Meta-Analysis of Combination Therapy of Chinese Herbs Plus Interferon and Ribavirin in Patients with Chronic Hepatitis C

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Background: We aimed to evaluate the combination therapy of Chinese herbs plus interferon and ribavirin in treatment of patients with chronic hepatitis C (CHC).

Material/Methods: Related databases were searched to identify randomized controlled trials (RCTs) that evaluated biochemical response, virological response, histological response, and/or adverse reactions to combination therapy of interferon and ribavirin with and without Chinese herbs. The RR (relative risk) with a 95% confidence interval (CI) was calculated. Sensitivity analysis was conducted by omitting one study at a time. Publication bias among the eligible studies was evaluated by Egger's test.

Results: A total of 17 RCTs matched the selection criteria. Overall, combination therapies of Chinese herbs plus interferon and ribavirin achieved significantly higher ALT (alanine transaminase) and ETVR (the end-of-treatment viral response), and significantly lower levels of HA (hyaluronic acid), LN (laminin), PC III (procollagen iii peptide), IV-C (type IV collagen), decreased LC (decreasing leukocyte count), ATF (abnormal thyroid function), psychosis, and anemia in CHC patients compared with those treated without Chinese herbs. Sensitivity analysis showed no changes and no potential publication bias was found.

Conclusions: The current evidence suggests that combination therapy of Chinese herb plus interferon and ribavirin yields better outcome and fewer adverse events in CHC patients than that of interferon plus ribavirin therapy.

MeSH Keywords: Hepatitis, Chronic • Interferon-alpha • Ribavirin

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Background

It is estimated that about 180 million people are chronically infected with hepatitis C virus (HCV) worldwide [1]; about 75% have no distinctive symptoms when they first acquire HCV infection. Over time, patients with chronic hepatitis C (CHC) may begin to experience persistent inflammation, become easily fatigued, and lose appetite [2]. Even worse, chronic HCV infection may progress to liver failure and hepatocellular carcinoma [3]. Unfortunately, there is still no effective and suitable HCV treatment for persons at the greatest risk for HCV infection [4].

Presently, combination antiviral therapy with interferon and ribavirin has been used as the standard treatment for CHC [5–8]. However, this regimen has some limitations in its ability to control CHC. Combination therapy of interferon and ribavirin for CHC is reported to produce a number of adverse effects, including fatigue, influenza-like symptoms, and gastrointestinal disturbances, and some adverse effects are severe and potentially life-threatening [9]. Some of these adverse effects can be overcome and reduced. Appropriate recognition of these adverse effects will both improve response to therapy and avoid unnecessary morbidity and mortality [10–12]. Complementary and alternative medicine (CAM) is defined as diagnosis, treatment, and prevention that complements mainstream medicine and is very popular in the West [13,14]. Recently, increasing number of clinicians has focused on CAM, and CAM has been applied in the treatment of chronic diseases [15,16]. Chinese herbs, as one of the main components of CAM, have rare and negligible adverse effects compared to common pharmaceutical drugs. Therefore, Chinese herbs have been widely utilized in medical systems, especially in China [17,18].

Research indicates that the treatment combined with Chinese herbs has achieved better safety and effectiveness in the treatment of CHC [19]. Nevertheless, the results of these individual studies related to Chinese herbs are often insufficient. Meta-analysis was proposed as an approach for contrasting and combining results from different studies [20–22]. The aim of this study was to assess the evidence from these randomized clinical trials (RCTs) for the efficacy and safety of Chinese herbs combined with interferon plus ribavirin in comparison with only interferon plus ribavirin therapies.

Material and Methods

Search strategy

A systematic search was performed through PubMed, EMBASE, Cochrane library, China National Knowledge Infrastructure, Wanfang Database, and China Biomedical Database for searching relevant articles up to July 2015. The key words used in the
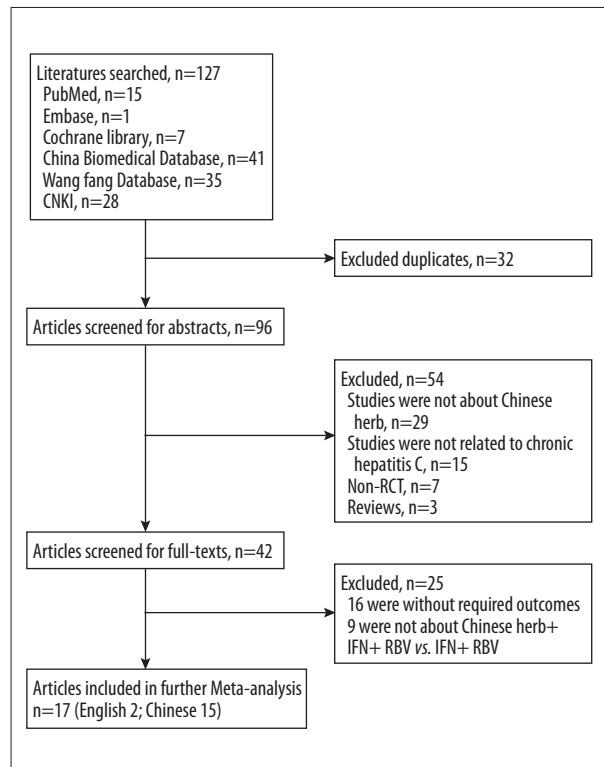

Figure 1. Flow chart of search strategy.

literature search included "chronic hepatitis C", "medicine-traditional", "Chinese herbal therapy", "drug and herbal", "medicine and Chinese", and "treatment and trial".

Inclusion criteria

To be included in this meta-analysis, the article had to fulfill inclusion criteria: 1) The study had to be an RCT that was clearly randomized and clinically controlled. 2) There was completed information, such as clear diagnostic criteria for CHC, sample size, publication date, and research year. 3) The RCT was designed to compare the combination therapy of interferon plus ribavirin combined with and without Chinese herbs. 4) The evaluation index contained biochemical response, such as alanine transaminase (ALT) value; virological response, including Early virological response (EVR), the end-of-treatment viral response (ETVR), sustained virologic response (SVR), non-response (NR), relapse, and rebound; histological responses, including hyaluronic acid (HA), laminin (LN), procollagen iii peptide (PC III), type IV collagen (IV-C), and/or adverse effects including Flu symptoms (FS), decreasing leukocyte count (LC), abnormal thyroid function (ATF), psychosis, alopecia, and anemia.

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

References	Treatment	Control	Sample size (M/F)		Duration (week)	Follow-up (week)
			Treatment	Control		
Wang JK, 2009	CH + α-IFN + RBV	α-IFN + RBV	84	80	48	0
Zhang FS, 2009	CH + PEG-IFNα-2a + RBV	PEG-IFNα-2a + RBV	30 (10/20)	30 (12/18)	48	0
Wu YN, 2009	Shuganlipi tablets + IFNα-lb + RBV	IFNα-lb + RBV	25 (17/8)	18 (12/6)	48	24
Chang ZJ, 2009	Supplementing gas nourishing liver + IFN a2-b + RBV	IFN a2-b + RBV	32 (23/7)	33 (21/9)	24	24
Meng SX, 2010	JianpiQinghuaRecipe + IFNα-l b + RBV	IFNα-l b + RBV	24 (15/9)	24 (14/10)	48	24
Cheng J, 2011	CH + IFN a2b + RBV	IFN a2-b + RBV	30	30	48	24
Ji XL, 2012	Hepatitis c granules Peg-IFNα-2a + RBV	Peg-IFN α-2a + RBV	26 (18/8)	30 (18/12)	12	NA
Qiu RX, 2012	Cacogongrassrootdecoction + Peg-IFN α-2a + RBV	Peg-IFN α-2a + RBV	40 (17/13)	60 (25/15)	48	24
Nie HM, 2012	FuzhengJiedurecipe + Peg-IFN α-2a + RBV	Peg-IFN α-2a + RBV+ FuzhengJiedu placebo	178	174	24	NA
Wang XM, 2012	FuzhengJiedurecipe + Peg-IFN α-2a +RBV	Peg-IFN α-2a + RBV	17 (9/8)	19 (11/8)	48	24
Fu MY, 2012	CH + Peg-IFN α-2a + RBV	Peg-IFN α-2a + RBV	32 (24/8)	30 (21/9)	48	NA
Tian LY, 2013	CH + α-IFN + RBV	α-IFN + RBV	32 (12/20)	30 (11/19)	48	NA
Wang HM, 2014	Chinese herbal granules + α-IFN +RBV	α-IFN + RBV	36 (17/19)	56 (30/26)	48	24
Xia J, 2014	CH + PEG-IFNα2a + RBV	PEG-IFNα2a + RBV	25 (14/11)	25 (12/13)	48	NA
Motoo Y, 2005	Ninjinyoeito + IFNα2b + RBV	IFNα2b + RBV	10 (9/1)	13 (8/5)	24	24
Rehan HS, 2015	Qurse-e-istisqua + IFNα2a + RBV	IFNα2a + RBV	30 (24/6)	30 (25/5)	48	24
Wei X, 2015	CH + PEG-IFN + RBV	IFN + RBV	67	61	48	24

RBV – ribavirin; IFN – interferon; CH – Chinese herb; M – male; F – female; NA – data were not shown.

Quality assessment and data collection

The methodological quality of the included studies was assessed according to the Cochrane Handbook *via* identifying, appraising, and synthesizing research-based evidence and presenting it in an accessible format [23].

Two investigators independently extracted the following data: 1) general information, including the first author, published date, and documents source; 2) the design of each study; 3) sample size, patient characteristics, and treatment outcomes; and 4) all of the experimental results.

Statistical analysis

In this study, results of the eligible studies were pooled using Stata 12.0 and Revman 5.3. The relative risks (RRs) and mean differences (MDs) with their 95% confidence intervals (CIs) were presented for categorical variables and continuous variables, respectively. Heterogeneity among the included studies
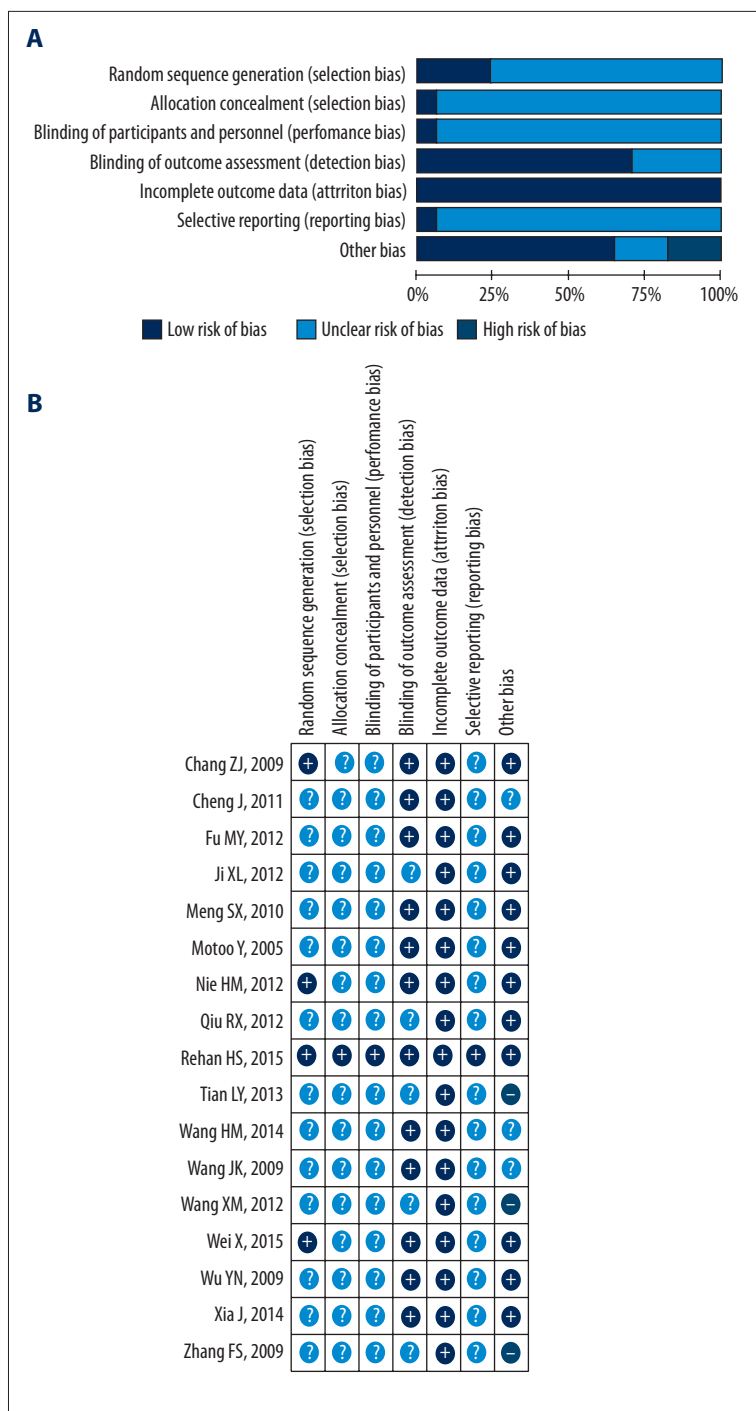
A

B

Figure 2. Cochrane Reviews for the eligible studies: (**A**) Risk of bias graph, (**B**) Risk of bias summary.

was explored using a chi square test and I^2 statistic, and $p<0.05$ and $I^2 >50\%$ was regarded as the presence of heterogeneity, then the random-effects model was used for meta-analysis; otherwise, the fixed-effects model was used. To detect the influence of each study on the overall effect, sensitivity analysis was conducted by omitting one study at a time. Publication bias among the eligible studies was evaluated by Egger's test [24].

Results

Search results

As shown in the flow chart (Figure 1), a total of 127 potentially related articles were finally identified by the initial search strategy (PubMed: 15; Embase: 1; Cochrane library: 7; China Biomedical Database: 41; Wan fang Database: 35; CNKI: 29).

Table 2. Summary of all the outcomes.

Outcomes	Studies	Participants (T/C)	Heterogeneity		Model (F/R)	Pooled results		P
			P	I^2		RR	95% CI	
Biochemical response								
Normalization of ALT	6	276/283	0.14	36%	F	1.17	(1.05, 1.29)	0.003
Virological response								
EVR	8	254/263	0.77	0%	F	1.06	(0.95, 1.18)	0.33
ETVR	12	566/570	0.69	0%	F	1.12	(1.05, 1.21)	0.001
SVR	10	311/321	0.009	59%	R	1.07	(0.95, 1.12)	0.27
NR	5	131/119	0.59	0%	F	0.84	(0.49, 1.42)	0.51
Relapse	4	104/125	0.94	0%	F	1.00	(0.44, 2.26)	1.00
Rebound	2	49/42	0.36	0%	F	0.85	(0.33, 2.20)	0.74
Histological response								
HA	2	49/42	0.71	0%	F	0.30	(0.12, 0.78)	0.01
LN	2	49/42	0.66	0%	F	0.10	(0.02, 0.54)	0.007
PC III	2	49/42	0.88	0%	F	0.09	(0.01, 0.67)	0.02
IV-C	2	49/42	0.50	0%	F	0.19	(0.06, 0.65)	0.008
Side effects								
FS	7	184/181	<0.01	91%	R	0.70	(0.46, 1.04)	0.08
Decreased LC	9	252/267	<0.01	78%	R	0.46	(0.30, 0.71)	0.005
ATF	8	256/263	0.60	0%	F	0.52	(0.34, 0.80)	0.003
Psychosis	6	166/157	0.15	39%	F	0.38	(0.18, 0.81)	0.01
Alopecia	7	225/219	<0.01	80%	R	0.50	(0.23, 1.09)	0.08
Anemia	4	96/91	0.13	46%	F	0.42	(0.27, 0.67)	0.002

ALT – alanine transaminase; EVR – early virological response; ETVR – the end of treatment viral response; SVR – sustained virologic response; NR – non-response; HA – hyaluronic acid; LN – laminin; PC III – precollagen III peptide; IV-C – type IV collagen; FS – flu symptoms; LC – leukocyte count; ATF – abnormal thyroid function; T – treatment group; C – control group; F – fixed effect model; R – random effect model; RR – risk ratio; CI – confidence interval.

After excluding 32 duplicates, the remaining articles were reviewed for abstracts and 54 were excluded, including 29 articles not about Chinese herbs, 15 articles not related to CHC, 7 non-RCT studies, and 3 reviews. Subsequently, the remaining 42 articles were further screened for full texts, of which 16 were without required outcomes and 9 were not about Chinese herbs. Thus, 17 articles were finally retrieved for the present meta-analysis (English: 2; Chinese: 15) [25–41].

Study characteristics

As shown in Table 1, all of the eligible studies were published from 2009 to 2015. All of these studies were performed as RCTs, thus Cochrane reviews were used for quality assessment. Figure 2A demonstrates that these studies were all with low risk or unclear risk of bias, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias, except for 3 studies which were found to have high risk

of unknown bias and attrition bias [27,34,40]. These results indicated a relatively high level of research selection (Figure 2B).

Comparison of the 2 therapeutic schedules

Table 2 summarizes all of the pooled results for comparison of the 2 therapeutic schedules.

Biochemical response

Biochemical responses were involved in 8 of the eligible studies. No significant heterogeneity was found among these 8 studies (p=0.14, I^2=36%), so the fixed-effects model was used for analysis. The pooled results showed that the ALT normalization rate at the endpoint of therapy was significantly higher in patients taking Chinese herbs than that of patients just taking interferon and ribavirin (RR=1.17, 95% CI: 1.05–1.29, P=0.003; Figure 3).
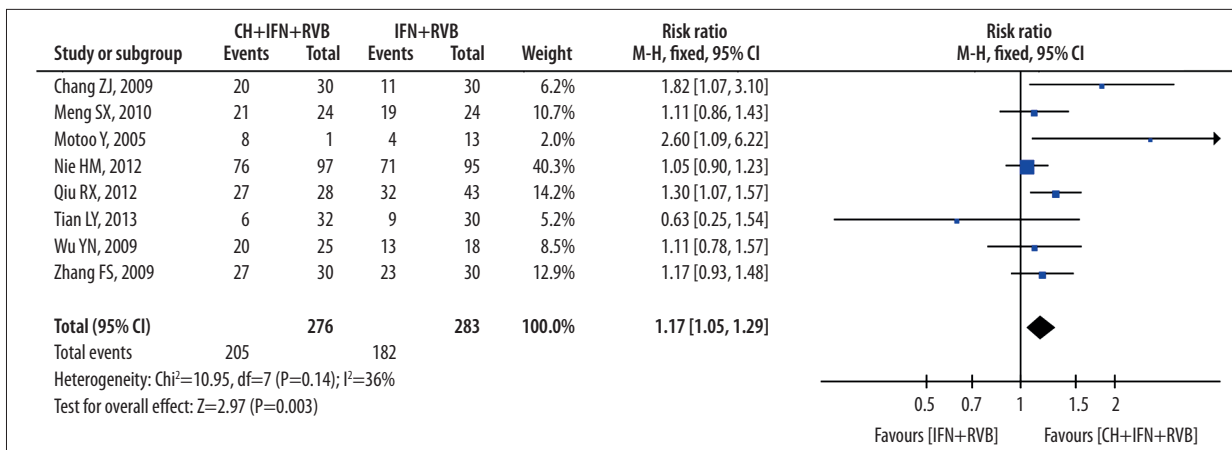
Figure 3. Comparison of alanine transaminase (ALT) normalization. CH – Chinese herbs; IFN – interferon; RBV – ribavirin; RR – relative risk; CI – confidence interval.
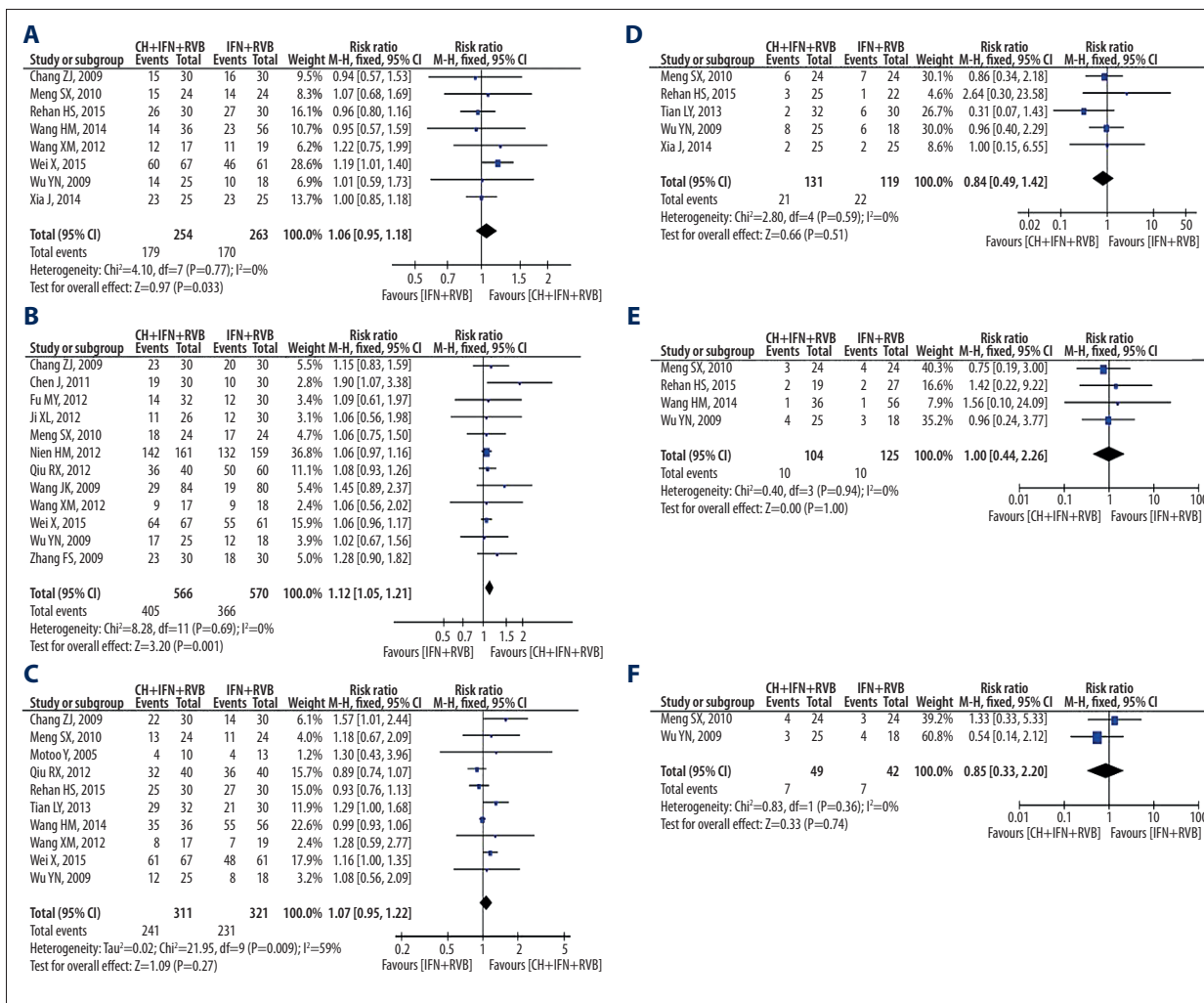

Figure 4. Comparison of virological response: (**A**) Forest plot for early virological response (EVR), (**B**) Forest plot for the end-of-treatment viral response (ETVR), (**C**) Forest plot for sustained virologic response (SVR), (**D**) Forest plot for non-response (NR), (**E**) Forest plot for relapse, and (**F**) Forest plot for rebound. CH – Chinese herbs; IFN – interferon; RBV – ribavirin; RR – relative risk; RR – relative risk; CI – confidence interval.
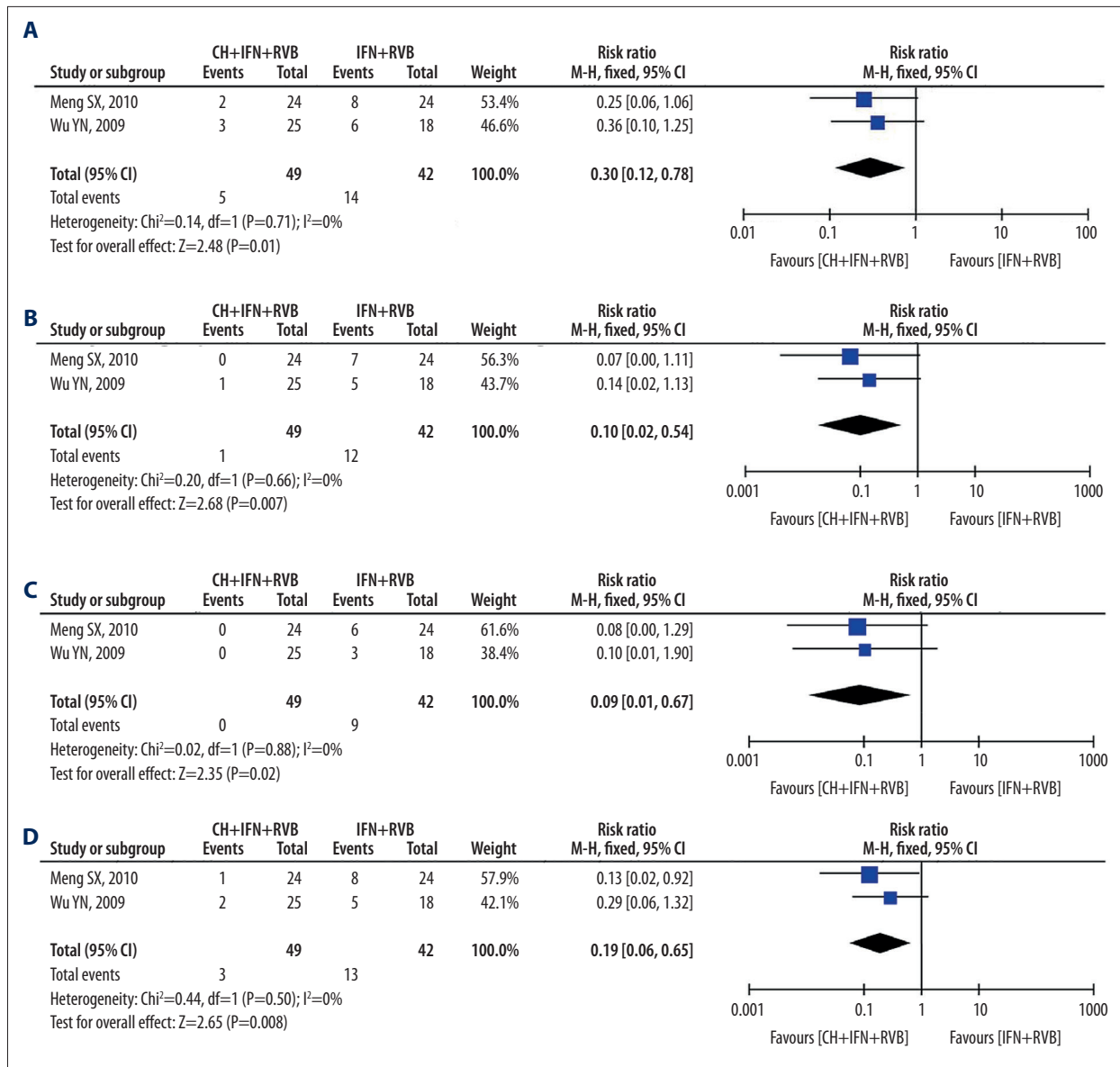
Figure 5. Comparison of histological responses: (**A**) Forest plot for the percentage of abnormal hyaluronic acid (HA), (**B**) Forest plot for laminin (LN), (**C**) Forest plot for procollagen iii peptide (PC III), and (**D**) Forest plot for type IV collagen (IV-C). CH – Chinese herbs; IFN – interferon; RBV – ribavirin; RR – relative risk; RR – relative risk; CI – confidence interval.

Virological response

Statistical heterogeneity was only found among studies involving SVR (P=0.009, I^2=59%), so the random-effects model was used for analysis of SVR and the fixed-effects model was used for analysis of the other indexes. Combined RR showed that ETVR was significantly higher in patients taking Chinese herbs plus interferon and ribavirin than that in patients treated with interferon and ribavirin (RR=1.12, 95% CI: 1.05, 1.21, P=0.001), while no significant difference was found in other index between the 2 groups of patients (P>0.05; Figure 4).

Histological responses

Data on histological response was only available in 2 trials [30,35]. For HA, LN, PC III, and IV-C, there was no statistical heterogeneity (p>005, I^2=0%) and the fixed- effects model was used to analyze these data. Our results showed that the percentage of abnormal HA (RR=0.30, 95% CI: 0.12–0.78, P=0.01,), LN (RR=0.10, 95% CI: 0.02–0.54, P=0.007), PC III (RR=0.09, 95% CI: 0.01–0.67, P=0.02), and IV-C (RR=0.19, 95% CI: 0.06–0.65, P=0.008) were significantly lower in patients treated with Chinese herbs plus interferon and ribavirin compared with that of patients treated without Chinese herbs (Figure 5).
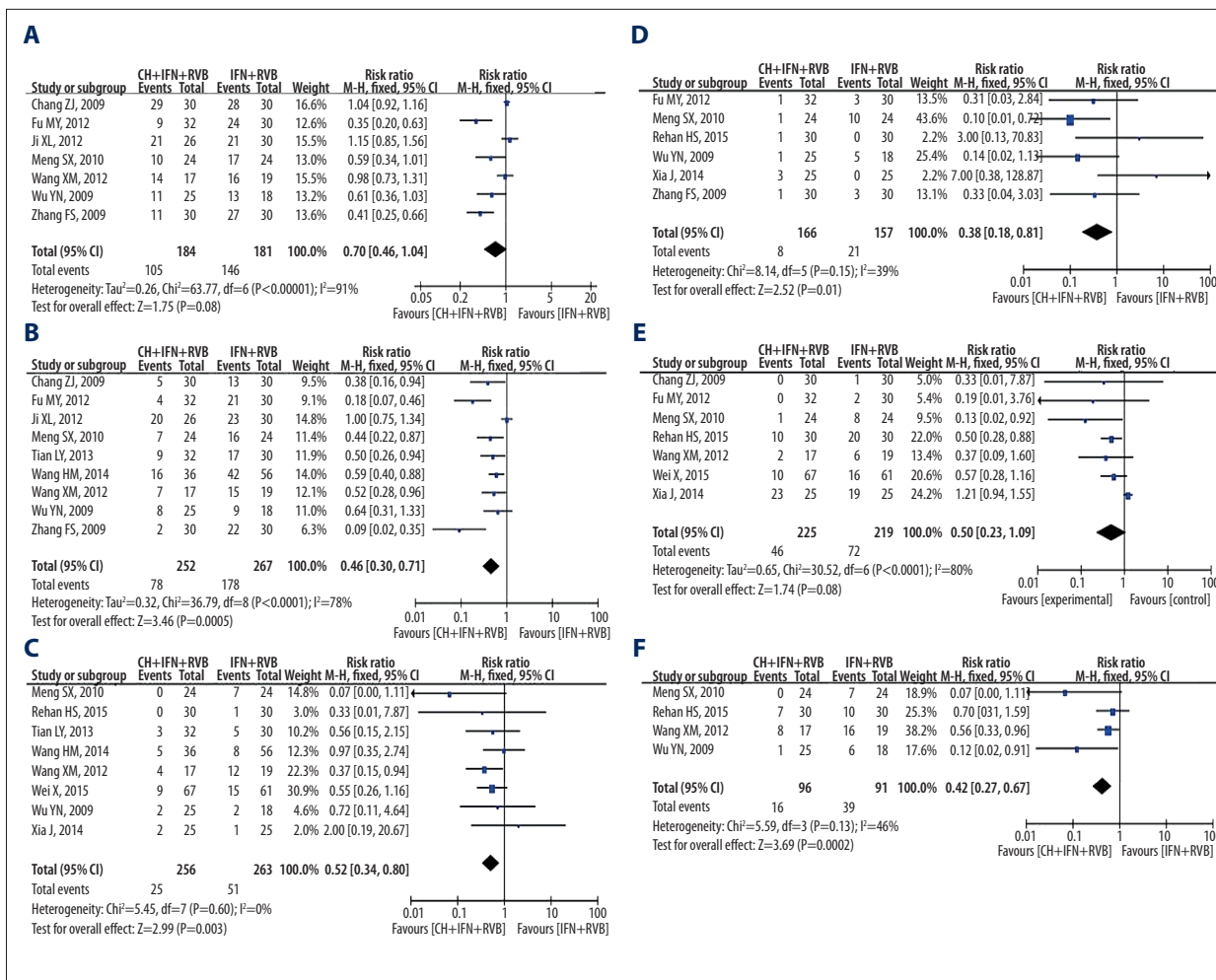
Figure 6. Comparison of adverse effects: (**A**) Forest plot for the percentage of flu symptoms (FS), (**B**) Forest plot for decreasing leukocyte count (LC), (**C**) Forest plot for abnormal thyroid function (ATF), (**D**) Forest plot for psychosis, (**E**) Forest plot for alopecia, and (**F**) Forest plot for anemia. RR, relative risk; CI, confidence interval; inconsistency among results: I^2 test for overall effect; Z statistic with *p*-value. CH – Chinese herbs; IFN – interferon; RBV – ribavirin; RR – relative risk; RR – relative risk; CI – confidence interval.

Adverse effects

Data on adverse effects were available in 7 studies and heterogeneity was only found among studies involving FS (*P*<0.01, I^2=91%), decreasing LC (*P*<0.01, I^2=78%), and alopecia (*P*<0.01, I^2=80%), so the random-effects model was used for meta-analysis of these indexes. Pooled results showed significant differences in decreased LC (RR=0.46, 95% CI: 0.30, 0.71, *P*=0.005), ATF (RR=0.52, 95% CI: 0.34, 0.80, *P*=0.003), psychosis (RR=0.38, 95% CI: 0.18, 0.81, P=0.01), and anemia (RR=0.42, 95% CI: 0.27, 0.67, *P*=0.002) between patients treated with combined Chinese herbs therapy and those treated without Chinese herbs (Figure 6).

Sensitivity analysis

Sensitivity analysis showed no change in any of the pooled results when removing any of the included studies, which indicated that the obtained results in this meta-analysis were relatively stable.

Discussion

This meta-analysis included 17 studies. We assessed effects of combination therapy of Chinese herbs plus interferon and ribavirin in CHC patients on biochemical response, virological response, histological response, and adverse reaction. Our results suggest that combination therapy of Chinese herbs plus interferon and ribavirin is better for CHC patients because

patients underwent this combined therapy showed higher ALT and ETVR; significantly lower levels of HA, LN, PC III, and IV-C; and decreased LC, ATF, psychosis, and anemia in CHC patients compared with those treated without Chinese herbs.

The combined therapeutic effect of Chinese herbs plus interferon and ribavirin may be consistent with the effect of Chinese herbs, such as anti-fibrotic and anti-inflammatory activities [42,43]. It also should be noted that patients receiving combined Chinese herbal therapy had fewer adverse effects, including decreased LC, ATF, alopecia, and anemia, than those without Chinese herbal therapy. In addition, sensitivity analysis showed no change when omitting each of the eligible studies, and potential publication bias was not found in the present study, which indicates that the pooled results of our study are relatively stable. Therefore, we believe that adding appropriate Chinese herbs to therapy may be a good choice for CHC patients who were administrated interferon and ribavirin.

It is important to mention that there were some weaknesses in the present meta-analysis. First, most of the included studies (15/17) were published in Chinese, which may be difficult to understand for non-Chinese-speaking scientists. Second, there were different kinds of Chinese herbs used in the selected studies, which may be the main course of heterogeneity for certain indexes. Third, the treatment cycle and follow-up time were different in the 17 trials and some studies did not include follow-up time. Finally, we did not specify individual herbs that are effective in treatment of HCV because Traditional Chinese Medicine (TCM) treatment is characterized by integrated application of different sets of Chinese herbs (a few or many different kinds), and because some studies included in the present meta-analysis did not specify the Chinese herbs in their TCM treatment in detail.

Conclusions

Despite the above limitations, our data indicate that combination therapy of Chinese herbs plus interferon and ribavirin may be more efficacious and does not result in any additional safety problems when compared with interferon plus ribavirin therapy without Chinese herbs. The combination with Chinese herbs may therefore be indicated as initial therapy in patients with CHC.

Conflict of interest

None.

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