Review Article

Add-On Therapy with Traditional Chinese Medicine Improves Outcomes and Reduces Adverse Events in Hepatocellular Carcinoma: A Meta-Analysis of Randomized Controlled Trials

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Background and Aims. Traditional Chinese medicine (TCM) therapy for hepatocellular carcinoma remains controversial. This study aimed to evaluate the efficacy and safety of TCM regimens in HCC treatment. *Methods.* Randomized controlled trials (RCTs) up to June 1, 2016, of the TCM treatment for hepatocellular carcinoma were systematically identified in PubMed, CNKI, Ovid, Embase, Web of Science, Wanfang, VIP, CBM, AMED, and Cochrane Library databases. *Results.* A total of 1010 and 931 patients in 20 RCTs were randomly treated with add-on TCM therapy and conventional therapy, respectively. The additional use of TCM significantly improved six-month, one-year, two-year, and three-year overall survival rates in HCC cases (RR = 1.3, $P = 0.01$; RR = 1.38, $P = 0.0008$; RR = 1.44, $P < 0.0001$; RR = 1.31, $P = 0.02$, resp.). Add-on TCM therapy significantly increased PR rate and total response rate (tRR) and reduced PD rate compared to those in control group (34.4% versus 26.3%, RR = 1.30, $P = 0.002$; 41.6% versus 31.0%, RR = 1.30, $P < 0.0001$; and 16.6% versus 26.5%, RR = 0.64, $P < 0.0001$, resp.). Additionally, TCM combination therapy significantly increased the quality of life (QOL) improvement rate and reduced adverse events including leukopenia, thrombocytopenia, anemia or erythropenia, liver injury, and gastrointestinal discomfort in HCC patients (all $P < 0.05$). *Conclusion.* Add-on therapy with TCM could improve overall survival, increase clinical tumor responses, lead to better QOL, and reduce adverse events in hepatocellular carcinoma.

1. Introduction

Primary liver cancer is the sixth most common cancer and the third most common cause of cancer-related deaths. 70%~90% primary liver cancers occurring worldwide are hepatocellular carcinoma (HCC), which is the fastest growing cause of cancer-related death globally [1, 2]. Recent epidemiology data revealed that liver cancer might account for more cancer-related deaths worldwide [3]. HCC has a 5-year survival rate of only 14% approximately [4]. Most HCCs are diagnosed at an intermediate to advanced stage, at which point surgical treatment and/or chemical embolism are no longer feasible [5]. Therefore, to improve outcome of HCC patients, an alternative or novel approach is required.

Previous report showed a large prevalence of a diversity of traditional Chinese medicine (TCM) clinical application for cancer patients [6]. Sufficient evidence has demonstrated that natural compounds with various types of medicinal ingredients can substantially inhibit tumor formation [7]. Many clinical articles have reported that TCM or TCM plus chemotherapy can significantly alleviate symptoms, stabilize tumor size, reinforce the constitution, enhance therapy tolerance and immunological function, obviously reduce the incidence rate of adverse events, and prolong patients' survival duration for unresectable HCC [8–11].

Unfortunately, reporting of RCTs on treatment of HCC with TCM is still in low quality, not meeting the CONSORT

and TREND statement. High quality of evidence based on the existing clinical information is still unavailable [6, 12]. A recent meta-analysis also announced that many RCTs of TCM therapy in HCC are not, in fact, randomized [13]. Thus, only RCTs reported randomized methods were included in our current meta-analysis. The purpose of this study is to systematically review and meta-analyze data from RCTs for evidence on the efficacy and safety of add-on therapy with TCM in the treatment of HCC.

2. Materials and Methods

2.1. Search Strategy and Study Selection. We searched Pub-Med, Chinese National Knowledge Infrastructure (CNKI) Database, Wanfang Database, Chinese Biomedical (CBM) Database, Chinese Science and Technology Periodical Database (VIP), Allied and Complementary Medicine Database (AMED), Ovid, Embase, Web of Science, and Cochrane Library databases until June 1, 2016. The following medical subject headings were used: "hepatocellular carcinoma;" "primary liver cancer;" "Traditional Chinese Medicine;" "alternative medicine;" "complementary medicine;" "Chinese herbal medicine;" "herb/herbal;" and "decotion/formulation." Electronic searches were supplemented with manual searches of reference lists used in all of the retrieved review articles, primary studies, and abstracts from meetings to identify other studies not found in the electronic searches. Literature was searched by two authors (Z Yang and X Liao) independently.

Two authors independently selected trials and discussed with each other when inconsistencies were found. Articles that satisfy the following criteria were included: (1) for study types, RCTs with randomized method; (2) for participants, HCCs; (3) for interventions, TCMs compared with placebo or no treatment; in addition, any cointervention had to be the same in both groups except for the TCM formulation; (4) for outcome, overall survival and/or solid tumors responses; and (5) available full texts. If the duration and sources of study population recruitment overlapped by more than 30% in two or more papers by the same authors, we only included the most recent study or the study with the larger number of HCC patients. Studies were excluded if they meet the following criteria: (1) studies "so-called" randomized without randomized methods; (2) studies without control subjects or control participants receiving TCM treatment including herbal medicine and acupuncture; (3) studies reporting only laboratory values and/or symptom improvement rather than survival outcomes and clinical responses.

2.2. Data Extraction and Methodological Quality Assessment. Two researchers independently read the full texts and extracted the following contents: publication data; study design; sample size; patient characteristics; treatment protocol; and outcome measures. The methodological qualities of the included RCTs were assessed according to Cochrane Collaboration's Tool described in Handbook version 5.1.0 [14]. Two authors (Z Yang and X Liao) independently assessed quality, and inconsistency was discussed with other reviewer-authors (Y Yu and X Chen) who acted as arbiters.

2.3. Definitions. All the diagnosis should be according to guidelines. The primary outcome overall survival was defined as the time from HCC diagnosis until the death due to any cause. Solid tumor response is categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and CR + PR as a proportion for total response rate (tRR) according to the World Health Organization (WHO) criteria [15] or the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines [16, 17]. Karnofsky performance status (KPS) [18] and adverse events were also measured in our study.

2.4. Statistical Methods. The effect measures of interest were risk ratios (RRs) and the corresponding 95% confidence intervals (CIs). Heterogeneity across studies was informally assessed by visually inspecting forest plots and formally estimated by Cochran's Q test in which chi-square distribution is used to make inferences regarding the null hypothesis of homogeneity (considered significant at $P < 0.10$). A rough guide to our interpretation of I^2 was listed as follows:

   (i) 0% to 40% shows that heterogeneity may not be important.

  (ii) 30% to 60% corresponds to moderate heterogeneity.

 (iii) 50% to 90% exhibits substantial heterogeneity.

 (iv) 75% to 100% indicates considerable heterogeneity [14, 19].

If the eligibility of some studies in the meta-analysis was uncertain because of missing information, a sensitivity analysis was performed by conducting the meta-analysis twice: in the first meta-analysis, all of the studies were included; in the second meta-analysis, only those that were definitely eligible were included. A fixed-effects model was used initially for our meta-analyses; a random-effects model was then used in the presence of heterogeneity. Description analysis was performed when quantitative data could not be pooled. Review Manager version 5.1 software was used for data analysis.

3. Results

3.1. Study and Patient Characteristics. Totally, 8990 abstracts were reviewed; among these articles, 393 were retrieved that are closely related to the current subject. The study selection process was summarized in Figure 1. Finally, 20 RCTs [20–39] were included in this meta-analysis. The baseline characteristics of included studies are described in Table 1.

3.2. Methodological Quality Assessment. The methods of randomization were described adequately in all studies [20–39], which were considered as random number table [20, 21, 23, 24, 27, 28, 30–32, 34], sealed envelopes [22, 26, 37–39], randomized block [25, 35], draw method [29, 36], and randomization according to hospitalized date [33]. We hence considered low risks in terms of selection bias. Except for study reported by Tian et al. [35], blind-methods of other studies were not available, which were considered high risk in terms of performance bias. Detection bias was unclear in all studies

TABLE 1: Characteristics of studies included in the meta-analysis.

Study	Number of cases Treatment	Number of cases Control	Control regimen	Chemo times	TCM intervention	TCM duration (days)	HCC staging	Child-Pugh score	KPS score	Randomized method
Huang et al. 2001 [20]	32	30	Palliatively supporting therapy	None	Jianpi Xiaoji oral liquid	30	III, IV	A, B, C	≥60	Random number table
Huang et al. 2009 [21]	40	37	TACE	1~2	Ganji decoction	28~42	II, III	A, B	≥60	Random number table
Li et al. 2008 [22]	50	46	TACE	2~7	Chinese toad bufotoxin injection	28~112	Okuda I, II, III	A, B	≥60	Sealed envelopes
Li et al. 2013 [23]	31	22	TACE	3	Hydroxycamptothecin and Chinese herbal compound	84	II, III	NA	NA	Random number table
Li et al. 2016 [24]	26	26	TACE	NA	Aidi injection	30	III, IV	NA	30~60	Random number table
Lin et al. 2005 [25]	52	33	TACE	2	Hydroxycamptothecin and Shentao Ruangan pill	56	II, III	A, B	≥60	Randomized block
Ling et al. 2001 [26]	162	151	TACE/PEI	NA	Sisheng decoction/Chinese toad bufotoxin injection/norcantharidin tablets	Irregular	II, III	NA	NA	Sealed envelopes
Liu 2011 [27]	32	30	Palliatively supporting therapy	None	Chinese herbal compound	21	III, IV	A, B, C	≥60	Random number table
Liu and Lü 2016 [28]	53	53	TACE + PMCT	3	Chinese herbal compound	90~135	NA	A, B	NA	Random number table
Lu 2008 [29]	69	69	TACE	NA	Aidi injection	20	NA	NA	60~90	Draw method
Lü et al. 2014 [30]	63	63	TACE	NA	Shenyi capsules	60	NA	NA	60~90	Random number table
Min and Zhou 2011 [31]	23	22	Palliatively supporting therapy	None	Chinese herbal compound	84	II, III	A, B	72 ± 8	Random number table
Ren and Cheng 2004 [32]	104	68	TACE	NA	Chinese herbal compound	≥90	II, III	NA	NA	Random number table
Shao et al. 2001 [33]	30	30	TACE	2~10	Chinese herbal compound	180~300	II, III	NA	NA	According to hospitalized date
Shi and Tang 2013 [34]	42	56	TACE	NA	Kang'ai injection and Carapacis Trionycis Bolus	56	NA	A, B	≥60	Random number table
Tian et al. 2008 [35]	49	48	TACE	NA	Chinese herbal compound	28	II, III	A, B	≥60	Randomized block, single blind
Xie et al. 2014 [36]	34	34	TACE	NA	Chinese herbal compound	40	NA	A, B	≥60	Draw method
Yang et al. 2011 [37]	30	30	TACE	NA	Aidi injection	30	NA	A, B, C	≥70	Sealed envelopes

Table 1: Continued.

Study	Number of cases		Control regimen	Chemo times	TCM intervention	TCM duration (days)	HCC staging	Child-Pugh score	KPS score	Randomized method
	Treatment	Control								
Yi et al. 2008 [38]	28	23	TACE	3	Kang'ai injection	45	II, III	NA	≥60	Sealed envelopes
Zhong et al. 2014 [39]	60	60	Hepatectomy	None	Chinese herbal compound	365	I~IIIa	A, B	NA	Sealed envelopes

TACE, transcatheter arterial chemoembolization; PEI, percutaneous ethanol injection; PMCT, percutaneous microwave coagulation therapy; KPS, Karnofsky performance status.
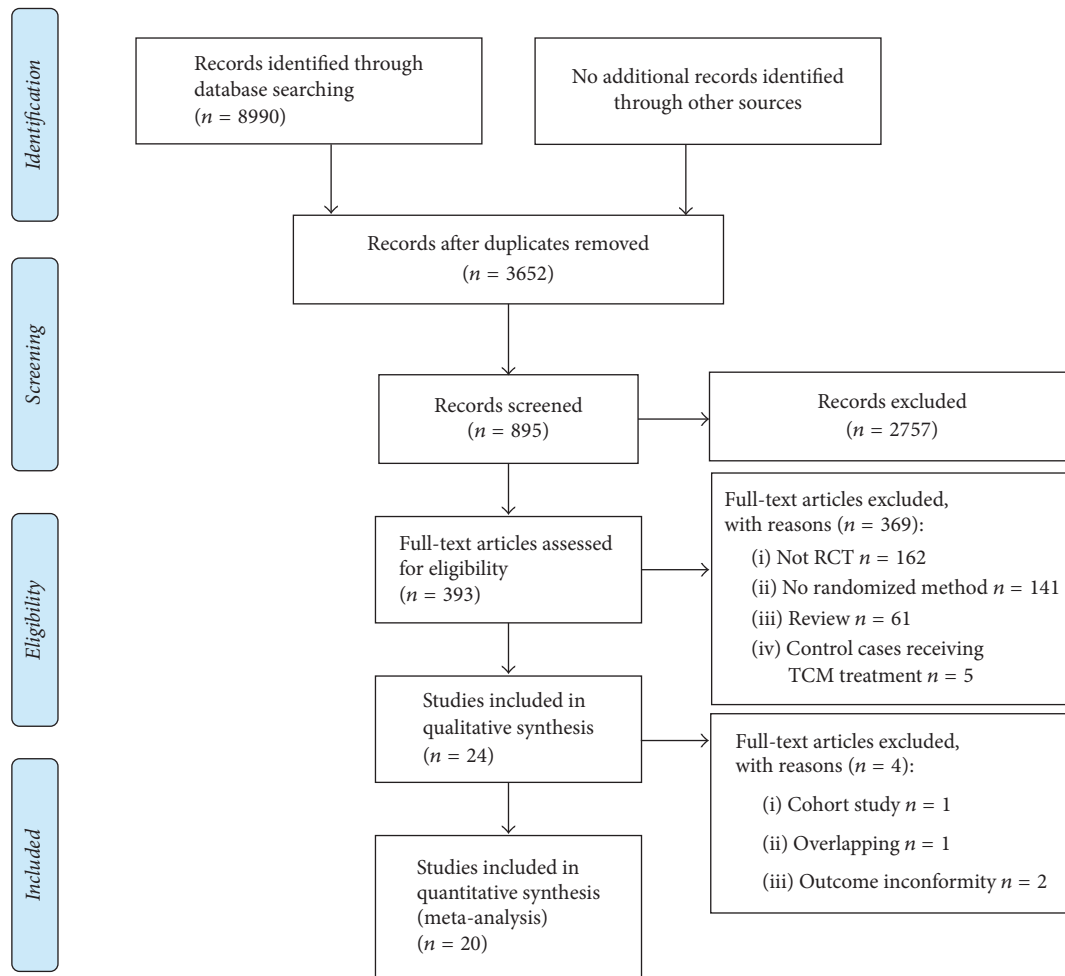
Figure 1: Flow diagram of study selection.

with no presenting of blinding of outcome assessment. Less than 15% of participants were lost to follow-up in the three studies [20, 21, 25, 35–37, 39]; these parameters were considered low risk in terms of incomplete outcome data. Selective reporting was found in three studies [21, 25, 35] because these researches failed to present the clinical data of participants in ITT analysis. Other potential biases were unclear in these trials (Figure 2).

3.3. Overall Survival. No heterogeneity was found among the included studies [21, 31, 35], which reported three-month survival in the two groups. No significance of three-month survival was found in HCC patients between TCM group and control group (RR = 1.03, 95% CI = 0.93–1.15, $P = 0.58$, Figure 3(3.1)). Heterogeneity was significant when we compared six-month survival and one-year survival ($P < 0.00001$, $I^2 = 80\%$ and $P < 0.00001$, $I^2 = 84\%$, resp.). As shown in Figure 3, TCM therapy could significantly prolong six-month survival and one-year survival of HCC patients compared to control (RR = 1.30, 95% CI = 1.06–1.59, and $P = 0.01$ and RR = 1.38, 95% CI = 1.14–1.67, and $P = 0.0008$, resp., Figure 3(3.2 and 3.3)).

No heterogeneity was found between studies comparing two-year survival and three-year survival between the two groups ($P = 0.18$, $I^2 = 30\%$ and $P = 0.13$, $I^2 = 40\%$, resp.). Meta-analysis of RCTs [22, 23, 25, 26, 28–30, 32, 33] using a random-effects model showed that the two-year survival rate of HCC patients in TCM group was significantly higher than that in control group [280/614 (45.6%) versus 176/535 (32.9%), RR = 1.44, 95% CI = 1.20–1.72, and $P < 0.0001$, Figure 3(3.4)]. Similarly, the three-year survival rate of HCC patients receiving TCM therapy was significantly higher than that in control group [194/541 (35.9%) versus 140/494 (28.3%), RR = 1.31, 95% CI = 1.05–1.63, and $P = 0.02$, Figure 3(3.5)].

3.4. CR, PR, SD, PD, and tRR. As shown in Table 2, no heterogeneity was among comparisons of CR, PR, SD, PD, and tRR. Thus, a fixed-effects model was used. The CR rate of HCC patients in TCM group was higher than that in control group, but no statistical difference was found (RR = 1.47, 95% CI = 0.96–2.24, and $P = 0.07$, Figure S1; see Supplementary Material available online at https://doi.org/10.1155/2017/3428253). However, meta-analysis of RCTs [20, 22–25, 27, 29, 30, 32, 34–36, 38] demonstrated that HCC patients receiving TCM

TABLE 2: Solid tumor responses comparisons of HCC patients.

Comparisons	Studies	Groups	Clinical responses (%)	Heterogeneity				RR	95% CI	P value
				Chi^2	df	P	I^2 (%)			
Complete response (CR)	[22, 23, 29, 30, 32, 34–36]	Treatment	44/442 (10.0)	3.07	7	0.88	0	1.47	0.96–2.24	0.07
		Control	26/406 (6.4)							
Partial response (PR)	[20, 22–25, 27, 29, 30, 32, 34–36, 38]	Treatment	210/610 (34.4)	9.96	12	0.62	0	1.30	1.10–1.53	0.002
		Control	145/551 (26.3)							
Stable disease (SD)	[20, 22–25, 27, 29, 30, 32, 34–36, 38]	Treatment	260/610 (42.6)	15.89	12	0.2	24	0.95	0.84–1.08	0.47
		Control	241/551 (43.7)							
Progressive disease (PD)	[20, 22–25, 27, 29, 30, 32, 34–36, 38]	Treatment	101/610 (16.6)	9.22	12	0.68	0	0.64	0.52–0.80	<0.0001
		Control	146/551 (26.5)							
Total response rate (tRR)	[20, 22–25, 27, 29, 30, 32, 34–36, 38]	Treatment	254/610 (41.6)	13.56	12	0.33	12	1.3	1.16–1.53	<0.0001
		Control	171/551 (31.0)							
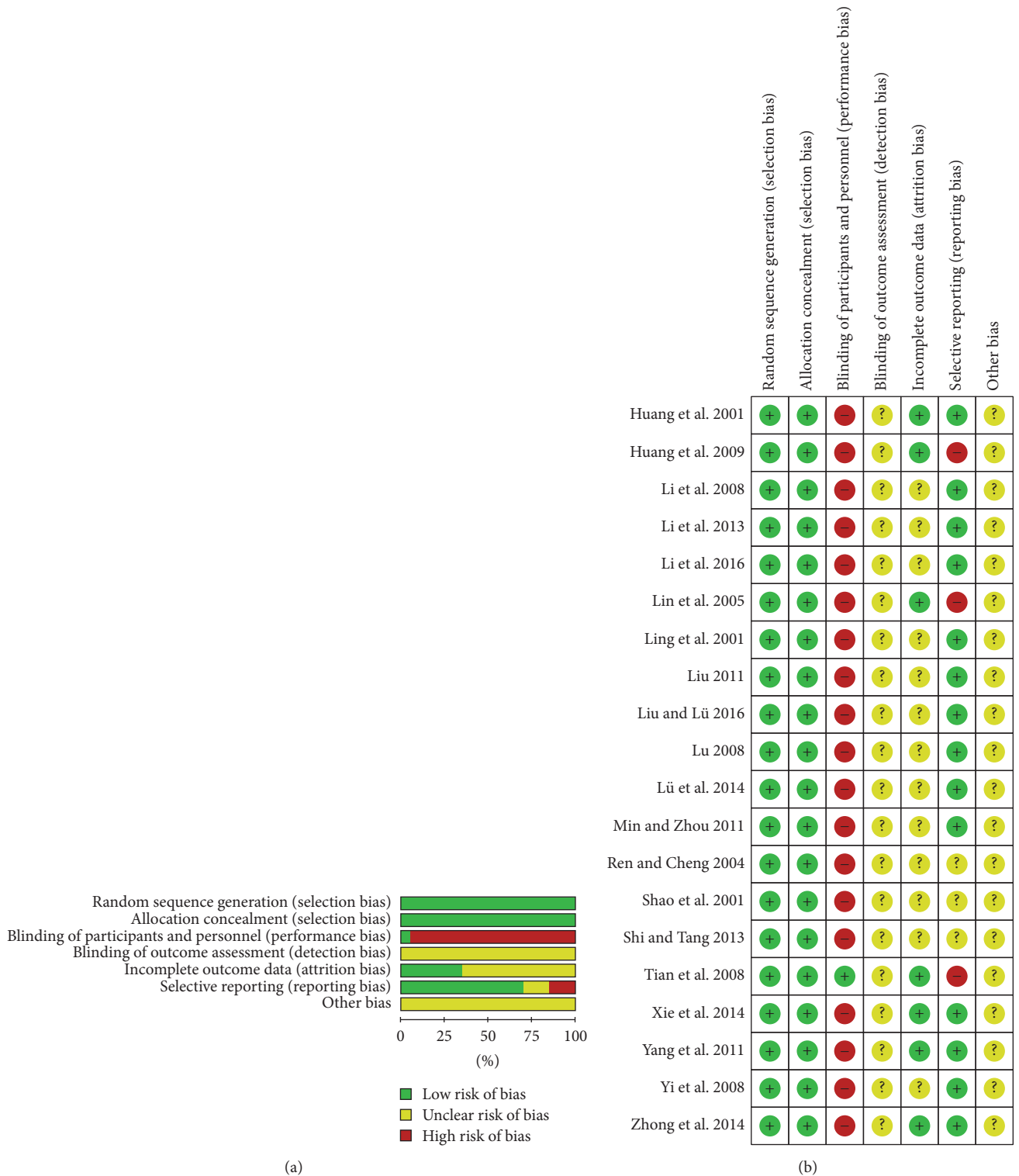
FIGURE 2: Risk of bias graph (a) and risk of bias summary (b).

therapy achieved significantly higher PR rate and tRR than those in control group (34.4% versus 26.3%, RR = 1.30, 95% CI = 1.10–1.53, and P = 0.002 and 41.6% versus 31.0%, RR = 1.30, 95% CI = 1.16–1.53, and P < 0.0001, resp., Figure S2 and

Figure S5). In contrast, HCC patients in TCM group suffered from lower PD rate significantly than those in control group (16.6% versus 26.5%, RR = 0.64, 95% CI = 0.52–0.80, and P < 0.0001, Figure S4). No statistical significance was found

Study or subgroup	TCM group Events	TCM group Total	Control group Events	Control group Total	Weight	Risk ratio M-H, random, 95% CI
3.1. Three-Month Survival						
Huang et al. 2009	31	40	26	37	3.2%	1.10 [0.84, 1.44]
Min and Zhou 2011	23	23	22	22	4.3%	1.00 [0.92, 1.09]
Tian et al. 2008	39	49	35	48	3.5%	1.09 [0.87, 1.36]
Subtotal (95% CI)		112		107	11.1%	1.03 [0.93, 1.15]
Total events	93		83			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.58$, df = 2 ($P = 0.28$); $I^2 = 23\%$
Test for overall effect: $Z = 0.56$ ($P = 0.58$)

3.2. Six-Month Survival						
Huang et al. 2001	21	32	12	30	1.9%	1.64 [0.99, 2.72]
Huang et al. 2009	25	40	14	37	2.0%	1.65 [1.02, 2.66]
Li et al. 2008	37	50	35	46	3.5%	0.97 [0.77, 1.22]
Lin et al. 2005	34	52	18	33	2.6%	1.20 [0.83, 1.73]
Ling et al. 2001	152	162	141	151	4.4%	1.00 [0.95, 1.06]
Liu 2011	21	32	12	30	1.9%	1.64 [0.99, 2.72]
Min and Zhou 2011	20	23	18	22	3.3%	1.06 [0.83, 1.37]
Shao et al. 2001	23	30	15	30	2.4%	1.53 [1.02, 2.31]
Tian et al. 2008	31	49	20	48	2.4%	1.52 [1.02, 2.26]
Yang et al. 2011	20	30	12	30	1.9%	1.67 [1.00, 2.76]
Subtotal (95% CI)		500		457	26.4%	1.30 [1.06, 1.59]
Total events	384		297			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 44.25$, df = 9 ($P < 0.00001$); $I^2 = 80\%$
Test for overall effect: $Z = 2.50$ ($P = 0.01$)

3.3. One-Year Survival						
Huang et al. 2001	13	32	7	30	1.1%	1.74 [0.80, 3.77]
Huang et al. 2009	13	40	5	37	0.8%	2.40 [0.95, 6.09]
Li et al. 2008	32	50	19	46	2.4%	1.55 [1.04, 2.32]
Li et al. 2013	8	31	3	22	0.5%	1.89 [0.56, 6.34]
Lin et al. 2005	17	52	7	33	1.1%	1.54 [0.72, 3.31]
Ling et al. 2001	131	162	107	151	4.1%	1.14 [1.01, 1.30]
Liu 2011	12	32	7	30	1.0%	1.61 [0.73, 3.53]
Liu and Lü 2016	44	53	43	53	3.8%	1.02 [0.86, 1.22]
Lu 2008	56	69	40	69	3.5%	1.40 [1.11, 1.76]
Lü et al. 2014	49	63	35	63	3.3%	1.40 [1.08, 1.81]
Min and Zhou 2011	9	23	6	22	0.9%	1.43 [0.61, 3.36]
Ren and Cheng 2004	54	104	24	68	2.6%	1.47 [1.01, 2.13]
Shao et al. 2001	17	30	10	30	1.6%	1.70 [0.94, 3.08]
Tian et al. 2008	17	49	8	48	1.1%	2.08 [0.99, 4.36]
Zhong et al. 2014	59	60	58	60	4.4%	1.02 [0.96, 1.08]
Subtotal (95% CI)		850		762	32.3%	1.38 [1.14, 1.67]
Total events	531		379			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 86.01$, df = 14 ($P < 0.00001$); $I^2 = 84\%$
Test for overall effect: $Z = 3.35$ ($P = 0.0008$)

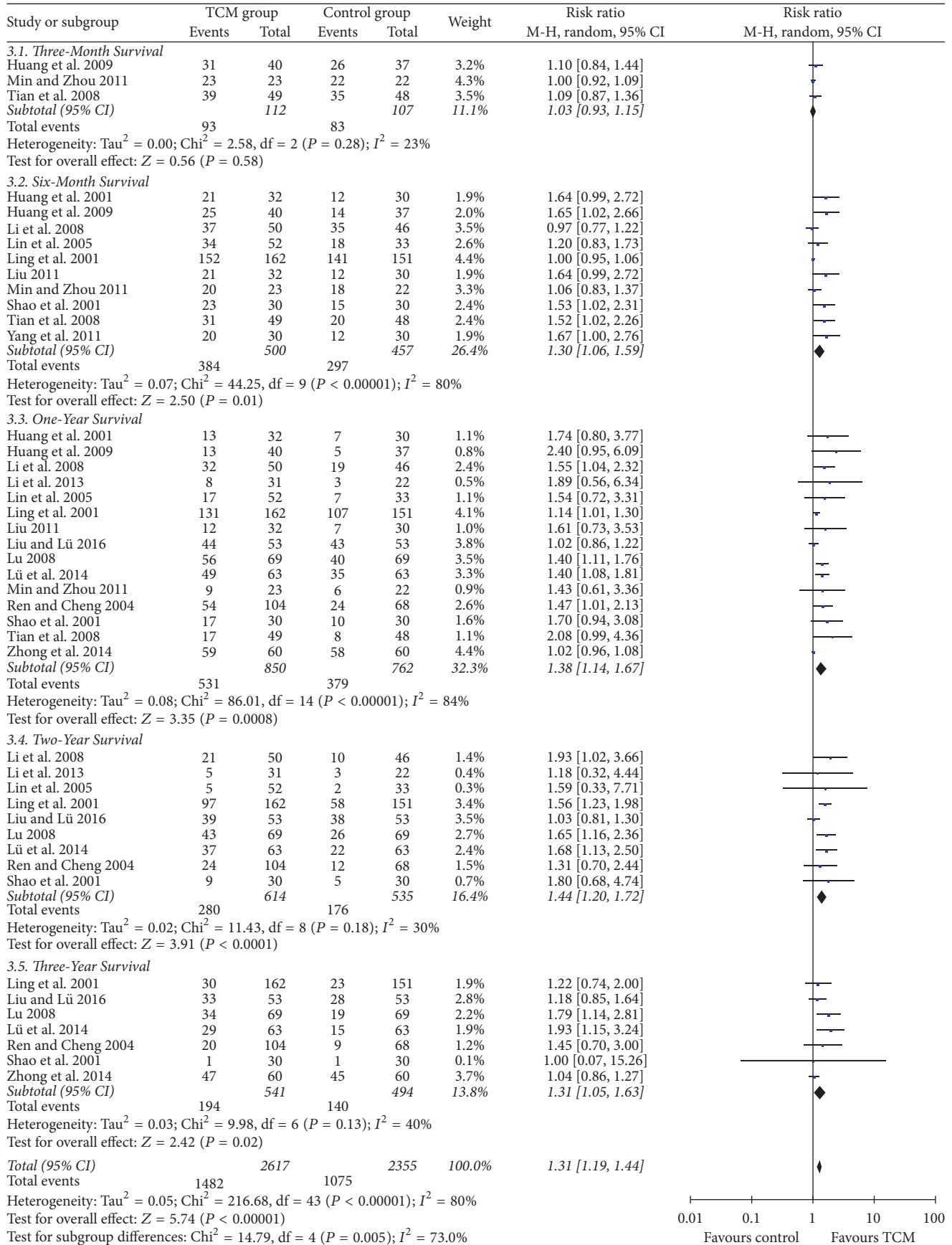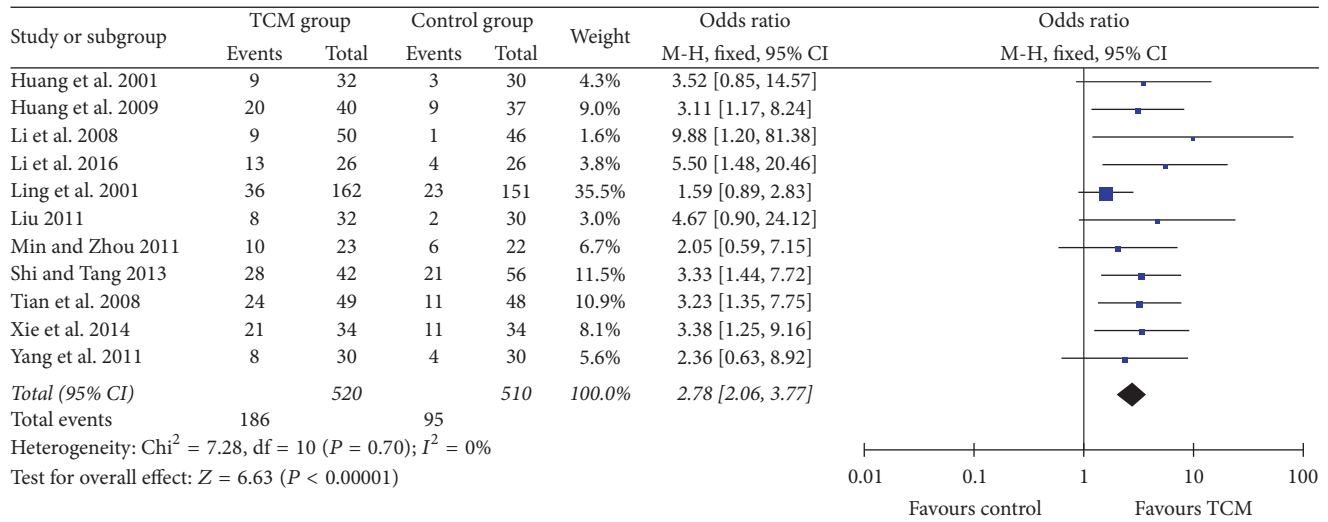|						
3.4. Two-Year Survival						
Li et al. 2008	21	50	10	46	1.4%	1.93 [1.02, 3.66]
Li et al. 2013	5	31	3	22	0.4%	1.18 [0.32, 4.44]
Lin et al. 2005	5	52	2	33	0.3%	1.59 [0.33, 7.71]
Ling et al. 2001	97	162	58	151	3.4%	1.56 [1.23, 1.98]
Liu and Lü 2016	39	53	38	53	3.5%	1.03 [0.81, 1.30]
Lu 2008	43	69	26	69	2.7%	1.65 [1.16, 2.36]
Lü et al. 2014	37	63	22	63	2.4%	1.68 [1.13, 2.50]
Ren and Cheng 2004	24	104	12	68	1.5%	1.31 [0.70, 2.44]
Shao et al. 2001	9	30	5	30	0.7%	1.80 [0.68, 4.74]
Subtotal (95% CI)		614		535	16.4%	1.44 [1.20, 1.72]
Total events	280		176			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.43$, df = 8 ($P = 0.18$); $I^2 = 30\%$
Test for overall effect: $Z = 3.91$ ($P < 0.0001$)

3.5. Three-Year Survival						
Ling et al. 2001	30	162	23	151	1.9%	1.22 [0.74, 2.00]
Liu and Lü 2016	33	53	28	53	2.8%	1.18 [0.85, 1.64]
Lu 2008	34	69	19	69	2.2%	1.79 [1.14, 2.81]
Lü et al. 2014	29	63	15	63	1.9%	1.93 [1.15, 3.24]
Ren and Cheng 2004	20	104	9	68	1.2%	1.45 [0.70, 3.00]
Shao et al. 2001	1	30	1	30	0.1%	1.00 [0.07, 15.26]
Zhong et al. 2014	47	60	45	60	3.7%	1.04 [0.86, 1.27]
Subtotal (95% CI)		541		494	13.8%	1.31 [1.05, 1.63]
Total events	194		140			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 9.98$, df = 6 ($P = 0.13$); $I^2 = 40\%$
Test for overall effect: $Z = 2.42$ ($P = 0.02$)

Total (95% CI)		2617		2355	100.0%	1.31 [1.19, 1.44]
Total events	1482		1075			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 216.68$, df = 43 ($P < 0.00001$); $I^2 = 80\%$
Test for overall effect: $Z = 5.74$ ($P < 0.00001$)
Test for subgroup differences: $Chi^2 = 14.79$, df = 4 ($P = 0.005$); $I^2 = 73.0\%$

Risk ratio M-H, random, 95% CI scale: 0.01   0.1   1   10   100   Favours control   Favours TCM

FIGURE 3: Overall surviving comparison.

Study or subgroup	TCM group		Control group		Weight	Odds ratio	Odds ratio
	Events	Total	Events	Total		M-H, fixed, 95% CI	M-H, fixed, 95% CI
Huang et al. 2001	9	32	3	30	4.3%	3.52 [0.85, 14.57]	
Huang et al. 2009	20	40	9	37	9.0%	3.11 [1.17, 8.24]	
Li et al. 2008	9	50	1	46	1.6%	9.88 [1.20, 81.38]	
Li et al. 2016	13	26	4	26	3.8%	5.50 [1.48, 20.46]	
Ling et al. 2001	36	162	23	151	35.5%	1.59 [0.89, 2.83]	
Liu 2011	8	32	2	30	3.0%	4.67 [0.90, 24.12]	
Min and Zhou 2011	10	23	6	22	6.7%	2.05 [0.59, 7.15]	
Shi and Tang 2013	28	42	21	56	11.5%	3.33 [1.44, 7.72]	
Tian et al. 2008	24	49	11	48	10.9%	3.23 [1.35, 7.75]	
Xie et al. 2014	21	34	11	34	8.1%	3.38 [1.25, 9.16]	
Yang et al. 2011	8	30	4	30	5.6%	2.36 [0.63, 8.92]	
Total (95% CI)		520		510	100.0%	2.78 [2.06, 3.77]	
Total events	186		95				

Heterogeneity: Chi^2 = 7.28, df = 10 (P = 0.70); I^2 = 0%

Test for overall effect: Z = 6.63 (P < 0.00001)

Favours control   Favours TCM

FIGURE 4: Improvement rate of quality of life according to KPS scores.

when we compared SD rate of HCC patients between TCM group and control group (42.6% versus 43.7%, RR = 0.95, 95% CI = 0.84–1.08, and P = 0.47, Figure S3).

3.5. Quality of Life (QOL). In this meta-analysis, KPS scores increasing more than 10 after treatment compared to that before treatment was considered improvement in QOL. 11 RCTs [20–22, 24, 26, 27, 31, 34–37] reported QOL assessment according to KPS scores, with no significance of heterogeneity which existed (P = 0.70, I^2 = 0%). As shown in Figure 4, the QOL improvement rate of HCC patients in TCM group was significantly higher than that in control group [186/520 (35.8) versus 95/510 (18.6), RR = 2.78, 95% CI = 2.06–3.77, and P < 0.00001].

3.6. Adverse Events. Nine RCTs [21, 24, 29, 30, 32, 34–36, 38] reported the adverse events incidence of HCC patients. The most frequent adverse events were leukopenia, thrombocytopenia, anemia/erythropenia, nausea, vomiting, fever, liver injury, and gastrointestinal discomfort. Meta-analysis indicated that HCC patients in control group had significantly higher risk of suffering from leukopenia, thrombocytopenia, anemia/erythropenia, liver injury, and gastrointestinal discomfort than those receiving TCM therapy (55.9% versus 25.1%, 50.0% versus 19.5%, 28.4% versus 16.8%, 44.4% versus 18.4%, and 32.4% versus 17.8%, respectively, all P < 0.05, Figure 5). No statistical significance of nausea/vomiting and fever was found between the two groups (P = 0.24 and P = 0.11, resp., Figure 5).

4. Discussion

Most newly diagnosed HCC cases are at an intermediate advanced stage, and the therapeutic options are limited to palliative approaches using TACE or chemotherapeutic agents [5, 40]. Even worse, many patients poorly respond to TACE or suffer from poor outcomes and side effects with

conventional systemic cytotoxic chemotherapy [40], leading to disappointing results of systemic chemotherapies and a poor prognosis. Therefore, novel therapeutic strategies are essential to improve the clinical management of patients with HCC.

With a long history of clinical use, essential components of TCM have gradually become a common used treatment for cancer in China [41]. In particular, TCM has been used to treat HCC extensively and it can be used throughout the whole course of HCC [42]. In the past decades, many compounds derived from Chinese herbals of both preclinical and clinical researches have shown promising potentials in novel anti-HCC natural product development [43]. Previous studies indicated that the effect of TCM has targeted the stimulation of the host immune response for cytotoxic activity against liver cancer by inhibiting proliferation and promoting apoptosis of tumor cells [7, 44], thereby improving survival and alleviating palliative approaches-related side effects in HCC patients [45–47].

This meta-analysis summarized evidence on the effects of TCM therapy for HCC patients, on top of conventional treatment. For survival, it is observed that the additional use of TCM significantly improved six-month, one-year, two-year, and three-year survival rates in HCC cases. Additionally, TCM combination therapy could increase PR rate and tRR and reduce PD rate in this population. Given above, results from our study demonstrated add-on benefits of TCM in improving outcomes of HCC patients. As the molecular pathogenesis of HCC is highly associated with multigene, multifactor, and multistep processes and is quite complicated, add-on TCM therapy combined with other therapeutic options has a promising potential for its multilevel, multitarget, and coordinated intervention effects against HCC [43]. Many active compounds from TCM have shown their noticeable potentials in inhibiting the promotion, proliferation, angiogenesis, and metastasis of HCC [43, 44], which may contribute to good tumor response and survival in clinical
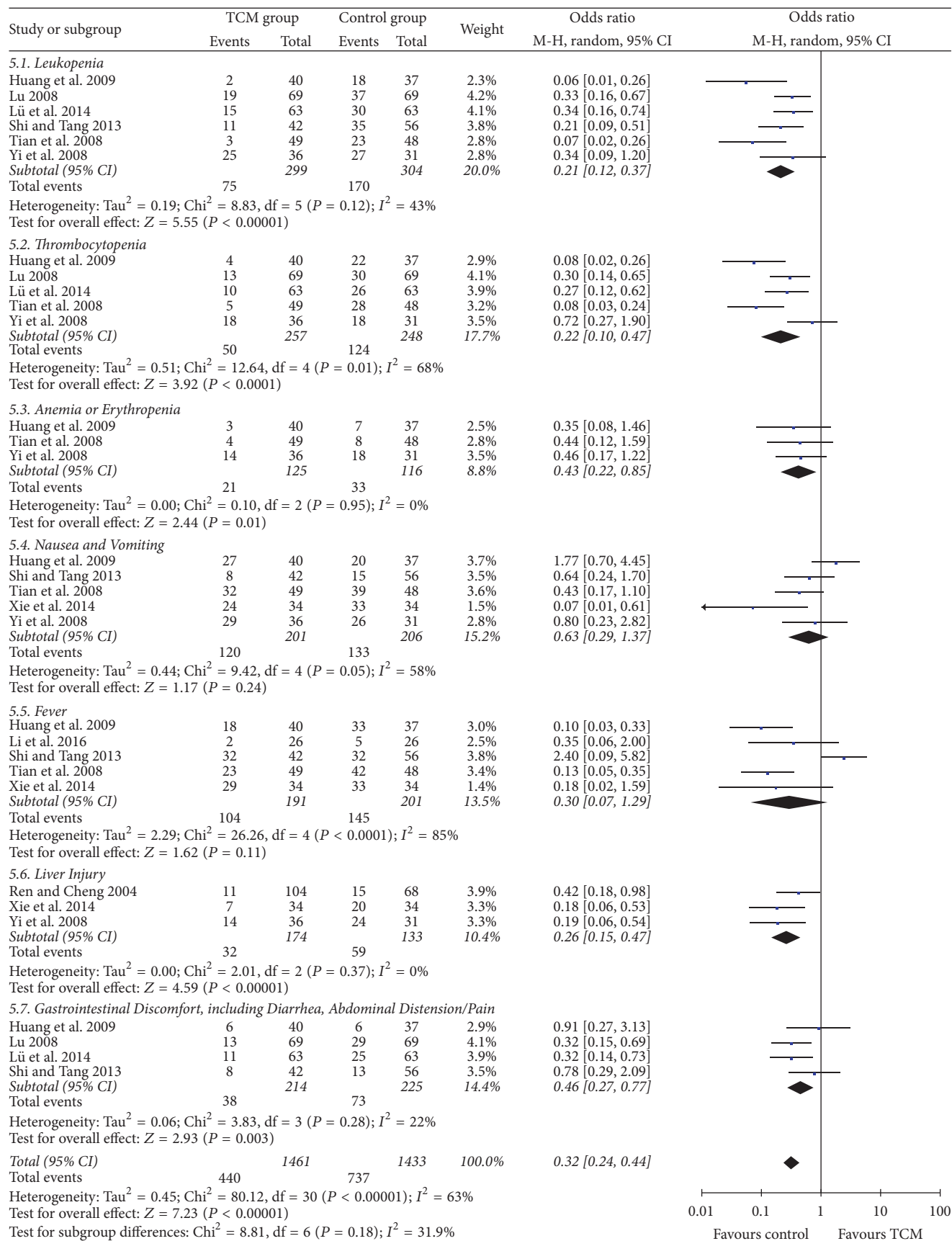
Study or subgroup	TCM group		Control group		Weight	Odds ratio	Odds ratio
	Events	Total	Events	Total		M-H, random, 95% CI	M-H, random, 95% CI
5.1. Leukopenia							
Huang et al. 2009	2	40	18	37	2.3%	0.06 [0.01, 0.26]	
Lu 2008	19	69	37	69	4.2%	0.33 [0.16, 0.67]	
Lü et al. 2014	15	63	30	63	4.1%	0.34 [0.16, 0.74]	
Shi and Tang 2013	11	42	35	56	3.8%	0.21 [0.09, 0.51]	
Tian et al. 2008	3	49	23	48	2.8%	0.07 [0.02, 0.26]	
Yi et al. 2008	25	36	27	31	2.8%	0.34 [0.09, 1.20]	
Subtotal (95% CI)		299		304	20.0%	0.21 [0.12, 0.37]	
Total events	75		170				

Heterogeneity: Tau^2 = 0.19; Chi^2 = 8.83, df = 5 (P = 0.12); I^2 = 43%
Test for overall effect: Z = 5.55 (P < 0.00001)

5.2. Thrombocytopenia							
Huang et al. 2009	4	40	22	37	2.9%	0.08 [0.02, 0.26]	
Lu 2008	13	69	30	69	4.1%	0.30 [0.14, 0.65]	
Lü et al. 2014	10	63	26	63	3.9%	0.27 [0.12, 0.62]	
Tian et al. 2008	5	49	28	48	3.2%	0.08 [0.03, 0.24]	
Yi et al. 2008	18	36	18	31	3.5%	0.72 [0.27, 1.90]	
Subtotal (95% CI)		257		248	17.7%	0.22 [0.10, 0.47]	
Total events	50		124				

Heterogeneity: Tau^2 = 0.51; Chi^2 = 12.64, df = 4 (P = 0.01); I^2 = 68%
Test for overall effect: Z = 3.92 (P < 0.0001)

5.3. Anemia or Erythropenia							
Huang et al. 2009	3	40	7	37	2.5%	0.35 [0.08, 1.46]	
Tian et al. 2008	4	49	8	48	2.8%	0.44 [0.12, 1.59]	
Yi et al. 2008	14	36	18	31	3.5%	0.46 [0.17, 1.22]	
Subtotal (95% CI)		125		116	8.8%	0.43 [0.22, 0.85]	
Total events	21		33				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.10, df = 2 (P = 0.95); I^2 = 0%
Test for overall effect: Z = 2.44 (P = 0.01)

5.4. Nausea and Vomiting							
Huang et al. 2009	27	40	20	37	3.7%	1.77 [0.70, 4.45]	
Shi and Tang 2013	8	42	15	56	3.5%	0.64 [0.24, 1.70]	
Tian et al. 2008	32	49	39	48	3.6%	0.43 [0.17, 1.10]	
Xie et al. 2014	24	34	33	34	1.5%	0.07 [0.01, 0.61]	
Yi et al. 2008	29	36	26	31	2.8%	0.80 [0.23, 2.82]	
Subtotal (95% CI)		201		206	15.2%	0.63 [0.29, 1.37]	
Total events	120		133				

Heterogeneity: Tau^2 = 0.44; Chi^2 = 9.42, df = 4 (P = 0.05); I^2 = 58%
Test for overall effect: Z = 1.17 (P = 0.24)

5.5. Fever							
Huang et al. 2009	18	40	33	37	3.0%	0.10 [0.03, 0.33]	
Li et al. 2016	2	26	5	26	2.5%	0.35 [0.06, 2.00]	
Shi and Tang 2013	32	42	32	56	3.8%	2.40 [0.09, 5.82]	
Tian et al. 2008	23	49	42	48	3.4%	0.13 [0.05, 0.35]	
Xie et al. 2014	29	34	33	34	1.4%	0.18 [0.02, 1.59]	
Subtotal (95% CI)		191		201	13.5%	0.30 [0.07, 1.29]	
Total events	104		145				

Heterogeneity: Tau^2 = 2.29; Chi^2 = 26.26, df = 4 (P < 0.0001); I^2 = 85%
Test for overall effect: Z = 1.62 (P = 0.11)

5.6. Liver Injury							
Ren and Cheng 2004	11	104	15	68	3.9%	0.42 [0.18, 0.98]	
Xie et al. 2014	7	34	20	34	3.3%	0.18 [0.06, 0.53]	
Yi et al. 2008	14	36	24	31	3.3%	0.19 [0.06, 0.54]	
Subtotal (95% CI)		174		133	10.4%	0.26 [0.15, 0.47]	
Total events	32		59				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.01, df = 2 (P = 0.37); I^2 = 0%
Test for overall effect: Z = 4.59 (P < 0.00001)

5.7. Gastrointestinal Discomfort, including Diarrhea, Abdominal Distension/Pain							
Huang et al. 2009	6	40	6	37	2.9%	0.91 [0.27, 3.13]	
Lu 2008	13	69	29	69	4.1%	0.32 [0.15, 0.69]	
Lü et al. 2014	11	63	25	63	3.9%	0.32 [0.14, 0.73]	
Shi and Tang 2013	8	42	13	56	3.5%	0.78 [0.29, 2.09]	
Subtotal (95% CI)		214		225	14.4%	0.46 [0.27, 0.77]	
Total events	38		73				

Heterogeneity: Tau^2 = 0.06; Chi^2 = 3.83, df = 3 (P = 0.28); I^2 = 22%
Test for overall effect: Z = 2.93 (P = 0.003)

Total (95% CI)		1461		1433	100.0%	0.32 [0.24, 0.44]	
Total events	440		737				

Heterogeneity: Tau^2 = 0.45; Chi^2 = 80.12, df = 30 (P < 0.00001); I^2 = 63%
Test for overall effect: Z = 7.23 (P < 0.00001)
Test for subgroup differences: Chi^2 = 8.81, df = 6 (P = 0.18); I^2 = 31.9%

0.01   0.1   1   10   100
Favours control   Favours TCM

FIGURE 5: Adverse events incidence.

practice. Although the mechanisms of TCM components in anti-HCC were well reviewed before [43], further in-depth mechanistic studies and well-designed clinical trials are warranted.

Previous work has suggested that QOL is an important predictor of survival for cancer patients [48]. Although more sophisticated approaches of QOL measurement were developed, the KPS scores are still widely recognized as a tool for the assessment of the functional status of cancer patients and highly reliable [49]. Based on the evidence we identified, TCM combination therapy may be considered as an alternative option to improve QOL in HCC patients. Previously, KPS as a predictor of survival has been demonstrated in patients with different kind of cancers [48, 49], and few studies focused on the relationship between KPS scores and HCC survival. Whether KPS has a role in predicting HCC outcomes should be focused on in future studies.

Evidence of this meta-analysis also showed that the combination of TCM and chemotherapy significantly reduced adverse events including leukopenia, thrombocytopenia, anemia or erythropenia, liver injury, and gastrointestinal discomfort in HCC patients. However, because of the toxic effects of chemotherapy and anticancer drugs on normal cells and tissues, anticancer drugs and approaches cause many side effects and adverse events with various symptoms, including hematocytopenia, gastrointestinal discomfort (nausea, vomiting, anorexia, and diarrhea), and liver injury. These side effects often influence patients' QOL and sometimes make the chemotherapy discontinued [50, 51]. Consistent with our results, growing evidences suggest that TCM appears to have beneficial effects for prevention and improvement of several chemotherapy-induced side effects [52, 53], leading to better outcomes in this population.

This meta-analysis had the following limitations. First, majority of the included studies had small samples, with mid- to low-quality designs. Second, all included studies were conducted in China. According to our experience, only positive results are published in Chinese medical journals. We cautiously drew the conclusion that publication bias might have been present in this meta-analysis. Third, most included studies failed to address blinding assessment, which may influence the objectivity of HCC outcomes. High-quality, well-designed, large sample trials focused on the efficacy and safety of TCM therapy for HCC should be performed in the future.

In conclusion, add-on therapy with TCM could improve overall survival, increase clinical tumor responses, and reduce adverse events in hepatocellular carcinoma. Previous surveys indicated that the trend of TCM use in patients with cancer is on the rise. Surveys have also found that many cancer patients were more inclined to use TCM therapies in combination with conventional therapy rather than in lieu of conventional therapy [54]. Thus, investigating the combined use of TCM and conventional therapy in the oncology setting is urgently essential for practitioners. Evidence-based approaches in the clinic have to be supplemented by experimental studies to unravel cellular and molecular modes of action of TCM treatments [45].

Conflicts of Interest

There are no conflicts of interest.

Authors' Contributions

Zongguo Yang and Xian Liao have contributed equally to this work.

Acknowledgments

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