A PRISMA-compliant systematic review and meta-analysis of integrated Chinese and Western medicine in treating hepatitis C

Xiuqin Li, MD*a, Lili Jia, MD*a, Jing Ouyang, PhDa, Ying An, MD*a, Guihua Luo, MD*a, Rui Song, BSb, Qiling Liu, PhDb, Bei Zhang, PhDb, Rongqiang Zhang, MD, PhDb−*

Abstract

Objective: To conduct a meta-analysis evaluating the effect of combining traditional Chinese medicine (TCM) with Western medicine in treating hepatitis C, and to provide an evidence-based medical strategy.

Methods: Randomized controlled trials (RCTs) comparing the effect of pegylated interferon (Peginterferon) combined with ribavirin (PR) alone and its combination with TCM were manually retrieved from the Weipu Information Resources System (VIP), Wan Fang Database, PubMed, and the Chinese Journal Full Text Database (CNKI). Studies meeting the inclusion criteria were selected and analyzed using the Review Manager 5.3 software. Suitable tests were also performed to determine the quality, heterogeneity, and sensitivity of the studies included in the meta-analysis.

Results: Twenty-eight RCTs met the inclusion criteria. The combination therapy or intervention group showed significantly greater HCV-RNA negative rate post-treatment compared to the monotherapy or the control group (P < .05). In addition, the serum levels of the liver function indicators alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin (ALB) were significantly improved after the combination therapy compared to PR alone (P < .05), while total bilirubin (TB) and r-glutamyltransferase (GGT) levels were not affected by TCM (P > .05). Finally, the parameters of liver fibrosis were also reduced by the combination therapy more effectively than the monotherapy.

Conclusion: The combination of TCM and PR can improve the Comprehensive Clinical Efficacy of hepatitis C and have a better negative rate of HCV-RNA with a better benefit in the liver function. The effect of TCM + PR is better than that of PR alone in treating hepatitis C.

Abbreviations: ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, GGT = r-glutamyltransferase, HA = Hyaluronic acid, HCV = hepatitis C virus, LN = laminin, PCIII = Type III collagen, PR = pegylated interferon (Peginterferon) combined with ribavirin, RCTs = randomized controlled trials, SMD = standard mean difference, TB = total bilirubin, TCM = traditional Chinese medicine.

Keywords: hepatitis C, meta-analysis, pegylated interferon (Peginterferon) combined with ribavirin (PR), traditional Chinese medicine

1. Introduction

Hepatitis C is an inflammatory disease of the liver caused by hepatocyte damage following hepatitis C virus (HCV) infection. The infected cells undergo necrosis, resulting in gradual fibrosis of the liver parenchyma, which can progress to cirrhosis and even liver cancer.[1] According to the World Health Organization, approximately 71 million people worldwide have chronic hepatitis C infection, resulting in 399,000 deaths every year.

The standard treatment for hepatitis C consists of pegylated interferon (Peginterferon) combined with ribavirin, also known as PR, which is commonly used in clinical practice. However, this
regimen lasts from 24 weeks to 72 weeks, and is limited by considerable side effects, poor patient compliance, and low virological response (SVR) rate to some HCV genotypes. Therefore, the latest treatment guidelines no longer recommend the PR program.[2] In addition, adverse reactions such as influenza-like syndrome, myelosuppression, central nervous system symptoms, and endocrii disorders are commonly associated with this program.[3]

Traditional Chinese medicine (TCM) gained considerable attention in recent years because of these issues. It is a holistic, individualized approach that targets both the symptoms and the root causes of diseases, resulting in fewer side effects, long-lasting therapeutic effects, and systemic improvement in the patients’ physical condition. As regard hepatitis C, TCM reduces the side effects of interferon and accelerates the recovery of liver function. Furthermore, it is especially suitable for Chinese considering the simple, convenient, and inexpensive formulations that can be easily accessed and well-tolerated by the patients.[4,5] However, the effects of TCM are slow, thus, being not feasible for hepatitis C infection. Therefore, the feasibility of combining Western medicine and TCM against hepatitis C has been explored in recent years. However, different studies used different methods, resulting in a lack of objectivity. Therefore, a meta-analysis on randomized controlled trials (RCTs) was conducted comparing the effects of integrated TCM+PR (Western medicine) with PR alone in hepatitis C treatment to provide evidence-based medical strategy to treat this disease.

2. Methods

2.1. Literature search

The Chinese Dissertation Database, China National Knowledge Infrastructure (CNKI), China Academic Literature Database, Weipu Information Resources System (VIP), Wanfang Data E-Resources (WANFANG), PubMed, and Embase repositories were used for the literature search using the following search terms: “hepatitis C” or “HCV” and “Combination of Chinese medicine and Western medicine.” The aim was to identify available and appropriate articles published through September 2019 according to the following inclusion and exclusion criteria. An ethical approval was not necessary, because our present study is a meta-analysis in which it is not necessary to select any animals or people as study subjects.

2.2. Inclusion and exclusion criteria

The studies were selected according to the following inclusion criteria:

1) Randomized controlled trials (RCTs);
2) Availability of clear diagnostic criteria for patients;
3) Control group treated with a PR regimen and intervention group with TCM+PR regimen;
4) Evaluation indicators included liver function indicators from serum, fibrosis indicators from serum, Comprehensive Clinical Efficacy, and HCV-RNA negative rate;
5) The clinical types of hepatitis C were not limited.

The studies were selected according to the following exclusion criteria:

1) Control group treated with a non-PR program;
2) The subjects were non-HCV patients;
3) Lack of conformity to the principles of RCT;
4) Errors in and/or lack of data;
5) RCT not explicitly described;
6) Lack of patient information;
7) Reviews;
8) Duplicate reports.

2.3. Study selection and quality assessment

Two reviewers (Xiuqin Li and Rongqiang Zhang) independently reviewed and selected the RCTs according to the established inclusion criteria, after the exclusion of the irrelevant papers. The results were compared, and any disagreements were solved by discussion or by a third reviewer.

The Jadad scale was used for quality assessment, which scored the studies in terms of:

1) Randomization;
2) Blinding;
3) Controlled;
4) Withdrawals and dropouts.

The studies scoring 1 to 3 were judged as low-quality studies and the ones scoring 4 to 7 as high-quality studies.

2.4. Data extraction

The following data were extracted from the selected studies: authors list, year of publication, number of treatment and intervention groups, interventions, diagnostic criteria, patient age, and duration of the treatment.

In addition, the primary evaluation indicators were as follows:

1) Liver function testing including ALT (alanine aminotransferase) and AST (aspartate aminotransferase). Liver function testing (ALT, AST, etc) indicates the degree of liver damage in patients infected with hepatitis B virus, thus, so liver function testing was the primary evaluation indicator in our study.
2) Comprehensive Clinical Efficacy, calculated as the number of patients with clinical outcome/total number of patients, according to the standard of the curative effect of the “Guiding Principles of Clinical Research on New Chinese Medicine”[6]; the Comprehensive Clinical Efficacy was used to evaluate the overall effect of hepatitis B treatment on patients.
3) The negative rate of HCV-RNA was used to evaluate the viral clearance.

The secondary evaluation indicators were as follows:

1) Liver function indicators such as ALB (albumin), TB (total bilirubin), and GGT (r-glutamyltransferase);
2) Liver fibrosis indicators such as HA (hyaluronic acid), LN (laminin), and PCIII (Type III collagen).

2.5. Sensitivity analysis

Sensitivity analysis was performed for each variable by removing one study and re-calculating the data with the remaining studies, in order to determine the effect of each of them on the statistics. The lack of any significant change indicated stable results.

2.6. Heterogeneity analysis

The heterogeneity between the studies was analyzed using the $I^2$ statistic as previously described.\[^7\]$ $I^2 \geq 50\%$ and $P < 50\%$
indicated significant heterogeneity, and the studies were analyzed by the random effects model. \( I^2 < 50\% \) and \( P \geq 0.05 \) indicated no heterogeneity, and the fixed effect model was used.

2.7. Publishing bias
Begg’s test and funnel plots were used to evaluate the publication bias by the Stata software. If the funnel plots were roughly symmetrical or the Begg’s test resulted with \( P > 0.05 \), no publication bias was present.\(^8\)

2.8. Statistical processing
The meta-analysis was performed using Review Manager 5.3 software. The standard mean difference (SMD) and 95% confidence interval (CI) were calculated, and \( P < 0.05 \) was considered statistically significant.\(^5\)

3. Results
3.1. Articles inclusion and selection
A total of 1910 articles were identified, and among them 1605 were excluded after reading the title and the abstract. In addition, 1577 were further excluded after reading the full text of the remaining articles and 28 were selected for the meta-analysis. The highest Jadad score was 5 and the average score was 2.18. The literature search and study selection are shown in Figure 1. The baseline characteristics of the included studies are shown in Table 1.

3.2. Meta-analysis results
3.2.1. Comprehensive Clinical Efficacy. Thirteen RCTs\(^11,10,17,18,20,21,23,24,26,29,30,34\) including 455 patients in the intervention group and 447 in the control group compared the clinical efficacy of both treatments. The \( I^2 \) was 0% and \( P > 0.05 \), indicating no heterogeneity. The fixed effect model was used for the meta-analysis, which showed a better clinical efficacy of TCM+PR compared to PR alone (RR = 1.21, 95% CI = 1.13–1.3, \( P < 0.05 \); Fig. 2).

3.2.2. HCV-RNA negative conversion rate. Ten RCTs compared the post-treatment viral response, and no evident heterogeneity was detected (\( I^2 = 38\% \), \( P > 0.05 \)). The meta-analysis revealed that in the 317 control cases, 175 showed HCV-RNA clearance after treatment, while 213 of the 316 intervention cases had a negative HCV-RNA status post-treatment. Thus, the combination treatment (TCM+PR) showed a greater antiviral effect compared to the monotherapy (PR) (RR = 1.21, 95% CI = 1.08–1.35, \( P < 0.05 \); Fig. 3).

3.2.3. ALT level. Twenty RCTs\(^11,9,10,12–15,17,19–27,29,33\) compared the changes in ALT level between the intervention and control group before and after the treatment, although the heterogeneity was high among the studies (\( I^2 = 67\% \), \( P < 0.01 \)). The random effects model was therefore used, and the meta-analysis showed a significantly lower ALT level in the intervention group compared to the one in the control group (SMD = –0.49, 95% CI = –0.69 to –0.29, \( P < 0.05 \); Fig. 4), indicating that the combination of TCM and PR was more effective.

3.2.4. AST level. Eighteen RCTs\(^11,9,10,14–17,19–26,29,32,33\) analyzed the AST level, and showed a considerable heterogeneity (\( I^2 = 55\% \), \( P < 0.05 \)). The meta-analysis revealed that the combination of TCM and PR significantly reduced the AST level compared to PR alone (SMD = –0.46, 95% CI = –0.64 to 0.28, \( P < 0.05 \); Fig. 5).

3.2.5. ALB level. Eight RCTs\(^10,16,17,20,21,25,26,33\) compared the ALB level in the intervention and control group before and after the treatment, and showed a significant heterogeneity (\( I^2 = 67\% \), \( P < 0.01 \)). The result of the meta-analysis revealed that the ALB level in the intervention group was significantly higher than that in the control group (SMD = 0.36, 95% CI = 0.06–0.65, \( P = 0.02 \); Fig. 6).

3.2.6. TB level. Eleven RCTs\(^10,14,16,20,21,23,25,26,29,33\) compared the changes in TB level between the intervention and control group before and after the treatment. The heterogeneity between the studies was not significant (\( I^2 = 28\% \), \( P > 0.05 \)). The meta-analysis revealed that the control and intervention group had a similar TB level (SMD = –0.07, 95% CI = –0.22 to 0.07, \( P = 0.32 \); Fig. 7).

3.2.7. GGT level. Four RCTs\(^11,13,20,21\) compared the GGT level between the intervention and control group, with a significant heterogeneity (\( I^2 = 63\% \), \( P < 0.05 \)). The result of the meta-analysis regarding the GGT level revealed no significant difference between the 2 groups before and after the treatment (SMD = –0.08, 95% CI = –0.45 to 0.29, \( P > 0.05 \); Fig. 8).

3.2.8. HA level. Four RCTs\(^11,3,20,21\) compared the HA level, with a high level of heterogeneity between the studies (\( I^2 = 96\% \), \( P < 0.01 \)). The meta-analysis revealed a significantly lower HA level post-treatment in the intervention group compared to the control group. Thus, the integrated TCM and PR were more beneficial in reducing HA level in the hepatitis C patients (SMD = –1.90, 95% CI = –3.61 to –0.19, \( P = 0.03 \); Fig. 9).

3.2.9. LN level. Four RCTs\(^11,13,20,21\) analyzed the LN level before and after the treatment, with a low homogeneity (\( I^2 = 80\% \), \( P < 0.05 \)). The post-treatment decline in LN level was significantly higher in the combination treatment group compared to that in the Western medicine group (SMD = –0.86, 95% CI = –1.52 to –0.20, \( P < 0.05 \); Fig. 10).

3.2.10. PCIII level. Four RCTs\(^11,13,20,21\) compared the PCIII level before and after the treatment. The homogeneity between
| First author Year | Treatment size | Control size | Treatment Age | Control Age | Treatment Disease duration | Control Disease duration | Treatment Diagnostic criteria | Control Diagnostic criteria | Intervention strategy |
|-------------------|----------------|--------------|---------------|-------------|----------------------------|--------------------------|---------------------------|---------------------------|-------------------------|
| Xu[9] 2016 & 40      | 32             | 30           | 36.16 ± 12.22 | 41.4 ± 11.86 | 48 wk                      | A + B + C                | PR                        |                         | PR                      |
| Cai[10] 2017 & 41 | 38             | 37           | 50.87 ± 13.65 | 47.16 ± 14.43 | 13.97 ± 3.83               | 4.97 ± 4.25              | PR                        |                         | PR                      |
| LeShi[10] 2013 & 41 | 30             | 30           | 42.87 ± 17.17 | 39.77 ± 13.74 | 24 wk                      | D + B                    | PR                        |                         | PR                      |
| Fu et al[11] 2012 & 4 | 32             | 30           | 32.7 ± 14.5   | 29.1 ± 16.2   | 48 wk                      | A                        | PR + TCM syndrome differentiation and treatment (12 herbs) |                         | PR                      |
| Wang et al[12] 2012 & 4 | 17             | 19           | 39.28 ± 21.2   | 37.2 ± 21     | 48 wk                      | A                        | PR + TCM compound decoction (6 herbs) |                         | PR                      |
| Wu[13] 2018 & 4 | 14             | 14           | 41.56 ± 3.81   | 41.6 ± 3.85   | 48 wk                      | B + F                    | PR                        |                         | PR                      |
| Jia and Li[14] 2013 & 4 | 40             | 39           | ±               | ±           | 24 wk                      | A                        | PR + minor bupleurum decoction (7 herbs) |                         | PR                      |
| Wang[15] 2015 & 4 | 38             | 36           | ±               | ±           | 24 wk                      | G + J                    | PR + Gnight medico decoction (11 herbs) |                         | PR                      |
| LeShi[10] 2013 & 4 | 30             | 30           | ±               | ±           | 24 wk                      | H                        | PR + Xiangqiu drug decoction (11 herbs) |                         | PR                      |
| Fu et al[11] 2012 & 4 | 32             | 30           | ±               | ±           | 24 wk                      | B                        | PR + TCM basic decoction (6 herbs) |                         | PR                      |
| Wang[15] 2015 & 4 | 38             | 38           | ±               | ±           | 24 wk                      | A                        | PR + TCM basic decoction (8 herbs) |                         | PR                      |
| TaoShi[16] 2016 & 4 | 20             | 20           | ±               | ±           | 24 wk                      | A                        | PR + Gnight medico decoction (8 herbs) |                         | PR                      |
| Jing et al[17] 2010 & 4 | 26             | 22           | ±               | ±           | 24 wk                      | A                        | PR + Chinese medicine decoction (11 herbs) |                         | PR                      |
| Hao et al[18] 2013 & 4 | 40             | 40           | ±               | ±           | 24 wk                      | A                        | PR + Chinese medicine decoction (11 herbs) |                         | PR                      |
| Li[19] 2008 & 4 | 30             | 30           | ±               | ±           | 24 wk                      | A                        | PR + Chinese medicine decoction (11 herbs) |                         | PR                      |
| Liu et al[20] 2014 & 4 | 35             | 37           | ±               | ±           | 24 wk                      | A                        | PR + Chinese medicine decoction (11 herbs) |                         | PR                      |
| Liang et al[21] 2014 & 4 | 33             | 31           | ±               | ±           | 24 wk                      | A                        | PR + Chinese medicine decoction (11 herbs) |                         | PR                      |
| Zhang et al[22] 2017 & 4 | 41             | 40           | ±               | ±           | 4 wk                       | A + D                     | PR + hepatitis C mixture (11 herbs) |                         | PR                      |
| Huai and Hao[23] 2013 & 4 | 26             | 24           | ±               | ±           | 4 wk                       | H                        | PR + hepatitis C mixture (11 herbs) |                         | PR                      |
| Ji et al[24] 2012 & 4 | 26             | 30           | ±               | ±           | 4 wk                       | H                        | PR + hepatitis C mixture (11 herbs) |                         | PR                      |
| Du[25] 2011 & 4 | 12             | 14           | ±               | ±           | 24 wk                      | A                        | PR + Gnight medico decoction (11 herbs) |                         | PR                      |
| Zhang and Li[26] 2009 & 4 | 32             | 30           | ±               | ±           | 24 wk                      | A                        | PR + Gnight medico decoction (11 herbs) |                         | PR                      |
| Yu[27] 2013 & 4 | 65             | 65           | ±               | ±           | 48 wk                      | A                        | PR + Yangko decoction (10 herbs) |                         | PR                      |
| Chen et al[28] 2014 & 4 | 30             | 30           | ±               | ±           | 48 wk                      | F                        | PR + LiHuaxue decoction (11 herbs) |                         | PR                      |

* A to K were the domestic and foreign diagnostic standards used to diagnose HCV patients from the original literature and these standards are currently used in clinical practice: A: Hepatitis C prevention guidelines; B: Standard of TCM syndrome differentiation; C: Traditional Chinese medicine diagnosis; D: Prevention and treatment of viral hepatitis; E: Traditional Chinese medicine syndrome classification standards; F: Western diagnostic criteria for chronic hepatitis; G: Chinese Medical Association guidelines for prevention and treatment of hepatitis C; H: Guidelines for the prevention and treatment of chronic hepatitis; I: Constipation of diagnosis and treatment of chronic hepatitis with integrated traditional Chinese and Western medicine; J: TCM syndrome standard for viral hepatitis (Trial); K: Hepatitis C diagnosis.
Figure 2. Meta-analysis results of the clinical effect in the control and intervention group.

Figure 3. Meta-analysis of the negative rate of HCV-RNA in the control and intervention group.

Figure 4. Meta-analysis of the ALT level in the control and intervention group.
Figure 5. Meta-analysis of the AST level in the control and intervention group.

Figure 6. Meta-analysis of the ALB level in the control and intervention group.

Figure 7. Meta-analysis of the TB level in the control and intervention group.
the studies was low ($I^2=87\%$, $P<.01$). The intervention group showed a significantly greater decline in PCIII after the treatment compared to the decline in the control group (SMD = −0.88, 95% CI = −1.71 to −0.04, $P<.05$; Fig. 11).

3.3. Sensitivity analysis

The sensitivity analysis towards the 4 primary indicators (ALT, AST, Comprehensive Clinical Efficacy, and negative rate of HCV-RNA) showed no significant changes after the removal of one study at a time (Fig. 12), indicating that the results of this meta-analysis were stable and reliable.

3.4. Publication bias assessment

The funnel plots of the 4 primary indicators (ALT, AST, Comprehensive Clinical Efficacy, and negative rate of HCV-RNA) indicated no significant publication bias in the meta-analysis, as shown in Figure 13.

4. Discussion

Although hepatitis C is usually asymptomatic, it is more likely to progress to cirrhosis and even liver cancer compared to hepatitis B. In an epidemiological survey conducted in 2006, it was found that 0.43% of the population was positive for anti-HCV antibodies. Currently, 6.5 million people are infected with HCV in China, with 30,000 new cases diagnosed every year.\textsuperscript{[36]} The prevention and treatment of chronic hepatitis C is a major health concern in China, and has been listed as a national infectious disease.\textsuperscript{[37]} Despite the encouraging results obtained with the PR regimen, the viral persistence increased, along with serious side effects that affect patient compliance. In addition, many patients do not achieve the final therapeutic effect.\textsuperscript{[38]}

In recent years, the attention has shifted to TCM, which is based on natural herbal extracts, and associated with fewer side effects. However, TCM preparations are not well-defined and the clinical research is scarce.\textsuperscript{[39]} To this end, a meta-analysis of 28 RCTs comparing the effects of Western medicine and its combination with TCM on a total of 6544 hepatitis C patients was conducted, and a greater clinical efficacy of the combination treatment was observed, both in terms of HCV-RNA clearance and liver function indicators. Similar results are reported by Zhang\textsuperscript{[40]} who tested the combination of Yubing decoction with different drugs to increase Qi, strengthen spleen and kidney, and increase immune function in the body. In the present study, TCM was represented by a treatment that includes many decoctions, mixtures, and granules, because our purpose was to evaluate the effect of the PR+TCM treatment against HCV.
Figure 11. Meta-analysis of the PCIII level in the control and intervention group.

Figure 12. Sensitivity analysis.

Figure 13. Funnel plots and Begg’s tests of the publication bias.
Our meta-analysis showed that the serum ALT and AST levels, which are reliable markers of liver damage and are increased in the serum of patients with cirrhosis or liver cancer, were significantly lower in the combination treatment group compared to the control group. Liver damage also causes protein deficiency, which is reflected in the decrease of serum albumin content. The combination group also showed higher ALB level compared to the levels after the use of the latter alone. Consistent with this, Ye [42] observed that the TCM formulation Long Chai not only improved liver fibrosis markers HA, LN, and PCIII compared to the levels after treatment of chronic hepatitis C patients. Combined with the results of this meta-analysis, it can be concluded that the combination of TCM and PR can significantly improve the clinical outcome in hepatitis C patients.

However, several limitations were present that need to be addressed. First, the different trials followed the treatment for a different length of time (12–48 weeks). Second, the treatment regimens and diagnostic criteria for hepatitis C were not uniform across the studies, and the research methods and blinding were not clearly defined. Finally, most trials used small cohorts, which could result in bias. Therefore, double-blind and high quality randomized clinical trials with large sample sizes are still necessary to validate the findings in this meta-analysis.

In conclusion, this meta-analysis showed that the combination of TCM and PR can improve the Comprehensive Clinical Efficacy of Hepatitis C and have a better negative rate of HCV-RNA with a better benefit in liver function of the patients. The effect of TCM + PR is better than the effect of PR alone in treating hepatitis C. The combination of TCM and PR could be promoted in clinical treatment practice if it is permitted.

**Author contributions**

Conceptionalization: Xiuqin Li, Rongqiang Zhang.

Data curation: Xiuqin Li, Lili Jia.

Formal analysis: Xiuqin Li, Ying An.

Funding acquisition: Xiuqin Li.

Investigation: Xiuqin Li.

Methodology: Xiuqin Li.

Resources: Xiuqin Li, Rongqiang Zhang.

Software: Xiuqin Li, Guihua Luo.

Validation: Xiuqin Li, Rongqiang Zhang.

Writing – original draft: Xiuqin Li, Rongqiang Zhang.

Writing – review & editing: Xiuqin Li, Rongqiang Zhang.

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