.

the outcome measurement was not likely to be influenced by lack of blinding.

Potential bias/limitations

First, potential selection bias was unavoidable because the pertinent English databases, such as AMED and EMBASE, were not searched, all of the included trials were retrieved from Chinese literature, and some negative previously unpublished studies might have been included. Second, we did not conduct meta-analysis in which different types of CHM formulations were combined as one general intervention. The results of the meta-analysis for the general picture of CHM treatment were not available from our review. In addition, most included trials had the following issues that contributed to the limited methodological quality:

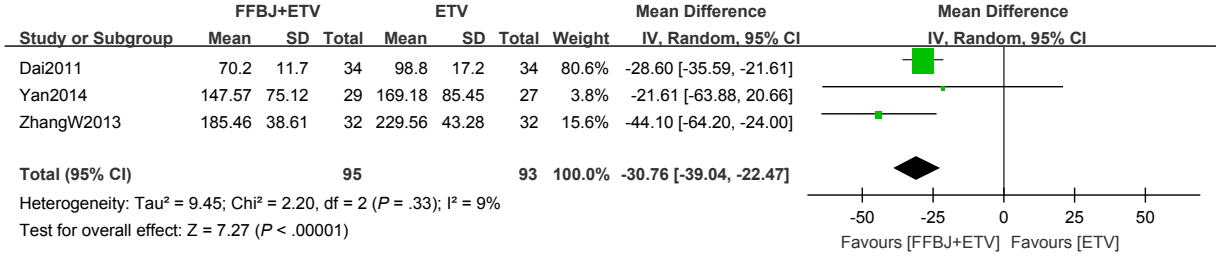

Figure 3 The effect on HA of FFBJ plus ETV with ETV.
Notes: HA, hyaluronic acid; ETV, entecavir; FFBJ, compound Biejia Ruangan tablets.

Table 4 The original data and mean difference of the comparison, CHM plus ETV versus ETV, examining the effect on HA, LN, PC-III, IV-C.

Study or Subgroup	CHM+ETV			CHM+ETV			Mean difference 95%CI
	Mean	SD	Total	Mean	SD	Total	
HA							
Ding, 2012[16]	117.3	21.5	26	153.6	23.2	24	−36.30 [−48.73, −23.87]
Lang, 2013[25]	73	23	76	221	59	76	−148.00 [−162.24, −133.76]
Li, 2013[27]	73.67	23.46	33	221.49	59.42	32	−147.82 [−169.91, −125.73]
Lv, 2012[33]	97.6	27.26	20	139.34	60.94	20	−41.74 [−71.00, −12.48]
Pei, 2012[35]	138.5	34.5	29	239.7	52.8	29	−101.20 [−124.16, −78.24]
Peng, 2014[36]	115.27	62.81	25	144.5	82.9	25	−29.23 [−70.00, 11.54]
Wang, 2012[45]	104.54	89.15	30	165.55	105.21	30	−61.01 [−110.36, −11.66]
Xiao, 2014[47]	296.5	92.4	30	356.3	112.5	30	−59.80 [−111.89, −7.71]
Yuan, 2013[50]	145.16	44.48	25	152.8	39.09	25	−7.64 [−30.85, 15.57]
ZhangFM, 2012[54]	85.61	27.43	20	125.45	20.78	18	−39.84 [−55.22, −24.46]
Zheng, 2012[56]	108.48	26.8	160	123.22	27.9	160	−14.74 [−20.73, −8.75]
LN							
Dai, 2011[14]	39.6	7.1	34	53.8	11.2	34	−14.20 [−18.66, −9.74]
Ding, 2012[16]	98.6	24.7	26	139.6	26.4	24	−41.00 [−55.20, −26.80]
Lang, 2013[25]	91	24	76	119	32	76	−28.00 [−36.99, −19.01]
Li, 2013[27]	91.25	24.37	33	119.43	32.87	32	−28.18 [−42.28, −14.08]
Lv, 2012[33]	35.64	6.53	20	63.92	5.49	20	−28.28 [−32.02, −24.54]
Pei, 2012[35]	39.8	7.3	29	53.9	10.6	29	−14.10 [−18.78, −9.42]
Peng, 2014[36]	79.6	45.58	25	110.43	64.3	25	−30.83 [−61.73, 0.07]
Wang, 2012[45]	87.47	59.53	30	142.8	16.9	30	−55.33 [−77.47, −33.19]
Xiao, 2014[47]	135.5	56.3	30	145.8	74.2	30	−10.30 [−43.63, 23.03]
Yan, 2014[48]	102.87	43.45	29	136.98	33.24	27	−34.11 [−54.29, −13.93]
ZhangFM, 2012[54]	103.31	31.52	20	146.42	21.35	18	−43.11 [−60.08, −26.14]
ZhangW, 2013[55]	116.51	28.74	32	153.45	29.25	32	−36.94 [−51.15, −22.73]
Zheng, 2012[56]	94.33	31.58	160	109.83	35.5	160	−15.50 [−22.86, −8.14]
PC-III							
Dai, 2011[14]	8.8	1.2	34	10.8	2.5	34	−2.00 [−2.93, −1.07]
Ding, 2012[16]	85.6	20.1	26	128	22.5	24	−42.40 [−54.26, −30.54]
Lang, 2013[25]	105	53	76	186	64	76	−81.00 [−99.68, −62.32]
Li, 2013[27]	104.92	53.48	33	186.39	64.33	32	−81.47 [−110.28, −52.66]
Lv, 2012[33]	33.44	13.8	20	39.64	10.11	20	−6.20 [−13.70, 1.30]
Pei, 2012[35]	169.3	58.3	29	193.6	47.6	29	−24.30 [−51.69, 3.09]
Peng, 2014[36]	63.5	23.1	25	97.3	24.5	25	−33.80 [−47.00, −20.60]
Wang, 2012[45]	7.26	3.52	30	9.26	5.19	30	−2.00 [−4.24, 0.24]
Xiao, 2014[47]	132.3	76.5	30	156.2	87.6	30	−23.90 [−65.52, 17.72]
Yan, 2014[48]	92.56	47.32	29	141.63	65.58	27	−49.07 [−79.21, −18.93]
Yuan, 2013[50]	97.38	52.01	25	160.38	63.15	25	−63.00 [−95.07, −30.93]
ZhangFM, 2012[54]	101.19	32.35	20	150.25	32.63	18	−49.06 [−69.75, −28.37]
ZhangW, 2013[55]	106.27	31.73	32	151.23	35.61	32	−44.96 [−61.49, −28.43]
Zheng, 2012[56]	115.47	32.26	160	131.73	29.61	160	−16.26 [−23.05, −9.47]
IV-C							
Dai, 2011[14]	82	11.9	34	115.9	18.3	34	−33.90 [−41.24, −26.56]
Lang, 2013[25]	63	14	76	140	24	76	−77.00 [−83.25, −70.75]
Li, 2013[27]	63.29	14.52	33	39.54	23.671	32	23.75 [14.17, 33.33]
Lv, 2012[33]	85.39	20.3	20	105.49	44.75	20	−20.10 [−41.64, 1.44]
Pei, 2012[35]	78.9	13.6	29	96.4	2.7	29	−17.50 [−22.55, −12.45]
Peng, 2014[36]	49.5	25.2	25	69.7	30.1	25	−20.20 [−35.59, −4.81]
Wang, 2012[45]	92.45	67.58	30	142.24	33.05	30	−49.79 [−76.71, −22.87]
Xiao, 2014[47]	78.5	26.2	30	83.5	35.3	30	−5.00 [−20.73, 10.73]
Yan, 2014[48]	47.36	22.41	29	62.38	23.19	27	−15.02 [−26.98, −3.06]
Yuan, 2013[50]	118.95	36	25	170.93	64.91	25	−51.98 [−81.08, −22.88]
ZhangFM, 2012[54]	67.52	25.16	20	106.24	25.56	18	−38.72 [−54.88, −22.56]
Zheng, 2012[56]	80.47	27.34	160	95.19	28.44	160	−14.72 [−20.83, −8.61]

HA: Hyaluronic acid; LN: Laminin; PC-III: Precollagen type III; IV-C: Type IV collagen; ETV: Entecavir; CHM: Chinese herbal medicine.

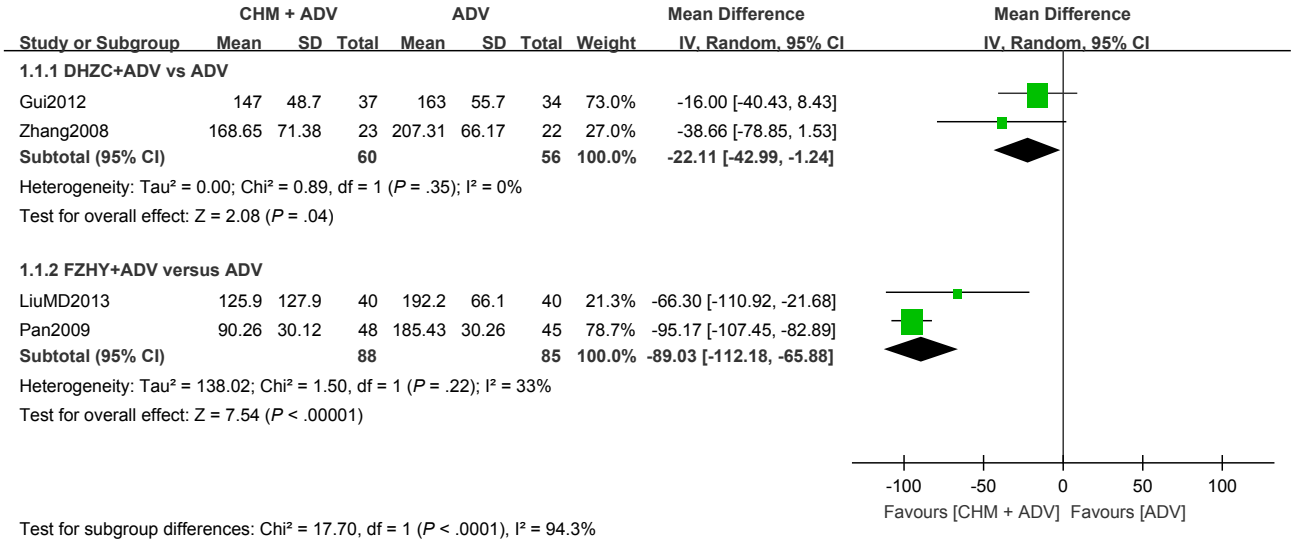

Figure 4 The effect on HA of DHZC/FZHY plus ADV with ADV.
Notes: CHM, Chinese herbal medicine; ADV, adefovir dipivoxil; HA, hyaluronic acid; DHZC, Da Huang ZHe Chong pill; FZHY, Fuzheng Huayu capsule.

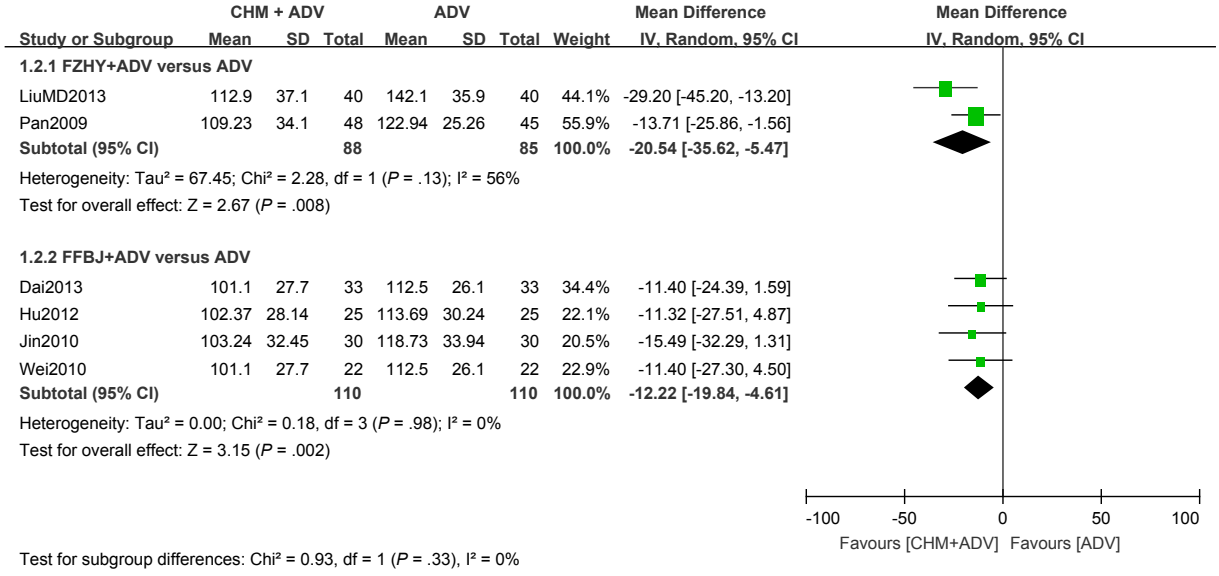

Figure 5 The effect on LN of FZHY/FFBJ plus ADV with ADV.
Notes: CHM, Chinese herbal medicine; ADV, adefovir dipivoxil; LN, laminin; FZHY, Fuzheng Huayu capsule; FFBJ, compound Biejia Ruangan tablets.

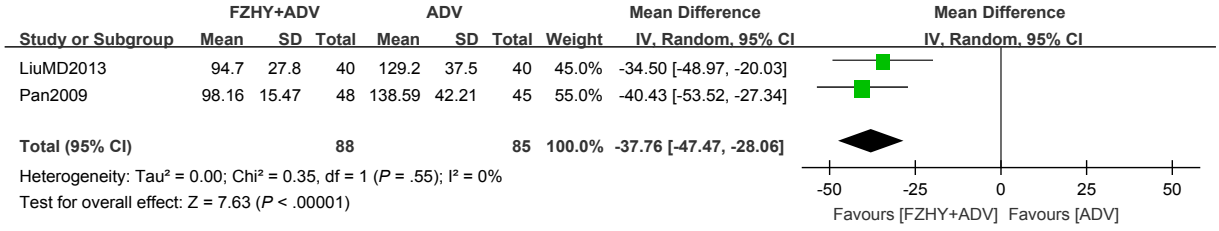

Figure 6 The effect on PC-III of FZHY plus ADV with ADV.
Notes: CHM, Chinese herbal medicine; ADV, adefovir dipivoxil; PC-III, precollagen type III; FZHY, Fuzheng Huayu capsule.

Table 5 The original data and mean difference of the comparison, CHM plus ADV versus ADV, examining the effect on HA, LN, PC-III, IV-C.

Study or Subgroup	CHM+ADV			CHM+ADV			Mean difference 95%CI
	Mean	SD	Total	Mean	SD	Total	
HA							
Hu, 2011[21]	81.2	13.4	35	121.23	24.41	35	−40.03 [−49.26, −30.80]
Li, 2012[26]	173.52	32.51	25	227.51	59.32	23	−53.99 [−81.38, −26.60]
Qian, 2011[37]	115.27	66.81	46	144.5	87.89	43	−29.23 [−61.83, 3.37]
Qin, 2012[38]	138.56	48.95	30	178.61	64.41	30	−40.05 [−69.00, −11.10]
Si, 2009[40]	189.4	34.5	28	281.8	16.7	30	−92.40 [−106.51, −78.29]
Xie, 2010[59]	128	53	40	242	130	40	−114.00 [−157.51, −70.49]
Yang, 2011[49]	142.8	43.4	33	180.8	49.7	30	−38.00 [−61.14, −14.86]
Zhu, 2012[58]	138.56	48.9	30	178.62	64.41	30	−40.06 [−69.00, −11.12]
LN							
Gui, 2012[19]	72	25.2	37	98	27.3	34	−26.00 [−38.25, −13.75]
Hu, 2011[21]	78.32	16.5	35	68.62	17.02	35	9.70 [1.85, 17.55]
Li, 2012[26]	124.92	19.73	25	165.52	58.41	23	−40.60 [−65.69, −15.51]
Qian, 2011[37]	76.56	45.58	46	106.43	67.31	43	−29.87 [−53.92, −5.82]
Qin, 2012[38]	103.24	32.45	30	118.73	33.94	30	−15.49 [−32.29, 1.31]
Si, 2009[40]	162.8	36.4	28	150.3	17.8	30	12.50 [−2.41, 27.41]
Xie, 2010[59]	166	34	40	228	52	40	−62.00 [−81.25, −42.75]
Yang, 2011[49]	68.9	19.2	33	88.3	23.2	30	−19.40 [−29.98, −8.82]
Zhang, 2008[51]	109.39	30.47	23	112.45	28.19	22	−3.06 [−20.20, 14.08]
Zhu2012[58]	104.4	39.6	30	142.3	50.4	30	−37.90 [−60.84, −14.96]
PC-III							
Dai, 2013[15]	129.4	46.6	33	130.5	50.1	33	−1.10 [−24.44, 22.24]
Gui, 2012[19]	144	23.4	37	167	27.2	34	−23.00 [−34.85, −11.15]
Hu, 2012[22]	108.44	13.66	25	159.31	22.19	25	−50.87 [−61.08, −40.66]
Jin, 2010[24]	104.53	32.86	30	119.79	32.86	30	−15.26 [−31.89, 1.37]
Li, 2012[26]	90.11	50.13	25	182.43	59.71	23	−92.32 [−123.65, −60.99]
Qian, 2011[37]	63.75	23.18	46	97.31	24.8	43	−33.56 [−43.55, −23.57]
Qin, 2012[38]	104.53	32.86	30	119.79	32.86	30	−15.26 [−31.89, 1.37]
Si, 2009[40]	171.2	38.2	28	192.1	37.8	30	−20.90 [−40.47, −1.33]
Wei, 2010[46]	129.4	46.6	22	130.5	50.1	22	−1.10 [−29.69, 27.49]
Yang, 2011[49]	142.5	25.1	33	160.7	24.8	30	−18.20 [−30.53, −5.87]
Zhang, 2008[51]	109.9	13.67	23	161.68	23.23	22	−51.78 [−62.98, −40.58]
Zhu, 2012[58]	90.3	46.4	30	89.2	55.6	30	1.10 [−24.81, 27.01]
IV-C							
Dai, 2013[15]	98.8	24.3	33	174.9	38.6	33	−76.10 [−91.66, −60.54]
Hu, 2011[21]	57.25	18.5	35	80.53	37.04	35	−23.28 [−37.00, −9.56]
Hu, 2012[22]	97.96	72.49	25	126.31	60.35	25	−28.35 [−65.32, 8.62]
Jin, 2010[24]	57.25	18.5	35	80.53	37.04	35	−23.28 [−37.00, −9.56]
Li, 2012[26]	79.4	54.41	25	124.41	62.22	23	−45.01 [−78.20, −11.82]
LiuMD, 2013[30]	77.9	34.9	40	101.9	35.9	40	−24.00 [−39.52, −8.48]
Pan, 2009[34]	85.27	18.36	48	83.21	20.18	45	2.06 [−5.80, 9.92]
Qian, 2011[37]	47.45	31.12	46	69.27	30.51	43	−21.82 [−34.63, −9.01]
Qin, 2012[38]	102.76	35.72	30	132.76	42.89	30	−30.00 [−49.97, −10.03]
Si, 2009[40]	145.2	26.7	28	196.7	32	30	−51.50 [−66.63, −36.37]
Wei, 2010[46]	98.8	24.3	22	174.9	38.6	22	−76.10 [−95.16, −57.04]
Xie, 2010[59]	74	38	40	130	75	40	−56.00 [−82.06, −29.94]
Zhang, 2008[51]	98.97	75.68	23	128.67	61.68	22	−29.70 [−69.96, 10.56]
Zhu, 2012[58]	112.9	65.4	30	157.4	99.8	30	−44.50 [−87.20, −1.80]

HA: Hyaluronic acid; LN, Laminin; PC-III: Precollagen type III; IV-C: Type IV collagen; ADV: Adefovir dipivoxil; CHM: Chinese herbal medicine.

1) did not report the methods of random sequence generation and allocation concealment;
2) did not report the information on withdrawal/dropout during the trials or, if reported, the detailed reasons were not reported;
3) did not report registration information.

Comparison with previous systematic reviews

One related systematic review[60] was found. Its objective was to review the effectiveness of CHM on treating liver fibrosis patients suffering from fatty liver, schistosomiasis japonica, or chronic hepatitis. The measures of intervention included CHM, western medicine, placebo, or no intervention. Twenty-three RCTs were included and the results led to the conclusion that apart from being compared with a placebo, these therapies significantly improved the levels of HA, LN, PC-III, and IV-C when compared with western medicine alone, CHM alone, or CHM plus western medicine. Compared to this study, we included trials in which participants suffered from compensated HBV-related cirrhosis, the intervention group was treated by CHM plus NAs, and the control group was treated with NAs alone. In addition to the liver fibrosis biomarkers ALT and AST, TBiL, ALB, liver biopsy, and liver stiffness were included in our outcomes. Finally, we found that CHM plus NAs (LAM, ETV, ADV, or multiple NAs) could improve the levels of HA, LN, PC-III, IV-C, ALT, AST, TBiL, and liver stiffness; however, none of the treatments affected ALB.

Implications for clinical practice and future studies

First, for participants with compensated HBV-related cirrhosis, CHM as a conventional treatment combined with NAs (LAM, ETV, ADV, or multiple NAs) appeared to be more beneficial in controlling liver fibrosis because it changed the result of the liver biopsy; reduced the levels of HA, LN, PC-III, IV-C, ALT, AST, TBiL; and decreased liver stiffness; however, ALB levels were not improved. ALB is synthesized by liver cells and the reason that combined therapy had little effect on ALB could be related to the number and quality of the trials or that the differences in ALB levels might not be obvious between the two methods. This should be heeded in clinical practice.

Second, substantial evidence related to the quality of life, incidence of decompensated cirrhosis or liver cancer, or traditional Chinese medicine (TCM) syndrome were lacking. As for TCM syndrome, the basic principle for treating diseases in TCM is syndrome differentiation; however, only seven studies[18,29,30,33,35,50,54] referred to syndrome differentiation among the trials included.

Third, none of the trials included could provide access to information on their registered protocols. Thus, to retrieve their valid conclusions, we encourage the authors to register their study protocols before trial implementation. We believe that future studies, especially on TCM clinical research, should be designed based on the theory of TCM. TCM syndrome or symptoms should be part of the outcomes, even the primary outcomes.

Conflicts of interest

None of the authors declared any conflicts of interest associated with this study.

Authors' contributions

Conceived and designed the experiments: TTL, TFW, YTF. Study selection and data extraction: TTL, XYW. Trial quality assessment: TTL, XLX. Data analysis: TTL, YTF. Paper was drafted by: TTL.

Acknowledgments

The current work was partially supported by the National Basic Research Program of China (973 Program, no. 2011CB505105).

We thank Guoyan Yang from National Institute of Complementary Medicine, University of Western Medicine for her suggestions in data synthesis.

Abbreviations

CHB	Chronic hepatitis B
HBV	Hepatitis B virus
HCC	Hepatic cell carcinoma
IFN	Interferon
NAs	Nucleotide analogues
HSC	Hepatic stellate cells
CNKI	China Network Knowledge Infrastructure Database
VIP	Chinese Scientific Journals Database
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALB	Albumin
TBiL	Total bilirubin
HA	Hyaluronic acid
LN	Laminin
PC-III	Precollagen type III
IV-C	Type IV collagen
RR	Risk ratio
CI	Confidence interval
WMD	Weighted mean difference
LAM	Lamivudine
ADV	Adefovir dipivoxil
ETV	Entecavir
FFBJ	Compound Biejia Ruangan Tablets
BSHY	Bushen Huayu Decoction
HLSG	Heluo Shugan Capsule
DHZC	Dahuang Zhechong Pill
FFDS	Compound Danshen Dripping Pills
YiGJ	Yiguanjian Decoction
XiXS	Xiaoxian Pulvis
FZHY	Fuzheng Huayu Capsule
QiGa	Qianggan Capsule
RJHY	Ruanjian Huayu Decoction
GLXD	Ganlu Xiaodu Pill
YQHYRJ	Yiqi Huayu Ruanjian Decoction
FZRG	Fuzheng Ruangan Pill
LWWL	Liuwei Wuling tablets
RuGa	Ruangan pill

ALHX	Anluo Huaxian Pill
YQPXXQ	Yiqi Poxue Xingqi Decoction
RGWJ	Ruangan Wenjing Paste
HYYG	Huayu Yigan Capsule
JWXY	Jiawei Xiaoyao Capsule
SGJPHX	Shugan Jianpi Huoxue Decoction
DaYe	Danye Capsule
RGHX	Ruangan Huaxian Capsule
WJBF	Wuji Baifeng Wan
NR	No report

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jtcms.2014.12.006.

References

1. Xue SR, Li RS. *Essentials of Internal Medicine* (English). Hangzhou: Zhejiang University Press; 2010:245.
2. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat*. 2004;11:97—107.
3. Chen Y, Gong ZJ. *Advances in Diagnosis and Treatment of Liver Diseases*. Wuhan: Hubei Science & Technology Press; 2008:99.
4. Fattovich G. Natural history and prognosis of hepatitis B. *Semin Liver Dis*. 2003;23:47—58.
5. Sherlock S, Dooley J. *Disease of the Liver and Biliary System. Translated by Niu JQ*. Tianjin: Tianjin Science and Technology Translation Publishing Company; 2013:336.
6. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol*. 2008;48:335—352.
7. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127:S35—S50.
8. Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. *Semin Liver Dis*. 2006;26:142—152.
9. Lok Anna SF, McMahon Brian J. Chronic hepatitis B: update 2009. *Hepatology*. 2009:25—26.
10. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med*. 2003;348:800—807.
11. Yu HJ, Luo F, Zhang FS. Observation of Fuzheng Huayu Capsule in the treatment of active cirrhosis of liver fibrosis. *Strait Pharm J*. 2010;22:133—134.
12. Lu HY, Zeng Y, Wu CH, et al. The clinical study of Fufang Biejia Ruangan tablet on chronic hepatitis B patients complicated with early hepatocirrhosis. *J Gastroenterol Hepatol*. 2007;16:605.
13. Zhou GD, Li WS, Zhao JM, et al. Clinical pathological study on the mechanism of effect of Fufangbiejiaruanganpian in treatment of liver fibrosis. *Med J Chin People's Lib Army*. 2004;29:563—564.
14. Dai WW, Feng YH, Chang JB, Qiu J. The clinical observation of treatment of hepatitis B cirrhosis using entecavir combined Fufang Biejia Ruangan tablets. *Gansu J TCM*. 2011;24:28—29.
15. Dai SM. Clinical observation of early HBV-related cirrhosis treated by adefovir dipivoxil combined with compound Biejia Ruangan Tablets. *J Huaihai Med*. 2013;31:350—351.
16. Ding E, Chen LY. Clinical observations on the treatment of chronic hepatitis B and decompensated cirrhosis by entecavir dispersible tablets and Bushenhuayu prescriptions. *Hubei J Tradit Chin Med*. 2012;34:8—9.
17. Higgins JPT, Altman DG, Sterne JAC. Chapter8: assessing risk of bias in included studies. In: The Cochrane Collaboration, Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 5.1.0th ed.; 2011 (updated March2011) www.cochrane-handbook.org. Accessed September 30, 2014.
18. Fu XW. Clinical observation of 37 cases of early HBV-related cirrhosis treated by Heluo Shugan tablets combined with adefovir dipivoxil. *Chin J Basic Med Tradit Chin Med*. 2008;14:932—933.
19. Gui YP, Wu XF, Wo C. Clinical observation on compensated HBV-related cirrhosis treated by Dahuang Zhechong pill combined with adefovir dipivoxil. In: *The Third Combination of Traditional Chinese and Western Medicine Liver Disease Conference and Combination of Traditional Chinese and Western Medicine Liver Disease New Development Study Class Proceedings, Jiangxi Province*. 2012:89—91.
20. Hao AQ. 28 cases of HBV-related cirrhosis treated by Lamivudine combined with Dahuang Zhechong pill. *Clin Focus*. 2008;23:1197—1198.
21. Hu X. Clinical observation on early active HBV-related cirrhosis treated by Heluo Shugan capsule combined with adefovir dipivoxil. *Heilongjiang Med J*. 2011;24:110—112.
22. Hu RW, Gao YH. Observation on curative effect of Fu fang Bie Jia Ruan Gan Pian with adefovir dipivoxil tablets on hepatitis B cirrhosis. *J Shanxi Med Coll Contin Educ*. 2012;22:17—19.
23. Hu ZB, Lv JL, Qiu H, Zhang RZ, Mao DW. Clinical observation of 60 cases on compensated cirrhosis treated by traditional Chinese medicine combined with western medicine. *Chin Med Mod Distance Educ China*. 2011;9:55—56.
24. Jin H. Clinical observation of 60 cases on compensated HBV-related cirrhosis treated by compound Biejia Ruangan tablets combined with adefovir dipivoxil. *Chin J Integr Tradit West Med Liver Dis*. 2010;20:365—366.
25. Lang XL, Wu LH, Jia CH. Clinical observation on compensated HBV-related cirrhosis treated by entecavir combined with compound Danshen dripping pills. *Hebei Med J*. 2013;45:38—39.
26. Li AZ, Feng XN, Zhang CJ, Dou ZZ. Clinical observation of 25 cases on early HBV-related cirrhosis treated by Yiguanjian decoction combined with adefovir dipivoxil. *Tradit Chin Med Res*. 2012;25:28—30.
27. Li ZG. Clinical observation of 33 cases on compensated HBV-related cirrhosis treated by Xiaoxian pulvis combined with entecavir. *China's Naturop*. 2013;21:61—62.
28. Liao ZX, Huang YH. Clinical observation on early HBV-related cirrhosis treated by adefovir dipivoxil combined with compound Biejia Ruangan pill. *Hubei J Tradit Chin Med*. 2009;31:31—32.
29. Liu XY, Liu JS. Clinical observation of 66 cases on Dahuang Zhechong pill combined with western medicine in treating compensated HBV-related cirrhosis. *Henan Tradit Chin Med*. 2013;33:56—57.
30. Liu MD. Clinical efficacy of righting blood capsule combined with adefovir ester in the treatment of HBVDNA negative compensatory phase cirrhosis. *J Clin Med Pract*. 2013;17:77—79.
31. Liu YJ. Clinical analysis on early cirrhosis treated by nucleoside drugs combined with traditional Chinese medicine. *World Latest Med Inf*. 2013;13:201—202.
32. Lu DB. Clinical observation of 28 cases on early HBV-related cirrhosis treated by Lamivudine combined with Qianggan capsule. *Chin J Integr Tradit West Med Liver Dis*. 2007;17:240—241.
33. Lv Z, Chen XR. Clinical study on oral administration of "Ruanjian Huayu Decoction" with external application of "Jiedu Xiaopi Powder" in treating early HBV-related cirrhosis of blood-stasis obstruction. *Shanghai J Tradit Chin Med*. 2012;46:30—33.

34. Pan JZ, Hu ZH, Huang YQ. Clinical observation of 48 cases on chronic HBV-related cirrhosis treated by adefovir dipivoxil combined with Fuzheng Huayu capsule. *Jiangxi J Tradit Chin Med*. 2009;40:22—23.
35. Pei JH. Clinical observation on combined entecavir with "Fuzheng Huayu Capsule" for hepatitis B liver cirrhosis. *Shanghai J Tradit Chin Med*. 2012;46:41—43.
36. Peng L, Xie HE. Clinical observation of 25 cases on compensated HBV-related cirrhosis treated by Ganlu Xiaodu pill combined with entecavir. *Chin Med Mod Distance Educ China*. 2014;12:53—54.
37. Qian HQ. The effect of adefovir dipivoxil combined with Yiqi Huayu Ruanjian decoction on relevant indexes of HBV-related cirrhosis. *Chin J Tradit Med Sci Technol*. 2011;18:146.
38. Qin JX, Wang L. Clinical observation of 60 cases on compensated HBV-related cirrhosis treated by Fuzheng Ruangan pill combined with adefovir dipivoxil. *Chin J Ethnomedicine Ethnopharmacy*. 2012;24:120—121.
39. Shen CM, Zhang BL, Li Y. Clinical observation of HBV-related cirrhosis treated by Liuwei Wuling tablets combined with entecavir. *China Med Eng*. 2014;22:60.
40. Si MZ, Fu CG, Xu JB. Clinical observation on early HBV-related cirrhosis treated by Ruangan pill combined with adefovir dipivoxil. *Hubei J Tradit Chin Med*. 2009;31:17—18.
41. Song J, Zhong HM, Zhu SM, et al. Therapeutic efficacy of oxymatrine combined with lamivudine in treatment of early cirrhosis after chronic hepatitis B: an analysis of 33 cases. *World Chin J Dig*. 2008;16:1124—1127.
42. Su TB, Zhang DH, Fu JP. The observation of Heluo Shugan capsule on early HBV-related cirrhosis in improving liver function and spleen shrinkage. *Clin J Tradit Chin Med*. 2009;21:300—301.
43. Wang J, Hu CL, Peng H. Clinical observation of 49 cases on early HBV-related cirrhosis treated by nucleoside analogues drugs combined with Anluo Huaxian pill. *Her Med*. 2009;28:1167—1168.
44. Wang QT. Clinical observation of 67 cases on early cirrhosis treated by adefovir dipivoxil combined with Dahuangzhechong pill. *China Pract Med*. 2010;5:143—144.
45. Wang ZX, Wang LF, Wang Y, et al. Effects of Qi-invigorating and blood-breaking medicine on hepatic fibrosis in patients with compensated cirrhosis of chronic hepatitis B. *Chin J Integr Tradit West Med Liver Dis*. 2012;22:5—7.
46. Wei ML. Clinical observation of adefovir dipivoxil capsules combined with compound Biejia Ruangan tablets in treating early cirrhosis. *Pract J Card Cereb Pneumal Vasc Dis*. 2010;18:1273—1274.
47. Xiao WS, Chen Q, Zhou XL. Clinical observation of Ruangan Wenjing paste in treating compensated HBV-related cirrhosis. *China's Rural Health*. 2014:189—190.
48. Yan XH. Clinical observation on entecavir combined with compound Biejia Ruangan tablets in treating decompensated liver cirrhosis of hepatitis B. *West J Tradit Chin Med*. 2014;27:84—86.
49. Yang JH, Xie XK. Clinical observation of adefovir dipivoxil combined with Jiawei Xiaoyao capsule in treating compensated HBV-related cirrhosis. *Mod Tradit Chin Med*. 2011;31:15—16.
50. Yuan Q. *Efficay Shugan Jian Pi Huoxue Method Joint ETV Treatment of Hepatitis B Live Cirrhosis* [master's thesis]. Nanjing University of Chinese Medicine; 2013:11—29.
51. Zhang BJ, Dou Q. Adefovir dipivoxil combined with Dahuangzhechong pill in the treatment of cirrhosis secondary to hepatic B. *J Emerg Tradit Chin Med*. 2008;17:611—612.
52. Zhang DH. Clinical observation of 112 cases of HBV-related cirrhosis treated by entecavir combined with compound Biejia Ruangan tablets. *Chin Community Dr*. 2012;14:83.
53. Zhang L, Zhan BL, Li Q. Study on Danye capsule combined with Lamivudine and adefovir dipivoxil in treatment of hepatitis B cirrhosis. *China Mod Med*. 2013;20:95—96, 98.
54. Zhang FM, Dong MG, Hu QC. Clinical observation on the effect of the method of regulating spleen qi in treatment of chronic hepatitis B liver cirrhosis in compensatory period. *Chin Foreign Med Res*. 2012;10:7—8.
55. Zhang W. Clinical observation of early HBV-related cirrhosis treated by entecavir combined with compound Biejia Ruangan tablets. *J Pract Tradit Chin Med*. 2013;29:1037—1038.
56. Zheng GZ, Wang J, Liu JH. Clinical observation of 160 cases of HBV-related cirrhosis treated by Ruangan Huaxian capsule combined with entecavir. *Tradit Chin Med Res*. 2012;25:34—37.
57. Zhou C, Zhang N, Wu X, Sun YQ, Liu HH, Luo SQ. Influence of compound Biejia Ruangan tablets on liver stiffness of patients with hepatitis B induced cirrhosis. *J New Chin Med*. 2013;45:38—39.
58. Zhu LJ. Clinical observation on compensated HBV-related cirrhosis treated by traditional Chinese medicine combined with western medicine. *Henan Tradit Chin Med*. 2012;32:1147—1148.
59. Xie HJ, Ye ZW. Clinical observation of 40 cases on compensated HBV-related cirrhosis treated by adefovir dipivoxil combined with Huayu Yigan capsule. *Chin J Integr Tradit West Med Liver Dis*. 2010;20:246—247.
60. Cheung F, Feng YB, Wang N, Yuen MF, Yao T, Wong Vivian Taam. Effectiveness of Chinese herbal medicine in treating liver fibrosis: a systematic review and meta-analysis of randomized controlled trials. *Chin Med*. 2012;7:5.