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REVIEW

Effect of traditional Chinese medicine combined with Western therapy on primary hepatic carcinoma: a systematic review with meta-analysis

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Abstract **Primary hepatic carcinoma (PHC) is a common malignant tumor in China. Cancer is comprehensively treated with various therapeutic regimes, including traditional Chinese medicine (TCM). TCM has been widely used to improve the quality of life, delay the time of cancer progression, and prolong the median survival time. This systematic review with meta-analysis aimed to assess the effect of TCM combined with Western therapy on primary hepatic carcinoma. A comprehensive literature search was conducted in six databases, including CNKI, VIP, Wan-Fang Database, CBM, PubMed, and Cochrane library. A total of 44 randomized controlled trials (RCTs) involving 3429 participants suffering from PHC were selected. Meta-analysis results indicated that the overall effect of TCM and Western integrative treatment on PHC was higher than that of Western intervention alone, which can postpone tumor recurrence and metastasis and prolong the overall survival time of patients with PHC. Although the obtained evidence remained weak because of the poor methodological quality of the included studies, this review provided relevant data supporting the efficacy and safety of TCM combined with Western therapies. In future research, individual RCT studies should incorporate accepted standards for trial design and reporting, proper outcome indicators according to international standards, blinding in allocation concealment, and valid follow-up periods.**

Keywords traditional Chinese medicine; primary hepatic carcinoma; meta-analysis

Introduction

More than 600 000 new cases of hepatocellular carcinoma are reported globally per year [1]. For instance, primary hepatic carcinoma (PHC) is a common malignant tumor in China, where the mortality rate is 20.37 out of 100 000 cases and thus accounts for the second-highest cancer mortality [2]. PHC is characterized as an aggressive cancer with a dismal outcome largely due to metastasis and postsurgical recurrence [3]. PHC is also a life-threatening condition because it can rapidly develop into advanced liver cancer and is a serious health risk among affected individuals because of poor treatment efficacy. Standard Western therapies, such as surgical resection and liver transplantation, play active roles in the treatment of PHC. However, most patients have lost the optimum time for surgery upon diagnosis because of liver cancer occult and rapid progression. Other treatment methods, such as chemotherapy, which reportedly yields a 10% response rate without survival benefits, are inefficient [4]. Therefore, patients may prefer alternative treatments, including traditional Chinese medicine (TCM), alone or in combination with Western therapy.

TCM treatments for tumors have been extensively explored. To a significant extent, TCM is an important part of comprehensive cancer treatment to improve the quality of life, delay the time of cancer progression, and prolong the median survival time. A clinical study has revealed that TCM combined with Western therapy improves the overall response rate of patients with PHC [5]. In basic research, TCM elicits active effects against hepatocarcinogenesis, proliferation, invasion, metastasis, and angiogenesis [6]. These outcomes may be advantageous to the clinical applications of TCM against cancers.

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The combination of TCM and Western therapy may also be a promising therapeutic strategy for PHC and other cancers. Although a review on the application of TCM injection to treat PHC was published in 2012, strong evidence has yet to be obtained to support the use of Chinese and Western integrative treatments for PHC [7]. Hence, this study aimed to perform a systematic review with meta-analysis on the efficacy and safety of TCM combined with Western techniques for PHC and provide clinicians with an overall recommendation for combination therapies to treat PHC.

Methods

Search strategy

The retrieval of literature language was set as Chinese and English. Chinese databases included Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP Chinese Science and Technology Periodical Database (VIP), China Biology Medicine disc (CBM), and Wan-Fang Database. English databases were PubMed and Cochrane. Each database was searched from their inception to June 30, 2015. The following search terms were used individually or in combination: primary hepatic carcinoma, traditional Chinese medicine, Chinese herbal medicine, and integrative medicine. We examined the reference lists from the retrieved articles and abstracts of conference proceedings to identify relevant studies. We also searched an important database of registry and results (www.clinicaltrial.gov), which is a significant data source of unpublished trials. Two independent reviewers (Bin Wang and Yuanxiong Long) performed the literature search. We jointly developed the following inclusion criteria: (1) all patients included in this study were diagnosed with PHC; (2) each included study was designed as a randomized controlled trial (RCT); (3) the experimental group was treated with TCM intervention combined with Western therapy, and the control group was subjected to Western therapy alone; and (4) outcomes, such as short-term clinical efficacy, quality of life, and survival time, were reported.

We also developed the following exclusion criteria: (1) one of the duplicated publications provided the same data; (2) data were incomplete or relevant information was not obtained from the raw data of studies; (3) TCM interventions were included in the control group; and (4) patients diagnosed with secondary liver cancer were chosen in case studies.

Data extraction

The following variables were extracted from each study: the first author's name, year of publication, study location, duration of follow-up, baseline condition of participants, the number of cases, clinical stage of the tumor, treatment duration, treatment measures, and clinical outcomes. Treatment measures consisted of Western therapy and TCM therapy; TACE, oral medication, chemotherapy, radiotherapy, and surgery are all included in the Western therapy. Clinical outcomes included the following: (1) Short-term (in-hospital/30 days) clinical efficacy rate (complete response [CR], partial response [PR]); (2) Survival rate; (3) Quality of life. The patient's quality of life was estimated by using Karnofsky performance score (KPS). With reference to WHO standards, the effectiveness of the quality of life was categorized into three grades, namely, alleviation, stabilization, and reduction. Alleviation was denoted by KPS scores that increased by greater than or equal to 10 after medication, stabilization was denoted by KPS scores that increased or decreased by less than 10 after medication, and reduction was denoted by KPS scores that reduced by greater than or equal to 10 after medication. For this systematic review, outcomes of alleviation and stabilization were considered the successful improvement of the quality of life.

Statistical analysis

Statistical heterogeneity was examined by Cochran's χ^2-test and by I^2-test, where I^2 values of 50% or more were considered to be indicators of a substantial level of heterogeneity [52]. When statistically significant heterogeneity was detected, the random-effect model was presented; otherwise, the fixed-effect model was used.

Review Manager Software version 5.2, which was the Cochrane Collaboration's program for preparing and maintaining Cochrane reviews, was used for meta-analysis in this research. The pooled effect size is expressed as odds ratio (OR) with 95% CI for dichotomous data and weighted mean differences (WMD) with 95% CI for continuous data. Funnel plots were generated to assess the potential publication bias. We also used Egger's test to assess publication bias with StatsDirect statistical software version 2.7.9. We examined the impact of each included study on the overall results in the sensitivity analysis. To test the robustness of pooled results, we conducted the sensitivity analysis according to results of risk bias assessments.

Results

Study description

From the six databases in Chinese and English, 3414 literature files were retrieved: CNKI (n = 997), VIP (n = 677), Wan-Fang (n = 1208), CBM (n = 427), PubMed (n = 105), and Cochrane (n = 0). After the titles and abstracts

were read, 875 studies were excluded because of irrelevant goals and 993 studies were carefully reviewed. Finally, 949 studies were further excluded on the basis of the eligibility criteria and 44 articles were included (Fig. 1). Furthermore, 6 studies were considered potentially relevant through the clinical trial database (www.clinicaltrial.gov). However, none of these potentially relevant studies satisfied the inclusion criteria (Supplementary data for website search).

In the 44 articles, the types of TCM treatment included Chinese herbal medicine (CHM) formula and Chinese medicine injection (CMI). Based on the TCM principle and treatment methods, CHM formulas in the experimental groups were divided into the following in descending order: detoxification dispersing stagnated liver (DSL), invigorating qi (IQ), and activating blood circulation (ABC). Among the CMIs, Aidi injection, Cinobufotalin injection, Xiaoaiping injection, and Kangai injection were the most commonly used.

Five kinds of Western conventional therapies were available: transcatheter arterial chemoembolization (TACE) operation was described in 23 articles, surgery operation in 4 articles, and other 17 articles mentioned radiotherapy, chemotherapy, and oral medication. Accumulated observed objects were in total of 3429 cases, of which 1802 were in the experimental group and 1627 were in the control group. In each article, the clinical stage of PHC was diagnosed as a middle or a late period. The specific information of included literature could be found in Table 1.

Results of meta-analysis

In the 32 included studies reporting the short-term clinical efficacy, merging effect analysis revealed that the short-term clinical efficacy rates (CR + PR) in the experimental group and the control group were 55.61% (689/1239) and 41.43% (493/1190), respectively. The fixed effect model was used because statistical heterogeneity was not significant (χ^2= 22.98, P= 0.85, I^2= 0%). The pooled effect of all independent trial results showed that TCM combined with Western treatment could improve the short-term clinical efficacy when compared with Western therapy alone (OR= 1.93, 95% CI, 1.62−2.30, $P <$ 0.00001) (Fig. 2). A subgroup analysis was performed to explore whether the clinical heterogeneity could be partially explained by the type of control group. The subgroup analysis indicated that no better improvement was observed for any of the included types of the control

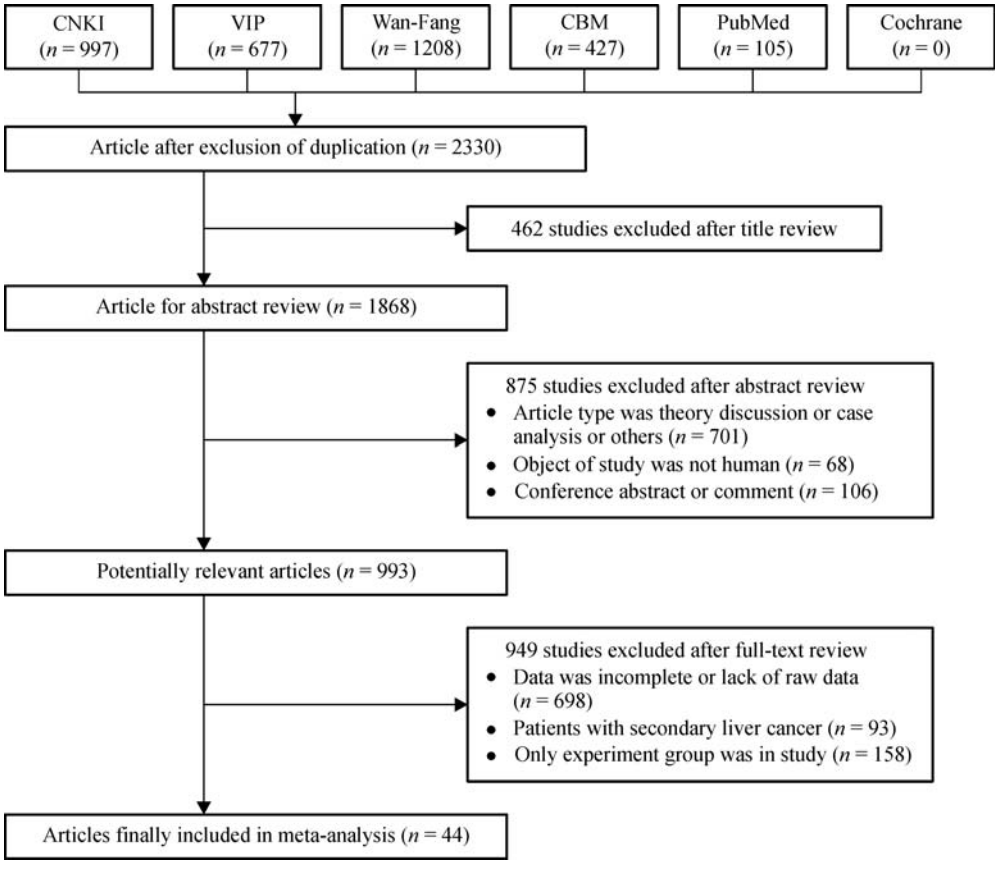

Fig. 1 Flow diagram of study inclusion and exclusion.

Table 1 Characteristics of included studies

Studies	Treatment measures		Sample size (E/C)	Outcomes	Average age (E/C)	Clinical stages	Treatment duration
	Experimental group	Control group					
Wang *et al.*, 2009 [8]	Chemotherapy plus CHM formula	Chemotherapy	40/37	C, D	51.67/52.4	Mid–late	4–6 weeks
Yan *et al.*, 2007 [9]	Oral medication plus CHM formula	Oral medication	87/42	B	52.3/51.5	Mid–late	1 month
Cui, 2013 [10]	Chemotherapy plus CHM formula	Chemotherapy	39/39	A, D	51.2/53.1	Mid	8 weeks
Han *et al.*, 2009 [11]	Oral medication plus CHM formula	Oral medication	24/24	A, B	–	Mid–late	3–4 months
Tian *et al.*, 2009 [12]	Oral medication plus Aidi injection and CHM formula	Oral medication	30/30	C, D	60.4/61.2	Late	3 months
Lin, 2012 [13]	Chemotherapy plus CHM formula	Chemotherapy	80/80	A, C	–	Late	2 months
Liu *et al.*, 2005 [14]	Chemotherapy plus CHM formula	Chemotherapy	33/33	A, B, D	58.15/57.61	Mid–late	1 month
Chen *et al.*, 2009 [15]	Chemotherapy plus Xiaoaiping injection	Chemotherapy	56/43	A, D	–	Mid–late	2–3 weeks
Zhou, 2010 [16]	Oral medication plus Cinobufotalin injection	Oral medication	29/29	A, C	–	Mid–late	20 days
Bai *et al.*, 2012 [17]	Radiotherapy plus Kangai injection	Radiotherapy	25/25	A, D	–	Mid–late	6 months
Lin *et al.*, 2009 [18]	Radiotherapy plus Kangai injection	Radiotherapy	42/40	A, D	50.6/49.3	Mid–late	4 weeks
Deng *et al.*, 2004 [19]	Radiotherapy plus CHM formula	Radiotherapy	56/39	C	–	Mid–late	1 month
Pang *et al.*, 2012 [20]	Radiotherapy plus CHM formula	Radiotherapy	48/52	A, C, D	–	Mid–late	2−3 months
Xiang, 2009 [21]	Surgery plus CHM formula	Surgery	40/40	A	59.38/50.56	Mid–late	3 month
Chen *et al.*, 2005 [22]	Surgery plus CHM formula	Surgery	30/30	C	48/49	Mid–late	1 month
Chen *et al.*, 2012 [23]	Surgery plus Cinobufotalin injection	Surgery	127/82	C	51.35/47.98	Early–mid	3–6 months
Chen *et al.*, 2005 [24]	Surgery plus CHM formula	Surgery	42/30	C	–	Mid–late	2 years
Lin *et al.*, 2005 [25]	TACE plus CHM formula	TACE	25/25	C	–	Mid–late	2 months
Zheng *et al.*, 2010 [26]	TACE plus CHM formula	TACE	30/31	A	46.2/45.2	Mid–late	1 month
Gu, 2011 [27]	TACE plus CHM formula	TACE	32/32	A, C	46.8/47.4	Mid–late	2 months
Lin, 2008 [28]	TACE plus CHM formula	TACE	58/58	A, B	56.5/57.6	Mid–late	2 months
Zhang *et al.*, 2012 [29]	TACE plus CHM formula	TACE	43/40	A, C, D	46.9/45.8	Mid–late	2 courses
Zeng *et al.*, 2011 [30]	TACE plus CHM formula	TACE	37/30	A, B, D	53.6/54.5	Mid–late	2 months
Di *et al.*, 2010 [31]	TACE plus CHM formula	TACE	32/30	A, B, C, D	54.6/56.1	Mid–late	4 months
Lu *et al.*, 2011 [32]	TACE plus CHM formula	TACE	34/32	B	55/56	Mid–late	3 months
Chi *et al.*, 2010 [33]	TACE plus CHM formula	TACE	60/60	A, B, C	–	Mid–late	2 months
Li *et al.*, 2011 [34]	TACE plus CHM formula	TACE	38/36	A, B, C	54.1/52.7	Mid–late	2 months
Zhang *et al.*, 2008 [35]	TACE plus CHM formula	TACE	31/30	A, C	51.3/49.1	Mid–late	2 months
Yang *et al.*, 2011 [36]	TACE plus Aidi injection	TACE	30/30	B, C	49.8/49	Mid–late	1 month
Yang, 2008 [37]	TACE plus Aidi injection	TACE	20/20	A, B	–	Late	2–3 months
Zhang *et al.*, 2009 [38]	TACE plus CHM formula	TACE	52/51	C	48/46	Mid–late	4 weeks
Ling, 2010 [39]	TACE plus CHM formula	TACE	64/64	A, B	–	Mid–late	2–3 months
Rong *et al.*, 2013 [40]	TACE plus CHM formula	TACE	30/30	A	–	Mid–late	1–2 months
Jiang *et al.*, 2012 [41]	TACE plus CHM formula	TACE	43/40	A, C	46.9/45.8	Mid–late	2 months
Tang *et al.*, 2014 [42]	Oral medication plus CHM formula	Oral medication	31/30	A, C	49.21/48.64	Mid–late	2 months
Zhang, 2014 [43]	Radiotherapy plus CHM formula	Radiotherapy	32/31	A, C, D	55.3/54.8	Mid–late	3 months
Tan, 2014 [44]	TACE plus CHM formula	TACE	34/34	A	52.9/51.29	Mid–late	3 months
Shang *et al.*, 2014 [45]	TACE plus CHM formula	TACE	30/29	A	–	Mid–late	1 month

(*Continued*)

Studies	Treatment measures		Sample size	Outcomes	Average age	Clinical stages	Treatment duration
	Experimental group	Control group	(E/C)		(E/C)		
Qiao *et al.*, 2014 [46]	TACE plus CHM formula	TACE	40/38	A	50.32/50.28	Mid–late	6 weeks
Li, 2014 [47]	TACE plus CHM formula	TACE	39/39	B	56.3/54.8	Mid–late	–
Qin, 2014 [48]	TACE plus CHM formula	TACE	40/40	A	63.5/61.5	Mid–late	–
Tang, 2014 [49]	Oral medication plus CHM formula	Oral medication	30/30	A	59.1/61.3	Mid–late	4 weeks
Wang, 2014 [50]	Oral medication plus CHM formula	Oral medication	30/30	B	46.9/47.1	Mid–late	3 months
Wang *et al.*, 2014 [51]	TACE plus CHM formula	TACE	38/22	B	53.5/52.1	Mid–late	4−6 weeks

A, short–term clinical efficacy. B, quality of life. C, survival rate. D, adverse effect.

group; the difference among results of subgroup analysis was not statistically significant (χ^2= 7.35, P = 0.12) (Fig. 2).

Based on KPS, "alleviation" and "stabilization" rate data among 14 RCTs showed the effect of the quality of life; the "alleviation" and "stabilization" rate in the experimental group was 84.07% (496/590) and 60.81%(315/518) in the control group. The fixed effect model was used because statistical heterogeneity was not significant (χ^2 = 6.65, P = 0.92, I^2 = 0%). The combined results showed that TCM with Western treatment could improve the quality of life with statistical significance compared with Western therapy alone (OR = 3.67, 95% CI, 2.74−4.91, $P < 0.00001$) (Fig. 3). A subgroup analysis was performed to explore whether the clinical heterogeneity could be partially explained by the type of the control group. The subgroup analysis indicated that no better improvement was observed for any of the included types of the control group; the difference among results of subgroup analysis was not statistically significant (χ^2 = 0.89, P = 0.64) (Fig. 3).

Thirteen RCTs (872 cases) showed that the half-a-year survival rates of the experimental group and the control group were 81.12% (361/445) and 69.32% (296/427), respectively. The fixed effect model was used because statistical heterogeneity was not significant (χ^2 = 8.54, P = 0.66, I^2 = 0%). The combined results showed that TCM with Western treatment could improve the half-a-year survival rate with statistical significance compared with Western therapy alone (OR = 2.04, 95% CI, 1.46−2.87, $P < 0.0001$). A subgroup analysis was performed to explore whether the clinical heterogeneity could be partially explained by the type of control group. The subgroup analysis showed that the result of the rest of the four subgroups was consistent with the above overall results except that the subgroup was related to surgery, in which the difference was not significant between TCM with surgery treatment and surgery alone for improving the half-a-year survival rate (OR = 0.69, 95% CI, 0.06−7.97, P = 0.77) (Supplementary data for meta-analysis).

Nineteen RCTs (1655 cases) indicated that the one-year survival rates of the experimental group and the control group were 65.21% (568/871) and 50.38% (395/784), respectively. The fixed effect model was used because statistical heterogeneity was not significant (χ^2 = 9.68, P = 0.94, I^2 = 0%). The overall pooled result showed that TCM with Western treatment could improve the one-year survival rate with statistical significance compared with Western therapy alone (OR = 2.01, 95% CI, 1.62−2.50, $P < 0.00001$). A subgroup analysis was performed to explore whether the clinical heterogeneity could be partially explained by the type of the control group. The surgery and radiotherapy subgroup analysis results indicated that the integrative treatment has no better effect than that of conventional Western therapy with statistical significance (the surgery subgroup: OR = 1.52, 95% CI, 0.85−2.71, P = 0.16; the radiotherapy subgroup: OR = 1.53, 95% CI, 0.89−2.61, P = 0.13) (Supplementary data for meta-analysis).

Ten RCTs (776 cases) revealed that the two-year survival rates of the experimental group and the control group were 56.67% (238/420) and 38.76% (138/356), respectively. The fixed effect model was used because statistical heterogeneity was not significant (χ^2 = 13.79, P = 0.13, I^2 = 35%). The overall pooled result showed that TCM with Western treatment could improve the two-year survival rate with statistical significance compared with Western therapy alone (OR = 2.16, 95% CI, 1.58−2.95, $P < 0.00001$). A subgroup analysis was performed to explore whether the clinical heterogeneity could be partially explained by the type of the control group. The subgroup analysis indicated that no better improvement was observed for any of the included types of control group. However, only one trial reported the two-year survival rate for the oral medication type of control group, which appeared to have a higher income with OR = 8.84 (95%CI, 1.77−44.07); the difference among the results of subgroup analysis was statistically significant (χ^2 = 8.77, P = 0.03) (Supplementary data for meta-analysis).

Twelve of the included trials reported adverse events, and no report showed that these adverse events were directly relevant to the intervention. Detailed adverse

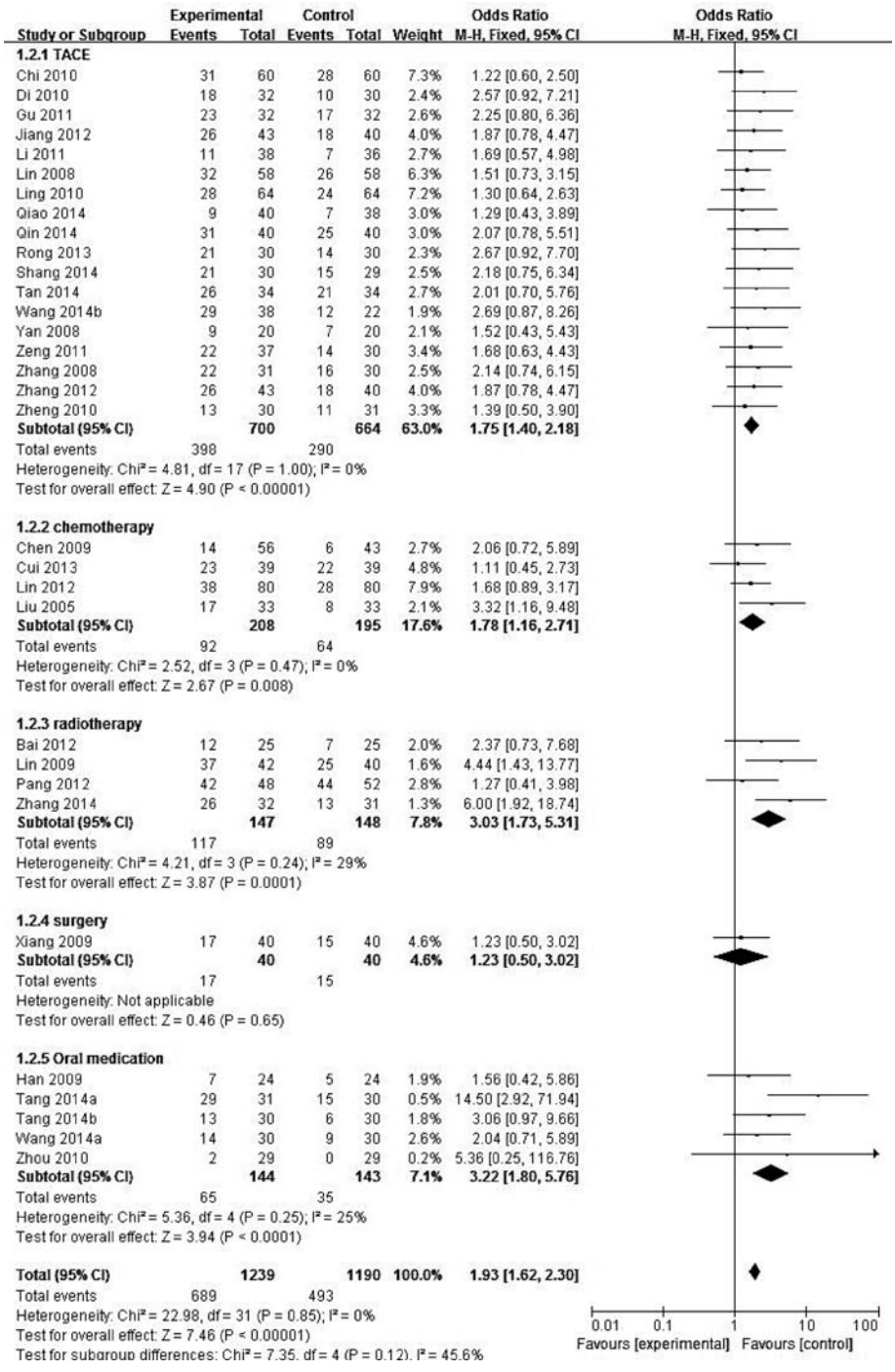

Fig. 2 Forest plot with a combined result of meta-analysis for odds ratio (OR) of short-term clinical efficacy.

events included nausea, bleeding, constipation, fever, diarrhea, fatigue, and hepatalgia. A total of 109 cases of nausea, 12 cases of bleeding, 47 cases of fever, 72 cases of hepatalgia were observed in the treatment group and 158 cases of nausea, 25 cases of bleeding, 92 cases of fever, 107 cases of hepatalgia in the control group. The significant difference between the two groups was determined (bleeding: OR = 0.38, 95%CI, 0.18−0.81; fever: OR = 0.21, 95%CI, 0.06−0.81; hepatalgia: OR = 0.26, 95%CI, 0.15−0.45; nausea: OR = 0.30, 95%CI, 0.20−0.46) (Fig. 4).

Assessment of risks of bias

According to the evaluation methods of *the Cochrane Collaboration Handbook for Systematic Reviews*, the risk

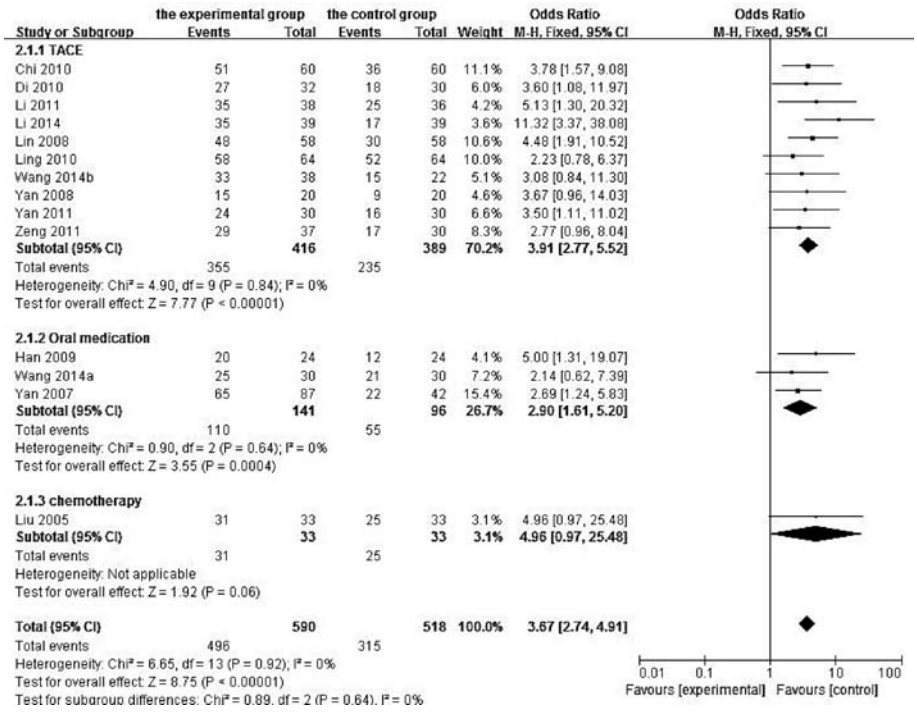

Fig. 3 Forest plot with a combined result of meta-analysis for odds ratio (OR) of the quality of life.

of bias was assessed rigorously in the following aspects [52]: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessments (detection bias), incomplete outcome data addressed (attrition bias), selective outcome reporting (reporting bias). The quality of the included trials was categorized as low, unclear, or high risk of bias. The assessment was conducted independently by two reviewers (Bin Wang and Yuanxiong Long); divergent viewpoints were resolved by discussing with a third researcher (Li Ma).

Each of the included studies involved randomization, but only 12 studies presented specific methods of random sequence generation. No study described allocation concealment and blinding. Only two studies were accessed "yes" in incomplete outcome data addressed; the selective outcome reporting was not shown in all of the included studies. Based on a methodological assessment of *the Cochrane Collaboration Handbook for Systematic Reviews*, 12 trials likely exhibited an "unclear" risk of bias and 32 trials possibly showed a "high" risk of bias (Supplementary Table 1).

Assessment of publication bias

Based on 32 kinds of literature reporting short-term clinical efficacy, although obvious publication bias was not implied in Fig. 5, primary symmetry trend on both sides could not be distinct. Furthermore, results of Egger's test indicated no evidence with potential publication bias with the exception of short-term clinical efficacy (Supplementary data for Egger's tests).

Assessment of clinical heterogeneity and sensitivity analysis

The clinical heterogeneity was assessed by noting the difference in the distribution of participants' characteristics among trials (age, gender, specific diagnosis subtypes, and duration of disorder) and comparing trial design factors (the type of TCM intervention and Western therapy). Potential sources of heterogeneity were investigated in subgroup analyses with variables. To maximize similarities among studies that would be combined, subgroup analysis was conducted based on types of Western therapies. A clinical heterogeneity is observed among these included studies: (1) CHM formula used in the experimental group was different Chinese herbal ingredients; (2) Western interventions used in trials were not exactly the same.

A sensitivity analysis was conducted by omitting several studies with high risk of bias and then recalculating pooled results. The overall effect estimates did not vary significantly; it indicated that pooled results were not substantially influenced by any of the individual study (Supplementary data for meta-analysis).

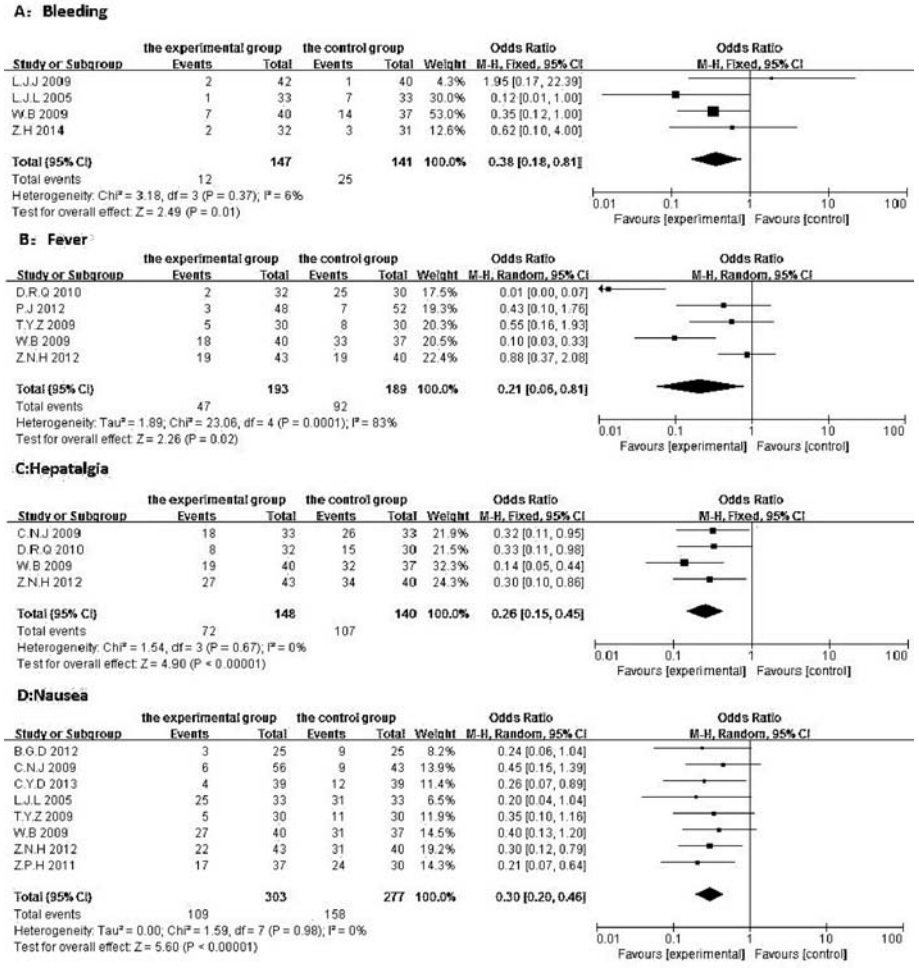

Fig. 4 Forest plot with a combined result of meta-analysis for odds ratio (OR) of adverse effect.

Summary of systematic review

PHC is a multifactor and multistage process and discovering a specific medication is relatively difficult. In China, there has been a long history of using TCM in the treatment of PHC and other malignancies. Based on Chinese Medicine theory, PHC is named "Ji-Ju." Basic pathogeneses leading to PHC are considered asthenia of healthy qi into the interior, toxicity condensation, and the stagnation of qi and blood activity [53]. Based on the development of the disease, TCM syndromes of PHC are usually classified into four types: qi stagnation and blood stasis, dampness stagnancy due to spleen deficiency, dampness-heat of liver and gallbladder, and yin deficiency of liver and kidney. In this research, detoxification, invigorating qi, and activating blood circulation were the major principles of TCM treatment, which was consistent with TCM syndromes description.

In China, there has been a long history of using TCM in the liver cancer treatment and other malignancies. Recently, accumulating evidence demonstrates that TCM attenuates hepatocellular carcinoma proliferation, invasion, and metastasis in basic research and improves survival and overall response rate as well in clinical study [54]. To the best of our knowledge, this study is the first to conduct a systematic review and meta-analysis of TCM combined with Western therapy for PHC. We applied our broad criteria to pool the studies and did not restrict the type of TCM or Western formulation. A total of 44 studies involving 3429 participants suffering from PHC were selected in this systematic review, the efficacy assessment of integrative TCM and Western therapies was presented by short-term clinical efficacy, quality of life, and survival rates. Meta-analysis results indicated that TCM and Western integrative treatment has better overall effect in PHC than the Western intervention alone. This evidence suggests that TCM is useful and effective for the treatment of PHC, displays that the combination with TCM and Western therapy can postpone tumor recurrence and metastasis, and prolong the overall survival time of patients with PHC. Despite apparent positive findings, insufficient evidence is available to support the routine use

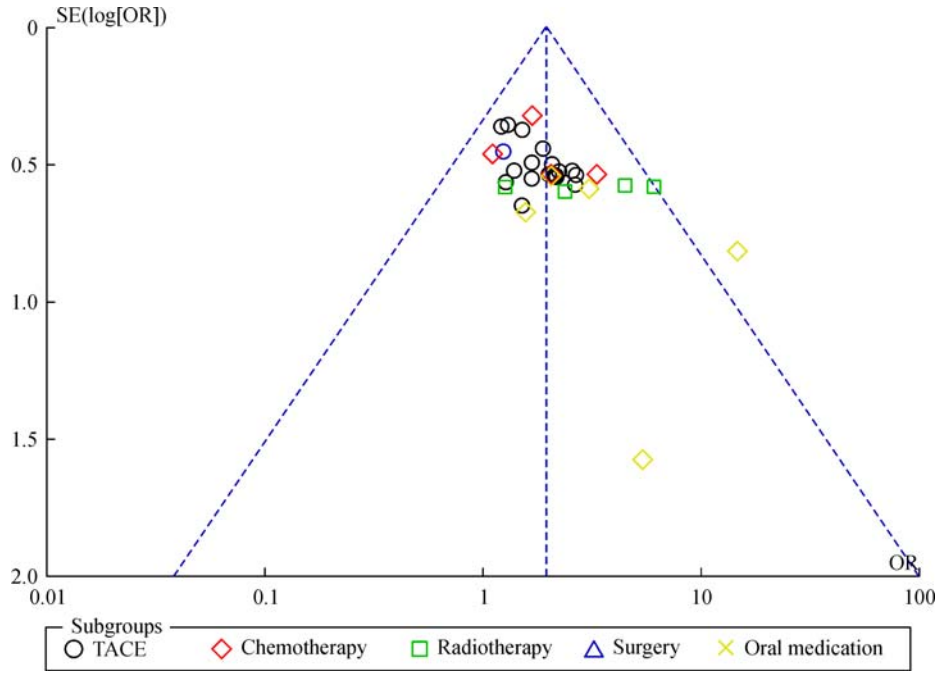

Fig. 5 Funnel plot of short-term clinical efficacy.

of TCM intervention for PHC due to the poor methodological quality and the limited number of trials of included studies. In this review, the subgroup analysis results of survival rate showed that TCM plus surgery and radiotherapy had no better effect than conventional Western medicine therapy, which is substantial for further investigation. Ping *et al*. [55] addressed that the surgery therapy and radiotherapy for PHC could cause damage to the normal liver tissue, and then the formed liver regeneration microenvironment would promote the recurrence and metastasis of liver cancer. TCM intervention was required immediately after the surgery or radiotherapy treatment because the liver regeneration microenvironment should be improved to increase the treatment efficacy. However, TCM therapy was not appropriate as patients were treated with surgical resection or radiotherapy. Therefore, TCM therapy combined with surgery or radiotherapy did not show the expected efficacy.

Furthermore, in this research, only 12 studies mentioned adverse events because adverse effects did not occur, or no severe adverse events were found and no treatment was stopped because of these adverse events in the experimental group. However, the evidence is limited to conclude on the issue of safety because of a small number of trials.

Inherent and methodological weaknesses should be addressed. First, only five studies provided specific information on the random sequence; none of them reported the allocation concealment. This would possibly exaggerate the treatment effect. None of the included studies mentioned blinding, which were possibly influenced by observer bias. Second, the included trials were of relatively small samples in individual studies, which may reduce the validity of their statistical analysis. Only one of the included studies was selected from English medical databases. Almost all of the included trials indicated that the positive effect of TCM combined with Western therapies was better than that of Western therapies alone. Vickers [56] reported that some Asian countries, including China, publish usually high proportions of positive results. These publications bias would be another limitation for the generalizability of the clinical use. Third, subgroups based on the four types of CHM formulas should be included independently in the meta-analysis. Unfortunately, this was limited by the small number of trials when types of Western therapies were further considered. Lastly, adverse effects should receive considerable attention because safety is a fundamental and critical factor in the provision of herbal medicine for systematic review. In this research, only 12 included studies mentioned adverse effects. Since World Health Organization (WHO) published WHO guidelines on safety monitoring of herbal medicines in 2004, all adverse events must be reported in prospective clinical trials.

Conclusions

This study aimed to provide supporting evidence for the effectiveness of TCM combined with Western therapies.

Bin *et al*. [57] showed that Chinese herb plus TACE therapy can alleviate the clinical symptoms of PHC to prolong the survival time of patients. Yang [58] showed that TCM combined with Western therapy can reduce the adverse effects of PHC and improve the quality of life. Although the evidence remained weak because of the poor methodological quality of the included studies, this review provided relevant evidence supporting the efficacy and safety of TCM combined with Western therapies for the treatment of PHC.

Our study revealed that many Chinese clinical practitioners have been exposed to inappropriate clinical epidemiology training. From a clinical perspective, our results are promising but should be interpreted with caution. In future studies, individual RCTs should incorporate accepted standards for trial design and reporting. These studies should be based on several guidelines, such as CONSORT statement [59], CONSORTPRO extension [60], guidelines for RCTs investigating Chinese herb medicine [61], and CONSORT for TCM. Appropriate outcome indicators consistent with international standards, blinding in allocation concealment, and valid follow-up periods should be employed in subsequent research.

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Compliance with ethics guidelines

Li Ma, Bin Wang, Yuanxiong Long, and Hanmin Li declare that there is no conflict of interests regarding the publication of this paper. This manuscript is a review article and does not involve a research protocol requiring approval by the corresponding institutional review board or ethics committee.

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