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Interferon plus Chinese herbs are associated with higher sustained virological response than interferon alone in chronic Hepatitis C: A meta-analysis of randomised trials

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ABSTRACT

Background/aims: Traditional Chinese herbal therapies are widely used for the treatment of chronic hepatitis C (CHC) in Asia. The aim of this study was to perform a meta-analysis of randomised controlled trials (RCTs) comparing interferon therapies with Chinese herbal therapies and/or interferon plus Chinese herb therapies for the treatment of CHC.

Methods: The Cochrane Central Register of Controlled Trials, Medline, Science Citation Index, EMBASE, China National Knowledge Infrastructure, Wanfang Database and China Biomedical Database were searched to identify RCTs that evaluated the virological response to interferon therapies, Chinese herbal therapies and interferon plus Chinese herb therapies in CHC patients. We statistically combined data using a random-effect meta-analysis according to the intention-to-treat principle.

Results: The literature search yielded 770 studies, and 26 RCTs comprising 1905 patients matched the selection criteria. Overall, the sustained virological response (SVR) was significantly higher in patients treated with interferon plus Chinese herbs than in patients treated with interferon alone (49% vs 33%, relative risk, 1.52; 95% confidence interval: 1.23–1.89; $p < 0.05$). Combined therapies of interferon plus Chinese herb therapies were also superior to interferon therapies alone in achieving the end-of-treatment viral response (ETVR), and resulted in fewer relapses, fewer adverse events and more rapid alanine transaminase normalisation. Interferon therapies achieved higher ETVR than Chinese herbal therapies, but they yielded a similar SVR.

Conclusions: The current evidence suggests that combined therapies of interferon plus Chinese herbs yielded a higher SVR, and resulted in fewer relapses and fewer adverse events than interferon therapies.

1. Introduction

Hepatitis C virus (HCV) has become the most important cause of chronic hepatitis and end-stage liver disease worldwide (Lauer and Walker, 2001). Peginterferon plus ribavirin has been used as the standard treatment for chronic hepatitis C (CHC) patients, with relatively high sustained virological response (SVR) (Fried et al., 2002; Ghany et al., 2009; Hadziyannis et al., 2004; Manns et al., 2001). However, this regimen is followed by frequent adverse effects and a large numbers of patients are not suitable candidates for treatment for a variety of reasons (Falck-Ytter et al., 2002; Liang et al., 2000). Complementary and alternative medicine (CAM) is therefore popular in the West. In 2002, 62% of adults surveyed in the United States (US) reported using CAM (Barnes et al., 2004), whereas 42% used CAM in 1997 (Eisenberg et al., 1998). The widespread use of CAM is emphasised among people with chronic diseases (Saydah and Eberhardt, 2006). As one of the main components of CAM, Chinese medicine has been used as a front line medicine and has been widely utilised in medical systems, especially in China and some areas of Asia. Adverse reactions to Chinese herbs are extremely rare and are negligible when compared to those commonly produced by pharmaceutical drugs. In recent years, a number of clinical trials have compared the efficacy and adverse effects of interferon therapies with Chinese herbal therapies alone or interferon plus Chinese herb therapies for the treatment of CHC. However, these

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studies, published in Chinese, cannot be accessed by non-Chinese speaking scientists. The aim of this study was to assess the evidence from these randomised clinical trials (RCTs) for the efficacy of interferon therapies compared with Chinese herbal therapies alone or interferon plus Chinese herbal therapies.

2. Materials and methods

The meta-analysis protocol used in this study was designed by Dr. Zhao Sihai.

2.1. Eligibility criteria

The inclusion criteria were the following: (i) the included RCT studies were designed to compare the therapeutic effects of interferon therapies with Chinese herbal therapies or interferon plus Chinese herb therapies in CHC patients; patients co-infected with HBV and/or HIV were excluded, (ii) patients were treated for at least 24 weeks, and (iii) the publications could be written in any language. Reports of duplicated studies were excluded by examining the author list, parent institution, sample size and results.

2.2. Outcome measure

The primary outcome was the SVR, and other measures included the end-of-treatment viral response (ETVR), relapse rate, alanine transaminase (ALT) normalisation and occurrence of adverse events. The SVR was defined as the lack of detectable HCV RNA in serum by a sensitive test six months after treatment cessation. ETVR was defined as undetectable HCV RNA at the end of treatment. Relapse was defined as undetectable HCV RNA at the end of treatment but detectable HCV RNA 24 weeks post treatment.

2.3. Information sources and searches

A search of the literature was conducted for studies that reported the therapeutic effects of interferon with or without Chinese herbal medicine therapies in CHC patients. The Cochrane Central Register of Controlled Trials, Medline, Science Citation Index, EMBASE, China National Knowledge Infrastructure, Wanfang Database and China Biomedical Database were searched to identify RCTs published in the field of antiviral therapy for CHC. The keywords used in literature searches included the following: chronic hepatitis C, hepatitis C virus, HCV, Chinese herbal therapy, Chinese traditional medicine, Chinese traditional drugs, herbs, interferon, peginterferon, PEGylated interferon, treatment and trial.

2.4. Study selection and data collection

Two authors (Enqi Liu and Sihai Zhao) independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. We extracted the data from the included trials independently for quantitative analyses, and any disagreement was subsequently resolved by discussion. The quantitative data included the sample size, the pre-treatment patient characteristics, including the age range and gender; the type of interferon (α-2a, α-2b or 1b); the doses of Chinese herbs, interferon and ribavirin; SVRs; ETVRs; ALT normalisation and adverse effects.

2.5. Assessment of study quality

Two authors (Yafeng Li and Kena Wei) independently assessed the quality of the included studies according to the descriptions provided by the authors of the included trials. The methodological quality of the trials was assessed based on adequate sequence generation, allocation concealment, blinding, management of incomplete outcome data, and early stopping for benefit (Kjaergard et al., 2001; Moher et al., 1998; Schulz et al., 1995).

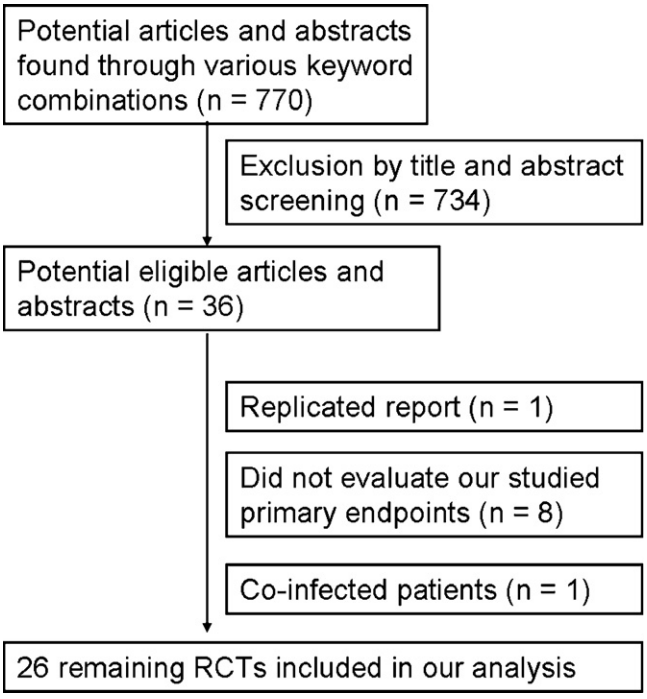

Fig. 1. Analysis of the search results.

2.6. Synthesis of results

In this meta-analysis, we used a random effect model because of the anticipated variability among trials with regard to patient populations (DerSimonian and Laird, 1986; Egger et al., 1997). The measure of association used in this meta-analysis was the relative risk (RR) with a 95% confidence interval (CI). The summary RR with the 95% CI was calculated by the Revman 5.0 software using the random or fixed effect model (REVIEW MANAGER Version 5.0 for Windows; The Cochrane Collaboration, Oxford, UK). A statistically significant result was assumed when the 95% CI did not include one.

Heterogeneity was explored using a Chi-square test, and the quantity of heterogeneity was measured using the I^2 statistic. When patients were discontinued, the data were analysed according to the intention-to-treat principle. Patients who did not achieve the selected endpoints were considered to have failed therapy; the total number of patients was used as the denominator.

2.7. Sensitivity analyses

To assess whether the trial quality could influence the results of our meta-analysis, a sensitivity analysis was performed by including only the trials that included a majority of adult patients with CHC.

3. Results

3.1. Literature search

Fig. 1 shows the results of the study screen. The literature search yielded 770 studies, 26 of which matched the selection criteria (25 in Chinese and 1 in English) (Chang and Li, 2009; Chen et al., 2005; Han, 2005; Hong et al., 2004; Jiang, 2007; Jing et al., 2002; Kong

Table 1
Characteristics of the trials included in the meta-analysis.

References	Sample size (treatment/control)	Gender (male/female)	Age	Duration (weeks)	Follow-up (weeks)
Chinese herbal therapies (treatment) vs interferon therapies (control)					
Kong et al. (2008)	40/25	37/28	36.5 (20–65)	48	24
Li et al. (2007)	28/20	20/23[a]	46.8	48	24
Wang and Chai (2009)	82/80	–/–	50 (18–82)	48	0
Han (2005)	8/8	–/–	3–13	24	24
Hong et al. (2004)	40/30	46/24	33.7 (20–56)	24	24
Jiang (2007)	15/45	–/–	42 (20–40)	24	24
Li et al. (2006)	20/20	21/19	37.9 (18–60)	24	0
Li and Chen (2005)	38/30	54/14	40.8 (18–69)	24	24
Niu et al. (2008)	20/20	23/17	37.1 (18–56)	24	0
Sun et al. (2003)	127/40	142/25	38.9 (18–60)	24	24
Xiao et al. (2005)	32/20	26/26	37.6 (19–57)	24	24
Xu et al. (2001)	12/22	18/16	4.7	24	0
Yin et al. (2002)	32/62	70/24	31.6	26	26
Zhou et al. (2001)	140/52	123/69	38.9 (20–56)	24	24
Chinese herbs plus interferon therapies (treatment) vs interferon therapies (Control)					
Meng et al. (2010)	24/24	29/19	38.5 (19–62)	48	24
Wang and Chai (2009)	84/80	–/–	50 (18–82)	48	0
Wu et al. (2009)	25/18	29/14	37.7 (18–65)	48	24
Zhang (2009)	30/30	22/38	18–65	48	0
Chang and Li (2009)	32/33	44/16[a]	37.7	24	24
Chen et al. (2005)	40/36	–/–	–/–	24	24
Han (2005)	9/8	–/–	3–13	24	24
Jiang (2007)	45/45	–/–	42 (20–40)	24	24
Jing et al. (2002)	18/15	26/7	31.7 (18–48)	24	0
Lin (2006)	21/19	24/16	18–63	24	24
Liu et al. (2008)	34/37	48/23	34.9 (26–51)	24	0
Ma (2008)	23/23	27/19	32(17–56)	24	24
Motoo et al. (2005)	10/13	17/6	51.1 (26–74)	24	24
Wu and Sun (2003)	30/26	–/–	–/–	24	24
Xu et al. (2001)	26/22	30/18	4.5	24	0
Yin et al. (2004)	36/36	–/–	16–63	24	0

[a] Five patients were discontinued and data not shown.

et al., 2008; Li et al., 2006; Li et al., 2007; Li and Chen, 2005; Lin, 2006; Liu et al., 2008; Ma, 2008; Meng et al., 2010; Motoo et al., 2005; Niu et al., 2008; Sun et al., 2003; Wang and Chai, 2009; Wu and Sun, 2003; Wu et al., 2009; Xiao et al., 2005; Xu et al., 2001; Yin et al., 2002; Yin et al., 2004; Zhang, 2009; Zhou et al., 2001). Twenty-two studies were designed as two group RCTs; ten trials compared Chinese herbal therapies with interferon therapies and twelve trials compared interferon plus Chinese herb therapies with interferon therapies. Four studies were designed as three group RCTs, and they compared the efficacy of Chinese herbal therapies, interferon plus Chinese herbal therapies and interferon therapies. The combined CHC patient total was 1905. There was unanimous agreement between the two authors regarding the selection of relevant articles (Sihai Zhao and Enqi Liu).

3.2. Patient characteristics and study quality

All RCTs included were published as full-length articles. The patients included in the twenty-six trials were randomly assigned to accept Chinese herbal therapies, interferon plus Chinese herb therapies or interferon therapies alone. Of the 1905 patients, 634 patients had therapy with Chinese herbs, 487 patients had therapy with interferon plus Chinese herbs, and 784 patients had therapy with interferon alone. All studies were single-centre trials. The baseline characteristics of the twenty-six included trials are summarised in Tables 1 and 2. Information on the methodological quality was incomplete in the majority of eligible RCTs; only the Chang and Li's (2009) study reported sequence generation and incomplete outcome data. The methodological quality of all eligible RCTs was not high.

3.3. Comparison of Chinese herbal therapies and interferon therapies

The combined ETVRs were lower for patients treated with Chinese herbs compared to the patients treated with interferon (37% vs 47%; RR: 0.73; 95% CI: 0.59–0.91; $p < 0.05$), the combined SVRs were similar between the two types of therapies (33% vs 33%; RR: 1.00; 95% CI: 0.81–1.23; $p = 0.99$) (Fig. 2). The relapse rates were also lower in patients treated with Chinese herbs compared to the patients treated with interferon (19% vs 36%; RR: 0.54; 95% CI: 0.39–0.76; $p < 0.05$) (Fig. 3). We also assessed ALT normalisation for patients treated with Chinese herbs or interferon. The results showed that ALT normalisation at the end of treatment for patients taking Chinese herbal therapies was similar to that of those taking interferon therapies (56% vs 56%; RR: 1.00; 95% CI: 0.82–1.23; $p = 0.98$), but that, at follow-up, more patients treated with Chinese herbs maintained normal ALT levels than patients treated with interferon (51% vs 38%; RR: 1.31; 95% CI: 0.99–1.74; $p = 0.06$) (Fig. 4). In this meta-analysis for SVR, relapse and ALT normalisation, there was no apparent heterogeneity, but for ETVR, the p value was 0.04, and the heterogeneity was $I^2 = 48\%$ (Fig. 2).

3.4. Comparison of interferon plus Chinese herbal therapies and interferon therapies alone

In this study, the combined therapies of interferon plus Chinese herbs were superior to interferon therapies alone. Patients treated with interferon plus Chinese herbs achieved higher SVR and ETVR than patients treated only with interferon (SVR: 49% vs 33%; RR: 1.52; 95% CI: 1.23–1.89; $p < 0.05$. ETVR: 57% vs 44%; RR:

Table 2
Interventions of the trials included in the meta-analysis.

References	Intervention	
	Control	Treatment
Chinese herbal therapies (Treatment) vs. *interferon therapies (Control)*		
Kong et al. (2008)	Interferon α (5 MU/3 times/week), RBV (1000 mg/day)	Oxymatrine capsules (0.9 g/day), point-injection therapy (hepatitis B vaccine, 80 μg/week)
Li et al. (2007)	Interferon α-2b (3 MU qd alt), RBV (1000 mg/day)	Oxymatrine injection (400 mg/day, 24 weeks), Shugan Jianpi formula (warm decoction, taken twice daily)
Hong et al. (2004)	Interferon α (3 MU qd alt)	Bingganning (to be decocted in water for oral dose)
Li et al. (2006)	Interferon α-2a (3 MU qd alt)	Jianpi Bushen formula (Taizishen 10 g, Fuling 10 g,Sanqi 10 g, Danshen 10 g, Chishao 10 g, Duzhong 10 g, Zhenzhucao 20 g, Tianjihuang 20 g, Tusizi 20 g, to be decocted in water for oral dose, taken twice daily)
Li and Chen (2005)	Interferon α-1b (5 MU qd alt)	Oxymatrine injection (4 ml/day)
Niu et al. (2008)	Interferon α-2b (beginning 2 weeks, 5 MU/day; the remain weeks, 5 MU qd alt), RBV (900 mg/day)	Yiganyin (Dangshen, Baishu, Danshen, Yujin, Kuweiyexiazhu, Huzhang, Zhiqiao, Chenpi, Gancao, 150 ml/2 times/day)
Sun et al. (2003)	Interferon α-1b (3 MU qd alt)	Qinggan granules (30 g/3 times/day)
Xiao et al. (2005)	Interferon α-2a (3 MU qd alt)	Jianpi Huoxue formula (Taizishen 15 g, Wuzhualong 15 g, Zhenzhucao 20 g, Danshen 20 g, Chishao 20 g, Sanqi 10 g, Fuling 10 g, Honghua 10 g, Baishu 10 g, Chushizi 20 g, to be decocted in water for oral dose, taken twice daily)
Yin et al. (2002)	Group A: Interferon α-1b (30 patients, 3 MU/3 times/week) plus RBV (300 mg/day) Group C: Interferon α-1b (32 patients, 3 MU/3 times/week)	Group A: Bingganning granules (one bag/3 times/day)
Zhou et al. (2001)	Interferon α-1b (3 MU qd alt)	Bingganning granules (one bag/day)
Chinese herbal plus interferon therapies (Treatment) vs. *interferon therapies (Control)*		
Meng et al. (2010)	Interferon α-1b (5 MU qd alt), RBV (800–1200 mg/day)	Interferon α-1b (5 MU qd alt), RBV (800–1200 mg/day), Jianpi Qinghua formula (6 g/day)
Wu et al. (2009)	Interferon α-1b (5 MU qd alt), RBV (800-1200 mg/day)	Interferon α-1b (5 MU qd alt), RBV (800–1200 mg/day), Shugan Lipi tablets (8 tablets/3 times/day)
Zhang (2009)	Peg interferon α-2a (180 μg/week), RBV (900 mg/day)	Peg interferon α-2a (180 μg/week), RBV (900 mg/day), Chinese medicinal formula (taken twice daily)
Chang and Li (2009)	Interferon α-2b (beginning 2 weeks, 5 MU/day; the remaining weeks, 5 MU qd alt), RBV (900 mg/day)	Interferon α-2b (beginning 2 weeks, 5 MU/day; the remaining weeks, 5 MU qd alt), RBV (900 mg/day) Yiqi Yanggan formula (150 ml/times/day)
Chen et al. (2005)	Interferon α-2b (beginning 4 weeks, 3 MU/day; the remaining weeks, 3 MU qd alt)	Interferon α-2b (beginning 4 weeks, 3 MU/day; the remaining weeks, 3 MU qd alt). Oxymatrine injection (beginning 4 weeks, 600 mg/day; the remaining weeks, 400 mg/day)
Jing et al. (2002)	Interferon α-2b (beginning 2 weeks, 3 MU/day; the remaining weeks, 3 MU qd alt)	Interferon α-2b (beginning 2 weeks, 3 MU/day; the remaining weeks, 3 MU qd alt), Xiaochaihu decoction (2 times/day)
Lin (2006)	Interferon α-2b (3 MU/3 times/week), Vitamin C (200 mg/3 times/day)	Interferon α-2b (3 MU/3 times/week), Oxymatrine capsules (200 mg/3 times/day)
Liu et al. (2008)	Interferon α-1b (5 MU qd alt), RBV (600 mg/day), Thymosin α1 (1.6 mg qd alt)	Interferon α-1b (5 MU qd alt), RBV (600 mg/day), Thymosin α1 (1.6 mg qd alt), Jianpi Qinghua formula (Shenhuangqi 20 g, Chenpi 20 g, Yiyiren 15 g, Weilingxian 15 g, Xuan mugua 15 g, Chaihu 15 g, Baihuasheshecao 30 g, Roucongrong 15 g, take a dose twice daily)
Ma (2008)	Interferon α (beginning 2 weeks, 3 MU/day; the remaining weeks, 3 MU qd alt) Interferon α-2b (beginning 2 weeks, 10 MU/6 times/week; the remaining weeks, 10 MU/3 times/week)	Interferon α (beginning 2 weeks, 3 MU/day; the remaining weeks, 3 MU qd alt), Xiaochaihu decoction (taken daily) Interferon α-2b (beginning 2 weeks, 10 MU/6 times/week; the remaining weeks, 10 MU/3 times/week)
Motoo et al. (2005)	RBV (body weight > 60 kg, 800 mg/day; body weight < 60 kg, 600 mg/day)	RBV (body weight > 60 kg, 800 mg/day; body weight < 60 kg, 600 mg/day) Ninjinyoeito extract granules (9 g/day)
Wu and Sun (2003)	Interferon α-2b (3 MU/3 times/week)	Interferon α-2b (3 MU/3 times/week), compound glycyrrhizin injection (beginning 8 weeks, 80 ml/day), compound glycyrrhizin tablets (the remaining 16 weeks, 3 tablets/3 times/day)
Yin et al. (2004)	Interferon α-1b (beginning 30 days, 3 MU/day; the remaining days, 3 MU qd alt)	Interferon α-1b (beginning 30 days, 3 MU/day; the remaining weeks, 3 MU qd alt). Oxymatrine injection (beginning 30 days, 600 mg/day), Oxymatrine capsules (the remaining days, 0.6 g/day)
Multi treatment groups study		
Wang and Chai (2009)	Group B: Interferon α plus RBV, the dose used in this study was determined according to WHO principles	Group A: traditional Chinese drugs (Renshen 10 g, Huangqi 100 g, Baishu 50 g, Fuling 50 g, Shanyao 50 g, Danggui 20 g, Chenpi 10 g, Shengma 10 g, Chaihu 10 g, Lulong 10 g; be decocted in water for oral dose, taken 3 times/day) Group C: Group A therapy plus Group B therapy
Han (2005)	Group B: Interferon α-2b (5 MU/3 times/week)	Group A: Interferon α-2b (5 MU/3 times/week). Oxymatrine capsules (0.1 g/d) Group C: Oxymatrine capsules (0.1 g/d)
Jiang (2007)	Group I: Interferon α-2b (20 patients, 3 MU qd alt; 25 patients, 5 MU qd alt)	Group II: Interferon α-2b (18 patients, 3 MU qd alt; 27 patients, 5 MU qd alt), traditional Chinese drugs (basic herbal medicine: Danshen 10 g, Chishao 15 g, Danggui 15 g, Huangqi 30 g, Yinchen 30 g, Lingzhi 30 g, Zhizi 15 g, Huzzhang 30 g, Sheshecao 30 g, Huagqin 15 g, Wuweizi 15 g; be decocted in water for oral dose, taken twice daily) Group III: Traditional Chinese drugs as above
Xu et al. (2001)	Group B: Interferon (for 1–6 years old children, beginning 12 weeks, 1 MU/day; the remaining weeks, 1 MU qd alt; for 6–13 years old children, 3 MU qd alt)	Group A: Interferon (for 1–6 years old children, beginning 12 weeks, 1 MU/day; the remaining weeks, 1 MU qd alt; for 6–13 years old children, 3 MU qd alt). Liganling syrups (20–30 ml/3 times/day) Group C: Liganling syrups (20–30 ml/3 times/day)

RBV, ribavirin; MU, million unit; qd alt, *quaque die alterna*.

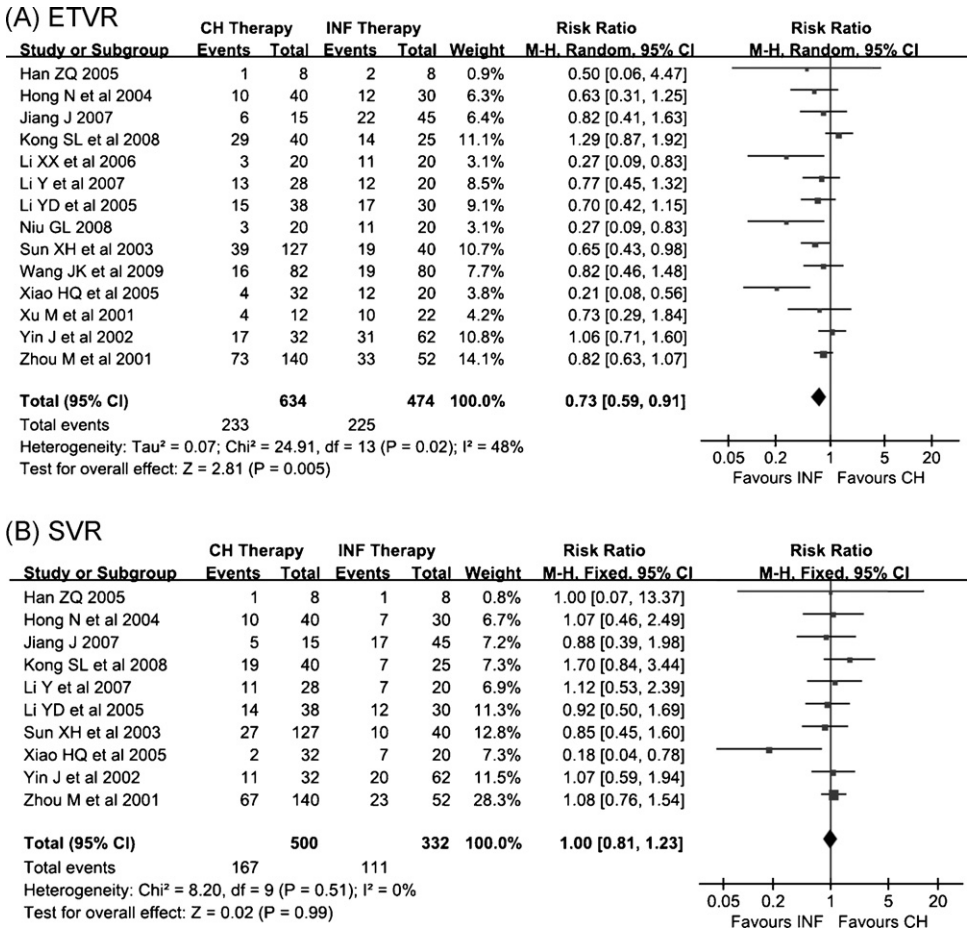

Fig. 2. (A) ETVR and (B) SVR: comparison of Chinese herbal therapies and interferon therapies. RR, relative risk; CI, confidence interval; Test for heterogeneity: Chi-squared statistic with its degrees of freedom (d.f.) and *p*-value; inconsistency among results: I^2 test for overall effect; *Z* statistic with *p*-value.

1.30; 95% CI: 1.14–1.48; $p < 0.05$) (Fig. 5). The relapse rates were also lower in patients treated with combined therapies compared to the patients treated with interferon alone, but the difference was not significant (26% vs 31%; RR: 0.83; 95% CI: 0.56–1.24; $p = 0.36$.) (Fig. 6). Patients treated with combined therapies also achieved significantly higher ALT normalisation at both the end of treatment and follow-up (End of treatment: 76% vs 57%; RR: 1.32; 95% CI: 1.18–1.48; $p < 0.05$. Follow up: 67% vs 43%; RR: 1.55; 95% CI: 1.29–1.86; $p < 0.05$). In this meta-analysis for SVR, ETVR, relapse and ALT normalisation, there was no apparent heterogeneity (Fig. 7).

3.5. Sensitivity analyses

Excluding the two trials that mainly included children with CHC did not change the pooled estimate (Han, 2005; Xu et al., 2001). The sensitivity analysis revealed that the RR for the outcome measure remained stable.

3.6. Safety profile evaluation

Five included trials clearly reported treatment discontinuation (Chang and Li, 2009; Kong et al., 2008; Li et al., 2007; Motoo

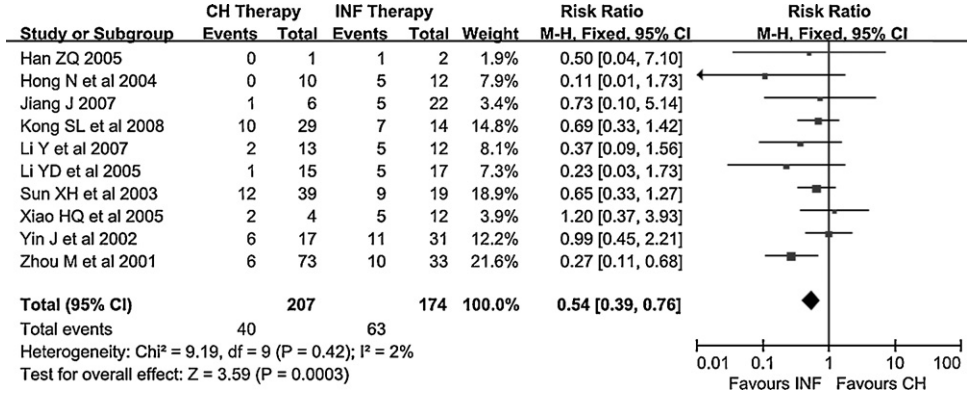

Fig. 3. Relapse, comparison of Chinese herbal therapies and interferon therapies. RR, relative risk; CI, confidence interval; test for heterogeneity: Chi-squared statistic with its degrees of freedom (d.f.) and *p*-value; inconsistency among results: I^2 test for overall effect; *Z* statistic with *p*-value.

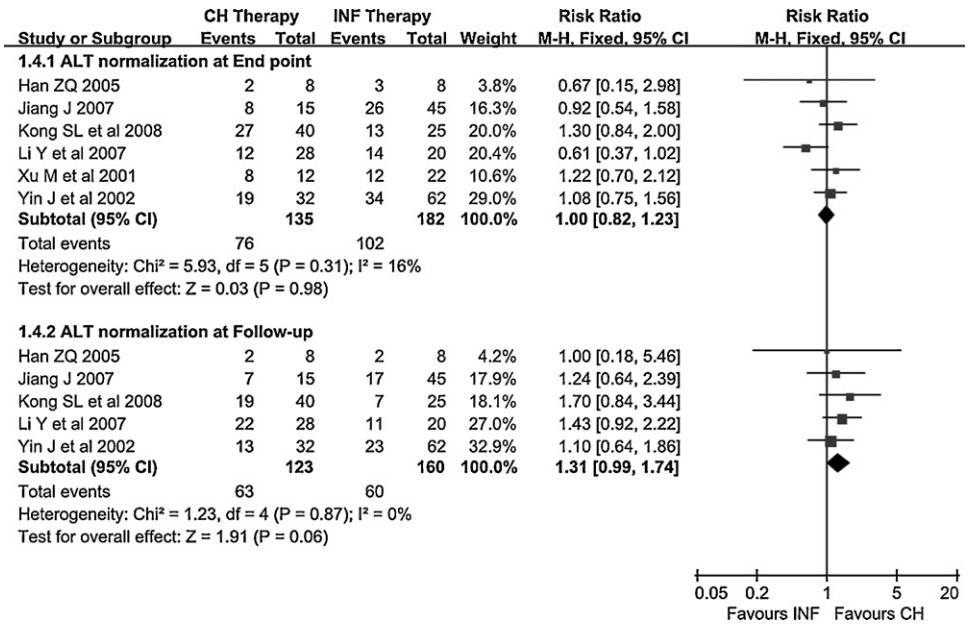

Fig. 4. ALT normalisation, comparison of Chinese herbal therapies and interferon therapies. RR, relative risk; CI, confidence interval; test for heterogeneity: Chi-squared statistic with its degrees of freedom (d.f.) and *p*-value; inconsistency among results: I^2 test for overall effect; *Z* statistic with *p*-value.

et al., 2005; Wang and Chai, 2009). Data from these trials yielded a RR of 0.60 (95% CI: 0.09–4.11) for Chinese herbal therapies vs interferon therapies and a RR of 0.47 (95% CI: 0.14–1.58) for interferon plus Chinese herbal therapies vs interferon therapies alone. Many other adverse events were also reported in the included trials (including thrombocytopenia, neutropenia, anemia, depression, fatigue, headache, insomnia, fever, nausea and dyspnoea). The overall adverse events or concurrent illnesses were less frequent

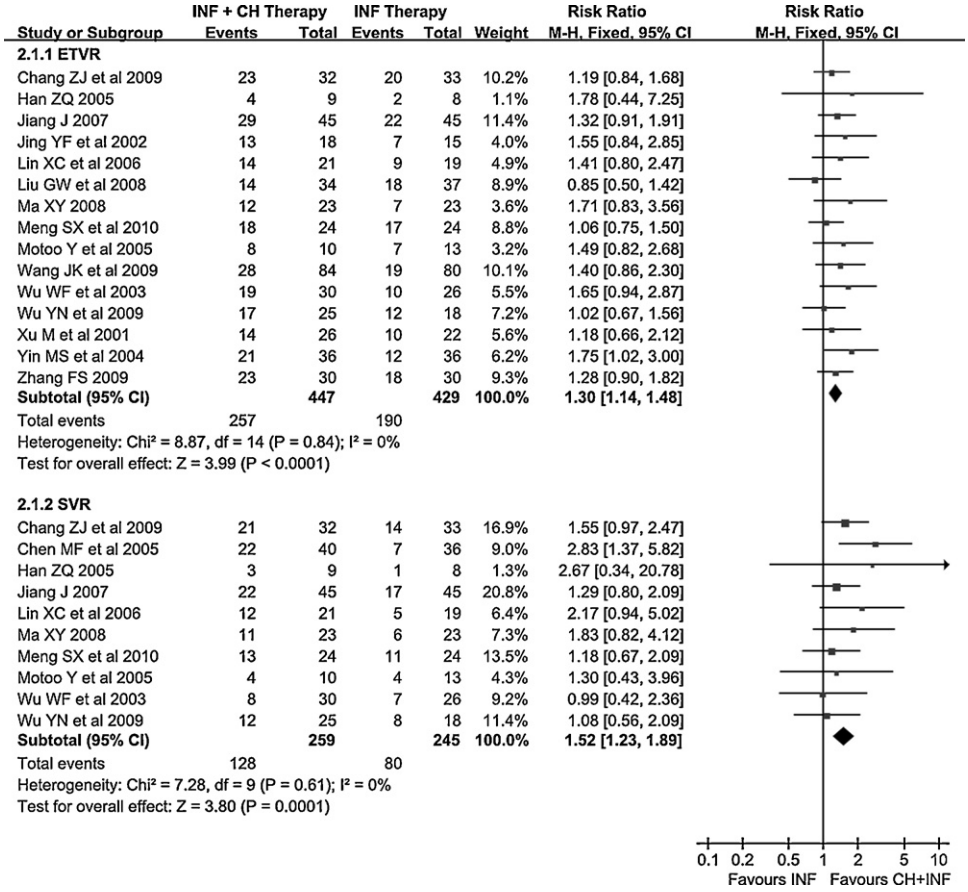

Fig. 5. ETVR and SVR, comparison of interferon plus Chinese herb therapies and interferon therapies. RR, relative risk; CI, confidence interval; test for heterogeneity: Chi-squared statistic with its degrees of freedom (d.f.) and *p*-value; inconsistency among results: I^2 test for overall effect: *Z* statistic with *p*-value.

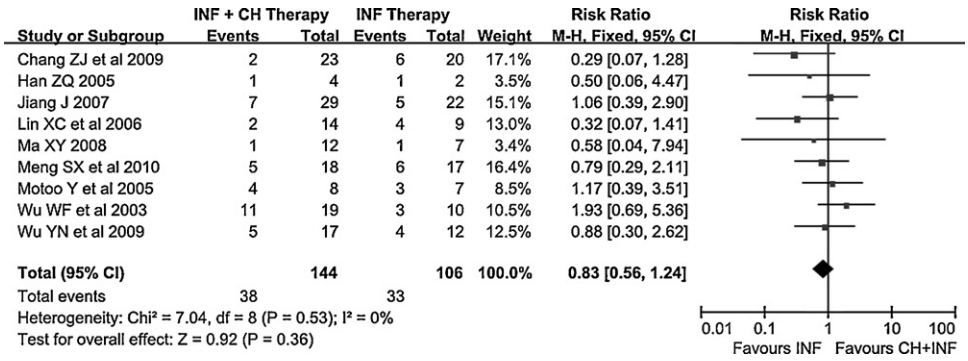

Fig. 6. Relapse, comparison of interferon plus Chinese herb therapies and interferon therapies. RR, relative risk; CI, confidence interval; test for heterogeneity: Chi-squared statistic with its degrees of freedom (d.f.) and *p*-value; inconsistency among results: I^2 test for overall effect; *Z* statistic with *p*-value.

in patients treated with Chinese herbs or interferon plus Chinese herbs than in patients treated with interferon alone, according to the reports of the included trials. We performed a meta-analysis of neutropenia incidence with data from six included trials (Chang and Li, 2009; Chen et al., 2005; Kong et al., 2008; Liu et al., 2008; Meng et al., 2010; Wu et al., 2009; Zhang, 2009). Interferon plus Chinese herb therapies yielded lower neutropenia incidence compared to the interferon therapies alone (RR: 0.24; 95% CI: 0.10–0.57).

3.7. Publication bias

We performed funnel plot analysis for SVRs to explore publication bias. Ten trials were included for the comparison of Chinese herbal therapies and interferon therapies separately, and of these nine trials included in the meta-analysis lay within the 95% CI line and one trial lay outside the 95% CI line. All ten trials included for a funnel plot analysis of interferon plus Chinese herbal therapies vs interferon therapies lay within the 95% CI line. These results implied the existence of some publication bias.

4. Discussion

Today, CHC is an unsolved medical problem and has become a serious worldwide public health problem, both in developed and developing countries. Though peginterferon plus ribavirin combined therapy was recommended, the achievement of SVR, expense, frequency of adverse effects and the large numbers of patients' intolerance were not satisfactory. With rare adverse reactions, good tolerance and less expense, Chinese herbs are commonly used as first line therapy for many chronic liver diseases, including HCV and hepatitis B virus infections in Asia (Wang, 2000). However, many of the studies on Chinese herbal therapies for the treatment of CHC published in Chinese cannot be accessed by non-Chinese-speaking scientists.

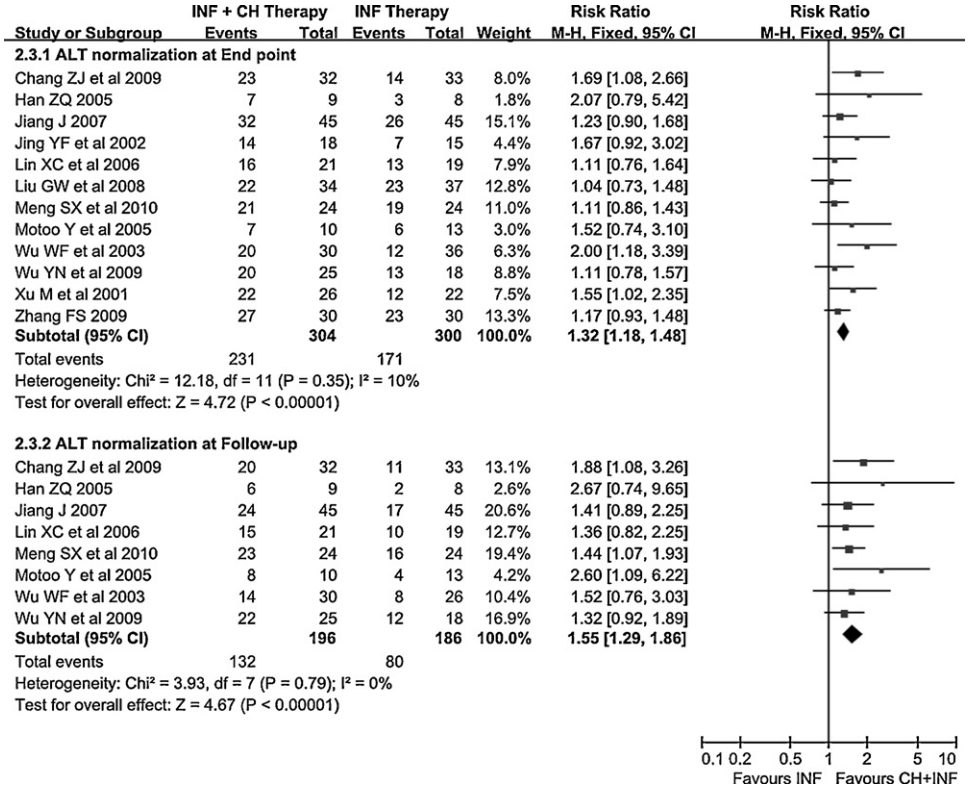

Fig. 7. ALT normalisation, comparison of interferon plus Chinese herb therapies and interferon therapies. RR, relative risk; CI, confidence interval; test for heterogeneity: Chi-squared statistic with its degrees of freedom (d.f.) and *p*-value; inconsistency among results: I^2 test for overall effect; *Z* statistic with *p*-value.

In this study, we have summarised the available evidence from RCTs comparing interferon therapies with Chinese herbal therapies or interferon plus Chinese herb therapies for the treatment of CHC. Our results suggest that combination therapies of interferon plus Chinese herbs may achieve significantly higher SVR than interferon therapies alone. Combination therapies of interferon plus Chinese herbs have also shown superior ETVRs, ALT normalisations and safety profiles. The incidence of adverse effects was lower in patients receiving Chinese herbal therapies or interferon plus Chinese herb therapies than those in patients receiving interferon therapies alone. Chinese herbs have also been revealed to have anti-fibrotic and anti-inflammatory activities (Chen et al., 2005; Han, 2005; Li et al., 2006; Liu et al., 2008; Meng et al., 2010; Niu et al., 2008; Sun et al., 2003; Xiao et al., 2005; Yin et al., 2004). These findings suggested that Chinese herbs are associated with higher SVR in the treatment of CHC patients when combined with interferon. For interferon intolerant patients and non-responders, Chinese herbal therapies may be a good choice. There have been rare side effects, although many herbal therapies have been shown to be quite safe. It also should be noted that side effects, such as drug-induced interstitial pneumonia, have been reported in Japanese patients during the "Sho-saiko-to" (TJ-9) administration periods (Yamashiki et al., 1997). TJ-9 is prohibited for use in combination with interferon because this combination is reported to increase the risk of interstitial pneumonia (Motoo et al., 2005). Though neither interstitial pneumonia nor any other side effects in relation to herbal therapies were found in the included clinical trials in this study, some herbal components, such as *Scutellariae radix*, should be carefully monitored or avoided in the treatment of CHC.

Peginterferon was used only in one included trial: patients treated with peginterferon plus ribavirin and Chinese herbs achieved a higher SVR than patients treated with peginterferon plus ribavirin (76% vs 60%) (Zhang, 2009). Interferon α-1b, 2a or 2b was used in the remaining included trials. The current recommended duration of interferon or peginterferon treatment is 48 weeks for genotypes 1 and 4, or 24 weeks for genotypes 2 and 3 (Di Bisceglie and Hoofnagle, 2002; Ghany et al., 2009). All included RCTs in this study comparing the efficacy of Chinese herbs and interferons were mainly performed by traditional Chinese medicine doctors and they usually decided the duration time based on traditional Chinese medicine principles. Patients in six included trials were treated for 48 weeks (Kong et al., 2008; Li et al., 2007; Meng et al., 2010; Wang and Chai, 2009; Wu et al., 2009; Zhang, 2009) and in the remaining included trials were treated for 24 weeks.

Current evidence suggests that combined therapies of interferon plus Chinese herb therapy appear to be more efficacious than interferon monotherapy, and do not result in any additional safety problems.

It is important to mention that there were limitations to the present meta-analysis. The quality of the included RCTs in this study was relatively low because the full accounting of all randomised patients, follow-up, and blinded methods were not used. This might be a limitation if the investigators were motivated to avoid dose reduction in one sub-group. Although the main worldwide biomedical databases were searched to identify potential RCTs, publication bias could not be avoided completely. Funnel plot analysis results implied the existence of some publication bias. In this study for SVR, there is no apparent heterogeneity, and the direction of the treatment effect is the same across all included trials.

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