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Traditional Chinese medicine combined with radiofrequency ablation improves primary liver cancer outcomes: A systematic review with meta-analysis

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ABSTRACT

Background & aims: Traditional Chinese medicine and radiofrequency ablation are becoming increasingly important in the treatment of primary liver cancer. However, the clinical outcome of traditional Chinese medicine plus radiofrequency ablation is contentious. This study aimed to conduct a meta-analysis of randomized controlled clinical trials to address this gap.
Methods: Short-term efficacy, alpha-fetoprotein level, immune function, liver function, and quality of life outcomes in patients with primary liver cancer treated with Chinese herbal medicine adjuvant radiofrequency ablation were systematically reviewed.
Results: Eighteen randomized controlled clinical trials with 1488 patients with primary liver cancer were included. The combination treatment significantly increased the objective remission rate and quality of patient survival compared to the control group. Combination treatment significantly improved immunity and liver function factors, including CD3, CD4, CD4/CD8, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and albumin levels. However, there were no statistical differences in CD8 levels across treatments. Trial sequential analysis showed that the cumulative Z-curve of the Objective response rate crossed the conventional and test sequence monitoring boundaries; however, it did not cross the required information size line.
Conclusions: Traditional Chinese medicine combined with radiofrequency ablation for primary liver cancer can effectively reduce alpha-fetoprotein and improve clinical efficacy, immune function, liver function, as well as the quality of life.

1. Introduction

Primary liver cancer (PLC) is one of the most common and aggressive [1] malignant tumors, with the second-highest mortality worldwide [2], accounting for approximately 782,000 deaths annually [3]. The main clinical therapeutic strategies include liver

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resection, liver transplantation, ablation therapy, and interventional therapy. Radiofrequency ablation (RFA), as the most common ablation method, has been developed for early hepatocellular carcinoma, and its efficacy and safety have been verified in various randomized controlled trials (RCTs); especially, RFA alone may be considered a definitive treatment for the tumors less than 3 cm [4–6]. Meanwhile, RFA is also considered as a crucial combined treatment for tumors between 3 and 5 cm, and larger than 5 cm in the system treatment protocol of PLC [7–9]. However, the prognosis of patients remains poor owing to the high recurrence rate, incomplete ablation [10], liver damage, infection, and other adverse effects of the RFA [11]. Adjuvant therapy following ablation is a significant unmet medical need [12].

In recent years, many researchers have explored Traditional Chinese medicine (TCM) combined with RFA to treat PLC. Previous studies have shown that using TCM as an adjunctive treatment can reduce recurrence rates, improve incomplete ablation, and reduce the incidence of liver damage and adverse effects [13]. TCM is a vital component of complementary and alternative medicine [14], playing a critical role in the treatment of cancer, yet it has not been fully explored. Chinese medicine emphasizes the internal balance of the body [15], focusing on treating the patient as a whole rather than directly inhibiting cancer itself [16]. TCM states that the causes of hepatocellular carcinoma (HCC) are yu (stasis), du (toxicity), and xu (deficiency) [16]. Therefore, treatment is based on the philosophy of huo-xue-hua-yu (removing blood stasis), Jian-Pi-Li-Qi (regulating the flow of qi and strengthening the spleen), or qing-re-jie-du (clearing heat and detoxifying toxins) [17]. Moreover, TCM can alleviate the tumor symptoms in patients as well as control the size of tumors, thereby improving their quality of life (QOL) and prolonging the survival time of these patients [18]. Based on this development and its advantages, it is vital to explore TCM's role in RFA for PLC.

Several clinical RCTs have been conducted on TCM combined with RFA for PLC. The reported results were inconsistent, with the major controversial points being the objective response rates (ORRs) and immune function. In a meta-analysis by Jiang et al. (2017), TCM combined with RFA was shown to be effective for PLC; however, immune and liver functions were not evaluated in this study. Several new RCTs have been published that focus on assessing immune and liver functions [19–22]. Therefore, it is necessary to supplement the evidence regardng TCM plus RFA for PLC. This study systematically evaluated the clinical efficacy of TCM combined with RFA in treating PLC.

2. Materials and methods

2.1. Literature search strategy

A comprehensive literature search was conducted by combining the medical subject headings and free words. Each database was searched from its inception to March 30, 2022. The Chinese databases included the Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP Chinese Science and Technology Periodical Database (VIP), China Biology Medicine disc (CBM), and Wan-Fang Database. For Chinese databases, the following terms were combined to search articles: "liver neoplasms" OR "hepatocellular carcinoma" OR "liver tumor" AND "Chinese herbal medicine" OR "Chinese medicine" OR "traditional Chinese medicine" OR "Chinese herbal extracts" AND "catheter ablation" OR "ablation therapy" OR "radiofrequency" OR "radiofrequency ablation" OR "radiofrequency therapy." The English databases included PubMed, EMBASE, Cochrane Library, and Web of Science. The English database used the following search strategy: "liver neoplasms" [Mesh] OR "primary liver cancer" OR "liver cancer" OR "hepatic neoplasm" OR "cancer of liver" OR "hepatocellular cancer" OR "hepatic cancer" OR "cancer of the liver" AND "Radiofrequency Ablation" OR "Radio Frequency Ablation" OR "Radio-Frequency Ablation" OR "Ablation, Radiofrequency" OR "Ablation, Radio Frequency" OR "Ablation, Radio-Frequency" AND "Drugs, Chinese Herbal" [Mesh] OR "Chinese Herbal Drugs" OR "Chinese Plant Extracts" OR "Chinese Drugs, Plant" OR "Herbal Drugs, Chinese" OR "Plant Extracts, Chinese" OR "Extracts, Chinese Plant."

2.2. Inclusion criteria

The inclusion criteria were as follows: (I) all patients included in this study were diagnosed with PLC; (II) the experimental group was treated with TCM intervention combined with RFA, and the control group was treated with RFA alone; and (III) all the included studies were confirmed as clinical RCTs.

2.3. Exclusion criteria

The study was manually excluded if any of the following situations were met: (I) duplicate literature; (II) overviews, case reports, or articles unrelated to the topic; (III) articles on other TCM interventions such as acupuncture; (IV) animal experiments; (V) articles in which the test subjects had received radiation and chemotherapy; (VI) the TCM intervention time was less than two weeks; and (VII) unavailable data or unreported target outcomes.

2.4. Outcome measures

The primary outcomes were ORR and immune function; the secondary outcomes were quality of life score, liver function indicators, and alpha-fetoprotein (AFP). (I) ORR evaluations were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) or WHO Solid Tumor Therapeutic Evaluation Criteria. RECIST classifies tumor response as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). ORR═CR + PR; (II) immune function assessment items included $CD3^{+}$, $CD4^{+}$, $CD8^{+}$, and CD4+/CD8+; (III) liver function is reflected by alanine aminotransferase (ALT), aspartate aminotransferase

(AST), total bilirubin (TBIL), and albumin (ALB) levels; and (IV) QOL of patients was assessed using the Karnofsky Performance Status (KPS) score.

2.5. Data extraction and risk of bias assessment

The literature was screened, extracted, and cross-checked by two investigators (Y. Kong and X.N. Zhu) independently. Any disagreement was resolved through discussion or consultation with a third party (H. Jia). The literature was initially screened by first reading the title of the text, and after excluding irrelevant literature, the abstract and full text were further read to determine inclusion. Data extraction included : (I) basic information about the included studies: study title, first author, and journal of publication; (II) baseline characteristics of the study population and interventions; (III) key elements of the risk of bias evaluation; and (IV) outcome indicators of interest and outcome measures data. The risk of bias of the included studies was evaluated independently by two investigators (Y. Kong and X.N. Zhu) and the results were cross-checked. The risk of bias assessment of the included literature was performed using the RCT risk of bias assessment tool recommended in the Cochrane Handbook 6.2 [23].

2.6. Statistical analysis

The study data were analyzed using RevMan 5.4 software and Stata 17.0. Dichotomous variables are demonstrated as relative risk (RR), and continuous variables are demonstrated as standardized mean difference (SMD). The effect indicators of each study are expressed as 95% confidence interval (CI). I^2 was used to assess heterogeneity. A random-effects model was adopted for high heterogeneity ($I^2 > 50\%$), and a fixed-effects model was adopted for low heterogeneity ($I^2 < 50\%$). When more than 10 studies were included, funnel plots were used to evaluate publication bias. In addition, Egger's test was used to assess funnel plot asymmetry. Sensitivity analysis of synthetic results was conducted using a leave-one-out meta-analysis in Stata 17.0.

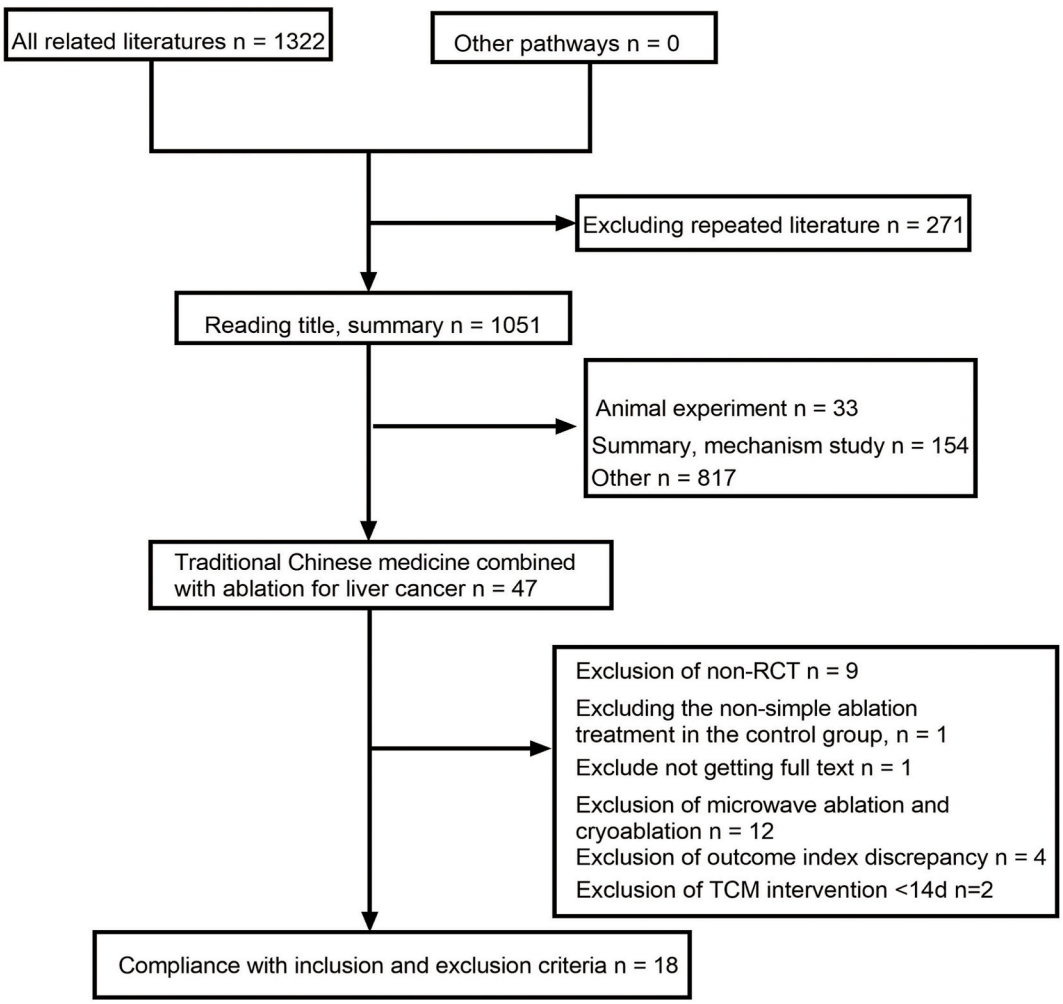


Fig. 1. Study selection process for the meta-analysis.

TSA 0.9.5.10 Beta software developed by the Clinical Trials Centre in Copenhagen, Denmark, was used for trial sequence analysis (TSA) to assess the results' stability and calculate the required information size (RIS) to obtain sound conclusions. When the cumulative Z-curve crossed the trial sequential monitoring boundary or entered the futility area, a sufficient level of evidence for the anticipated intervention effect was reached, and no further trials were required. If the Z-curve did not cross any boundary and the required information size (RIS) was not reached, the evidence to was insufficient and more trials were needed to confirm the results. TSA was used to reduce the risk of reaching a false-negative conclusion [24].

3. Results

3.1. Retrieval results

The initial search yielded 1322 articles, 271 of which were excluded because of duplication. From the retrieval results, 1004 articles were excluded based on irrelevance to the study (n = 817) or other reasons stated (n = 187). From this, potentially eligible studies were identified. After a detailed evaluation of the full text, non-RCT studies (n = 9), studies in which control groups were not treated with a single radiofrequency ablation (n = 1), studies where full text was not available (n = 1), studies with microwave ablation and cryoablation (n = 12), inconsistent outcome indicators (n = 4), and TCM interventions <14 days (n = 2) were excluded from the analysis. In total, 18 trials were included in the final analysis, including 1193 patients with PLC (Fig. 1).

3.2. Basic characteristics of included studies

The basic characteristics of the included studies are shown in Table 1. Eighteen RCTs published between 2003 and 2022 evaluated the efficacy and safety of TCM combined with RFA compared with RFA alone for the treatment of PLC. All of them showed good response with the TCM combined with RFA strategy. Eleven of them displayed higher level of evidence due to focusing on the ORR as the endpoint [19–22,25,26,27,28–30,31,31]. Nine trials reported on the indicators of immune function [19,20,25,32,26,33,29,34,35]. Eleven trials reported on the indicators of liver function [20,21,25,32,36,27,28,33,30,31,35]. Six trials compared the KPS scores of patients the experimental and control groups [20,25,36,28,30,34]. Eight trials reported on the level of AFP [21,25,32,37,33,28,30,38,31].

3.3. Assessment of risk of bias

The risk of bias was evaluated using the RCT risk of bias assessment tool recommended in the Cochrane Handbook 6.2 [18]. The overall risk of bias is graphically summarized in Fig. 2.

Table 1
Baseline characteristics of the included studies.

Study	Type	Intervention	Cases (treatment group/control group)	average age		outcomes
				T	C	
[19]	RCT	RFA + fushengkang capsule	42/42	48.14 ± 6.71	49.01 ± 6.76	①②③
[20]	RCT	RFA + Qinggan Huayu Recipe	49/45	–	–	①③④⑥⑦⑩
[21]	RCT	RFA + Yipi Yanggan Decoction	22/20	49.1 ± 7.2	49.3 ± 7.3	①⑥⑦⑧⑨⑪
[22]	RCT	RFA + Jiawei Xiaoyao Powder	21/21	51.32 ± 4.68	53.61 ± 5.33	①
[25]	RCT	RFA + Kangai Injection	42/40	50.6 ± 4.5	49.3 ± 5.3	①②③④⑤⑥⑦⑧⑨⑩⑪
[36]	RCT	RFA + Aitongxiao Gr anule	15/15	–	–	⑥⑦⑩
[32]	RCT	RFA + Aidi Injection	42/47	52 . 3 ± 15.6	50 . 7 ± 13.8	③④⑤⑥⑪
[26]	RCT	RFA + Fuzheng Jiedu Tongluo	45/45	53.79 ± 8.12	55.41 ± 6.38	①③④⑤
[37]	RCT	RFA + Xiaoaiping	31/30	51.3	49.1	⑪
[27]	RCT	RFA + Xiaoji Huoxue Kangai RFA + Prescription	39/39	54.14 ± 6.71	54.56 ± 6.60	①⑥⑦⑧⑨
[33]	RCT	RFA + Aidi Injection	36/31	50.2 ± 16.3	50.2 ± 16.3	③④⑤⑥⑪
[28]	RCT	RFA + Jiawei Xiaoyao Powder	21/21	51.32 ± 4.68	53.61 ± 5.33	①⑥⑧⑨⑩⑪
[29]	RCT	RFA + Jiawei Sijunzi Decoction	30/30	55.11 ± 0.26	54.23 ± 0.29	①②③④⑤
[30]	RCT	RFA + Jia wei Chai shao liu jun zi tang	20/19	50.4 ± 15.1	49.6 ± 14.7	①⑧⑨⑩⑪
[38]	RCT	RFA + ailiyou	31/30	–	–	⑪
[34]	RCT	RFA + Tianzhicao capsule	50/40	48	49	②③④⑤⑩
[31]	RCT	RFA + Modified Shenling Baizhu Powder	37/37	56.6 ± 3.1	55.3 ± 2.6	①⑧⑨⑪
[35]	RCT	RFA + Aidi injection	34/34	55.6	56.8	①③④⑤⑥⑦⑧⑨

Abbreviations: RCT, Randomized controlled trial; RFA, radiofrequency ablation; T, treatment; C. control; ①, ORR; ②, CD3; ③, CD4; ④, CD8; ⑤, CD4/CD8; ⑥, ALT; ⑦, AST; ⑧, TBIL; ⑨, ALB; ⑩, KPS; ⑪, AFP.

3.4. Outcome measures

3.4.1. Tumor progression

3.4.1.1. Objective response rate. Eleven RCTs were included with 753 patients, including 380 and 373 patients in the trial and control groups, respectively. Meta-analysis of the fixed-effect model showed that the experimental group showed increased tumor ORR compared to the control group (RR = 0.78, 95% CI [0.46, 1.09], $p < 0.001$) (Fig. 3a).

3.4.1.2. AFP. Eight RCTs with a total of 496 patients were included, of which 251 and 245 patients were in the trial and control groups, respectively. Meta-analysis of the random-effects model revealed that the experimental group showed decreased tumor AFP levels compared to the control group (SMD = −0.83, 95% CI [−1.15, −0.51], $p < 0.001$) (Fig. 3b).

3.4.2. Immune function

3.4.2.1. $CD3^+$. The four studies included 316 patients, of which 164 and 152 patients were in the trial and control groups, respectively. Meta-analysis of the fixed-effects model showed that the trial group had a significantly enhanced ratio of $CD3^+$ cells in the body compared to the control group (MD = 1.25, 95% CI [0.97, 1.54], $p < 0.001$) (Fig. 3c).

3.4.2.2. $CD4^+$. Nine RCTs were included with a total of 724 patients with $CD4^+$ data, including 370 and 354 patients in the experimental and control groups, respectively. Meta-analysis of the random-effects model showed that the percentage of $CD4^+$ cells in the experimental group was significantly higher compared to that in the control group (SMD = 1.01, 95% CI [0.42, 1.59], $p < 0.001$) (Fig. 3d).

3.4.2.3. $CD8^+$. Eight RCTs were included with 640 patients, including 328 patients in the experimental group and 312 patients in the control group. Meta-analysis of the random-effects model showed that the percentage of $CD8^+$ cells was lower in the experimental

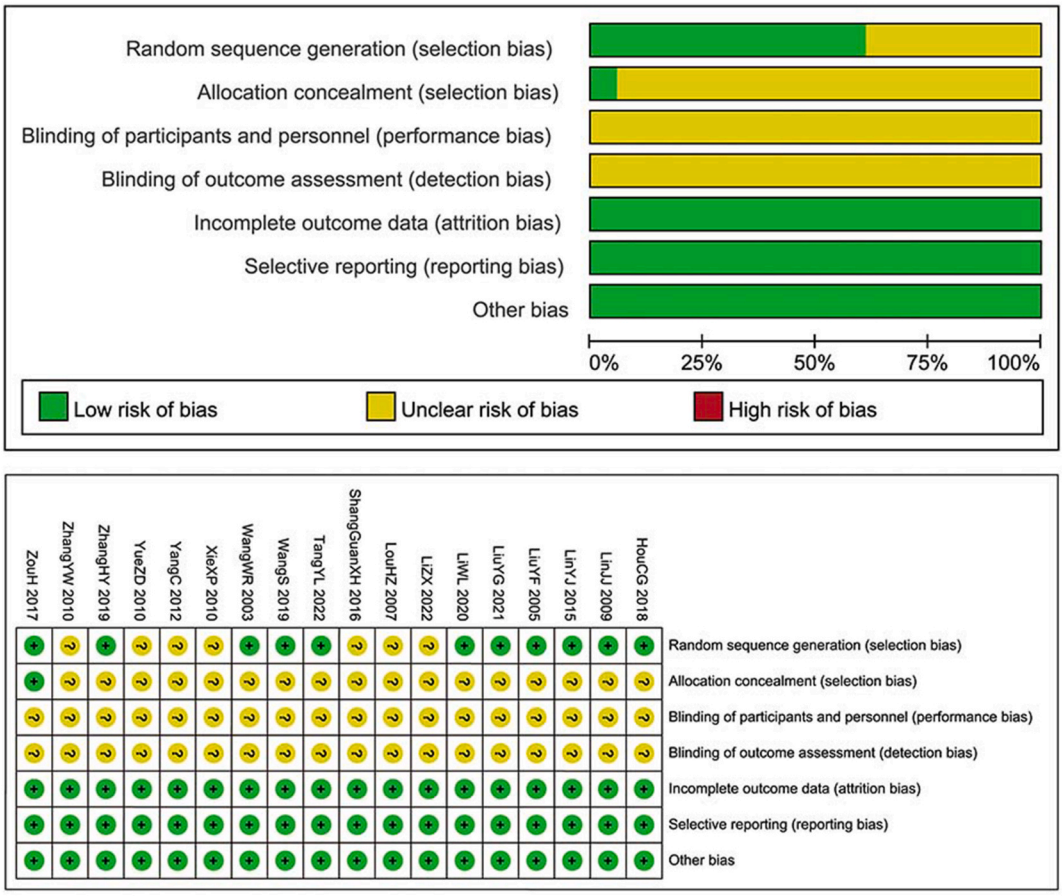


Fig. 2. Risk of bias in the included studies.

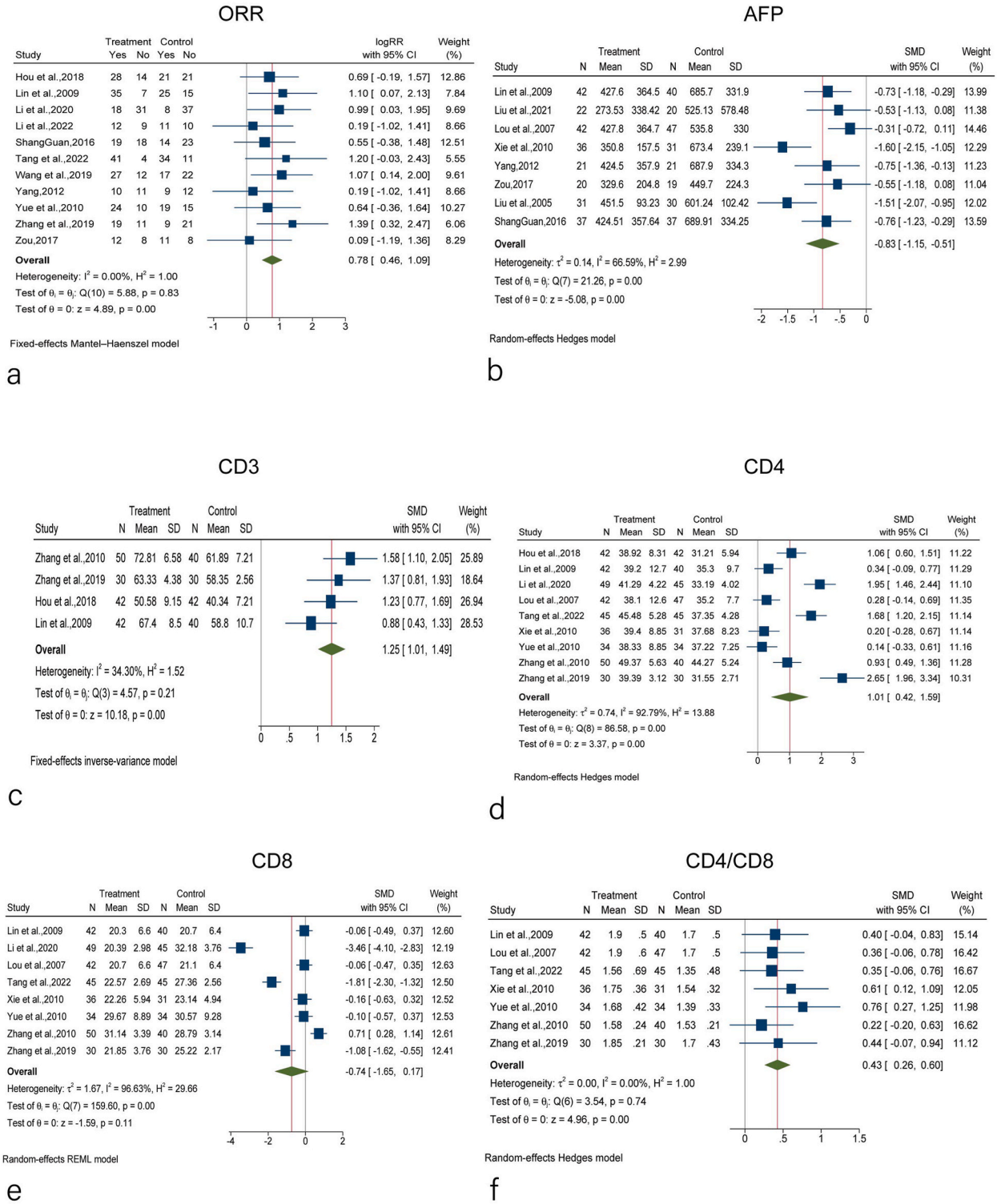


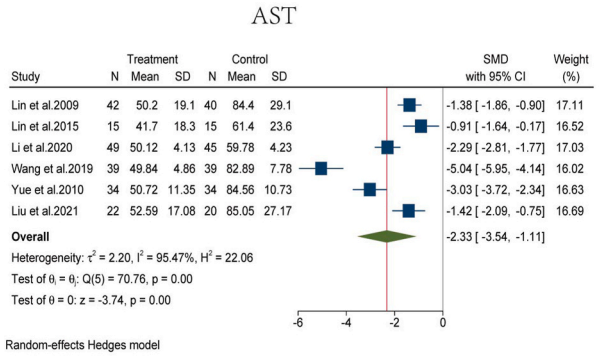
Fig. 3. Meta-analysis of ORR, AFP, CD3, CD4, CD8, and CD4/CD8.

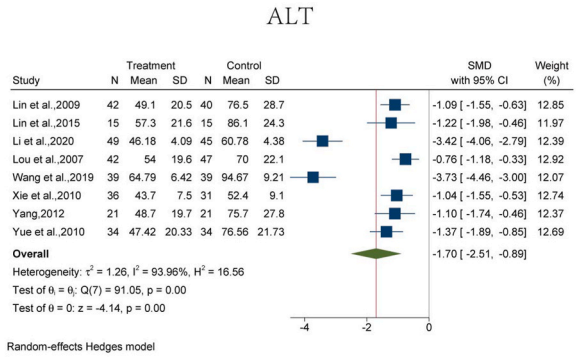
group than in the control group (SMD = − 0.74, 95% CI [− 1.67, 0.18], $p = 0.12$) (Fig. 3e).

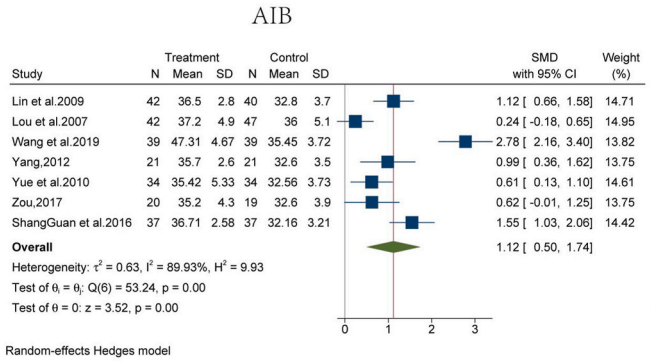
3.4.2.4. $CD4^+/CD8^+$. Seven RCTs with 642 patients were included, with 327 and 315 patients in the experimental and control groups, respectively. Meta-analysis of the fixed-effects model showed that $CD4^+/CD8^+$ cells were higher in the experimental group than in the control group (SMD = 0.43, 95% CI [0.26, 0.60], $p = 0.00001$) (Fig. 3f).

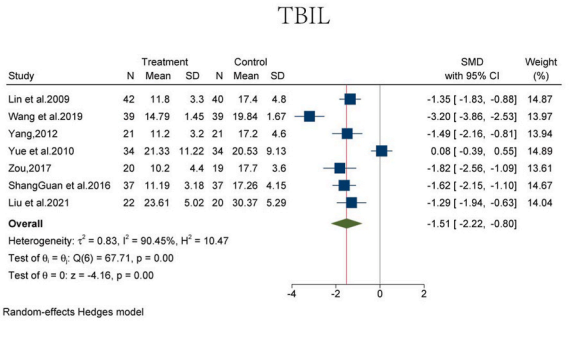
3.4.3. Liver function

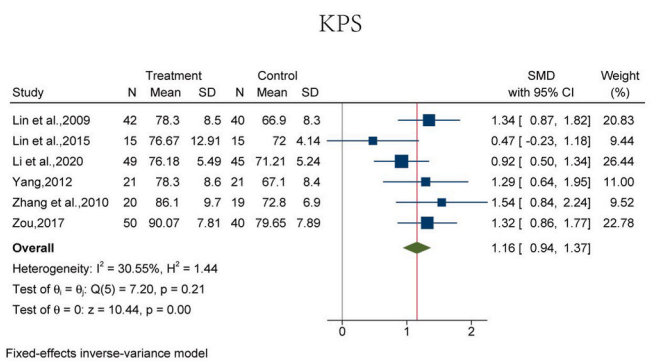
3.4.3.1. ALT. Six RCTs with a total of 646 patients were included, which included 326 and 320 patients in the experimental and











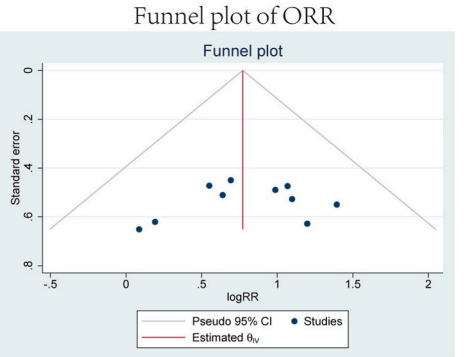
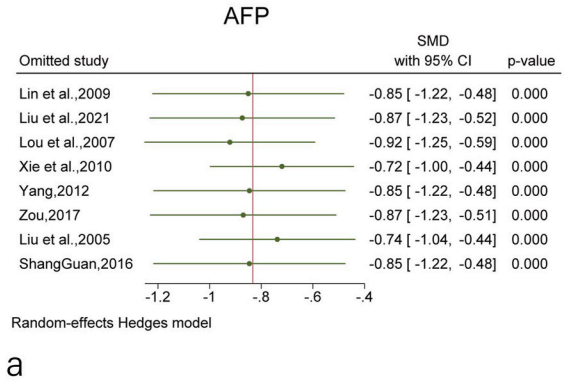


Fig. 4. Meta-analysis of AST, ALT, AIB, TBIL, and funnel plot of ORR.



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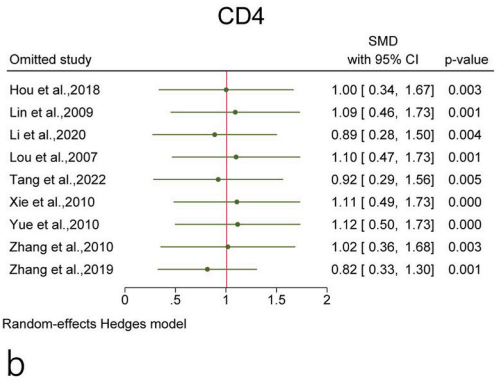

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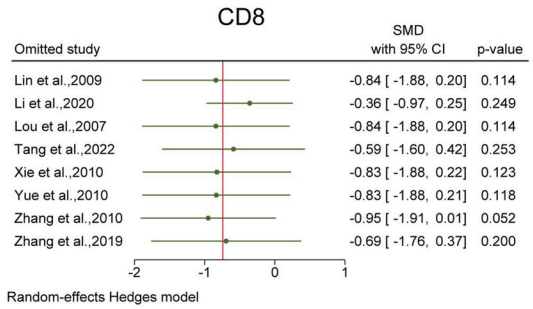

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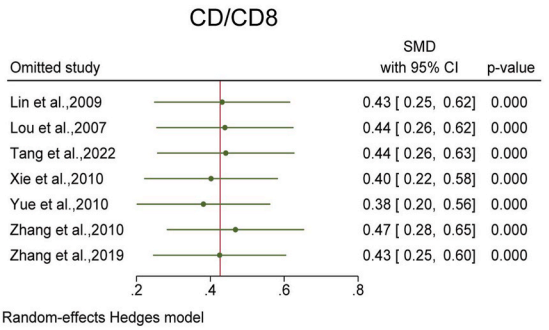

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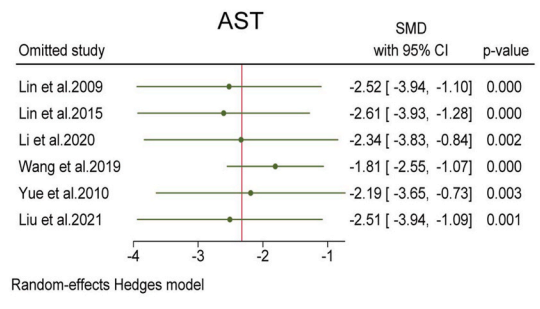

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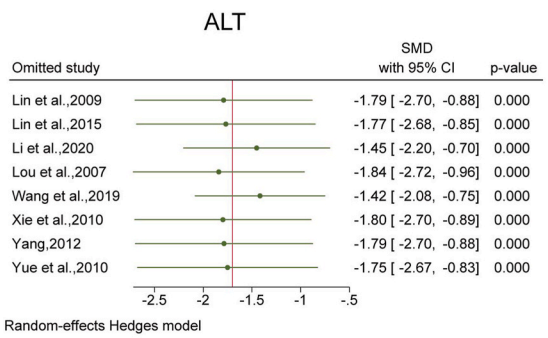

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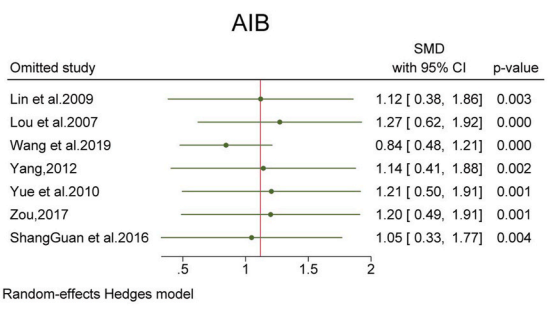

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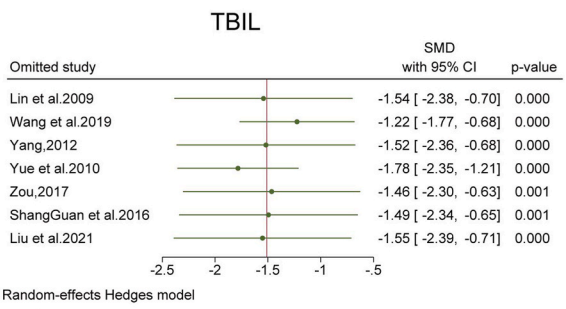

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Fig. 5. Sensitivity analysis of AFP, CD4, CD8, CD4/CD8, AST, ALT, AIB, and TBIL.

control groups, respectively. Meta-analysis of the random-effects model showed that ALT levels were lower in the experimental group compared to that in the control group (SMD = −1.70, 95% CI (−2.51, −0.89), p < 0.00001) (Fig. 4b).

3.4.3.2. AST. Six RCTs with 448 patients were included, of which 227 patients were in the experimental group and 221 patients were in the control group. Meta-analysis of the random-effects model showed that AST levels were lower in the experimental group compared to that in the control group (SMD = −2.33, 95% CI [−3.54, −1.11], p < 0.001) (Fig. 4a)

3.4.3.3. ALB. Six RCTs were included with 472 patients, including 235 and 237 patients in the experimental and control groups, respectively. Meta-analysis of the random-effects model showed that ALB was higher in the experimental group compared to that in the control group (SMD = 1.12, 95% CI [0.50, 1.74], p < 0.001) (Fig. 4c).

3.4.3.4. TBIL. Six RCTs were included with 383 patients, including 193 and 190 patients in the experimental and control groups, respectively. Meta-analysis of the random-effects model showed that TBIL levels were higher in the experimental group compared to that in the control group (SMD = −1.51, 95% CI [−2.22, −0.80], p < 0.001). (Fig. 4d).

3.4.3.5. KPS. Six RCTs were included with 377 patients, including 197 and 180 patients in the experimental and control groups, respectively. Meta-analysis of the fixed-effects model showed that the patients in the experimental group showed improved quality of life than patients in the control group (SMD = 1.16, 95% CI [0.94, 1.37], $p < 0.001$). (Fig. 4e).

3.4.4. Publication bias

The funnel plot test was used to evaluate the publication bias of ORR studies. Moreover, the funnel plot showed a left-right symmetrical distribution, indicating that there was no potential publication bias (Fig. 4f). A regression-based Egger test of t = 1.03 and $p = 0.33$ further demonstrated the absence of publication bias.

3.4.5. Analysis of sensitivity

We conducted sensitivity analyses using a leave-one-out meta-analysis. Each study was excluded once, and the remaining studies were included in the meta-analysis. No additional variation was observed, indicating the robustness of the data analysis (Fig. 5).

3.4.6. Trial sequence analysis

A trial sequential analysis (TSA) of ORR was conducted, demonstrating the following results: 11 studies reporting ORR were analyzed with a Type I error defined as 5%, an information axis set at cumulative sample size, and a statistical power of 80%, with the sample size as the RIS. The [relative risk reduction (RRR)] and control event rate was set at −30% and 47%, respectively, based on the meta-analysis results. The final TSA bounding graph is shown in Fig. 6. The cumulative Z-curve crossed both the conventional and TSA

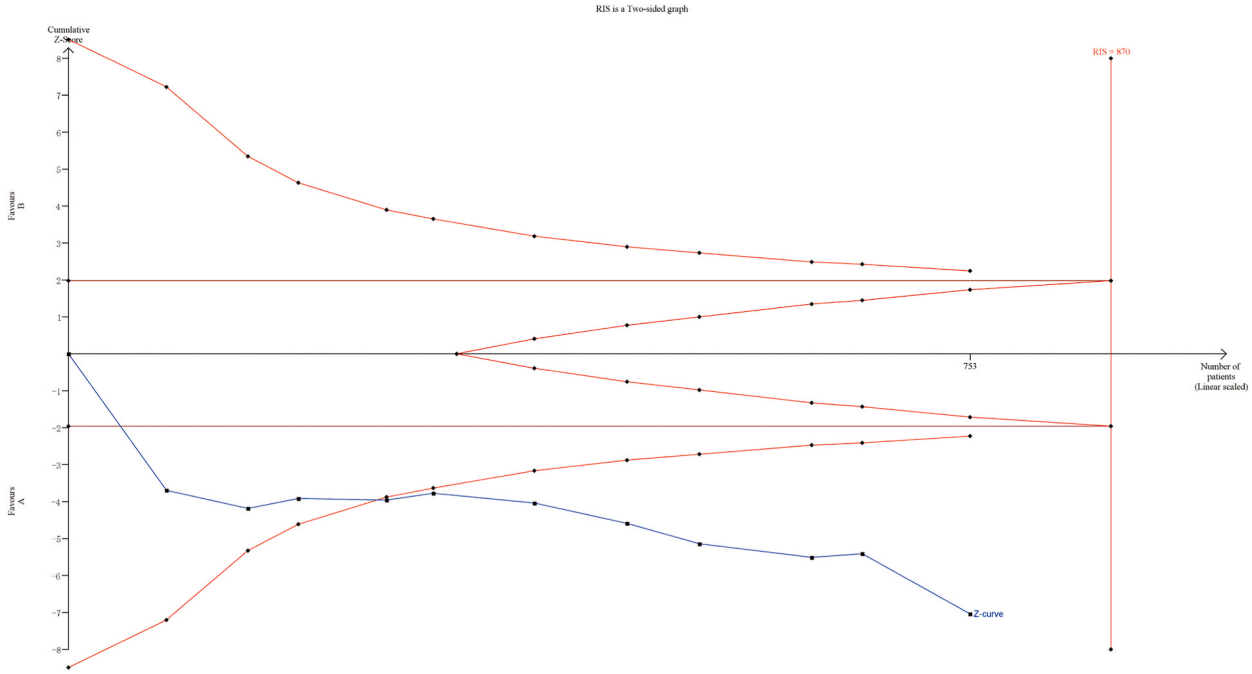

Fig. 6. TSA bounding graph.

boundaries after inclusion in Study 5, and a stable conclusion could be obtained in advance, although RIS was not reached. This result further demonstrates the clinical effectiveness of TCM combined with RFA in treating PLC.

4. Discussion

RFA was a vital treatment for PLC. However, the high recurrence rate, liver damage, and other adverse effects of PLC led to a poor patient prognosis [39]. TCM has been used clinically as an adjuvant treatment [40]. Several publications have reported that Chinese medicine combined with RFA for PLC can benefit patients [41]. However, the exact efficacy has not been systematically and wholly studied. In this meta-analysis, we selected 18 RCTs with a total of 1488 patients, according to the established criteria. The experimental group (755 patients) was treated with TCM plus RFA and the control group (733 patients) was treated with RFA. Our findings revealed that TCM combined with RFA for PLC significantly increased objective tumor response rates, reduced AFP levels, promoted the restoration of immune function, and improved QOL.

Our study showed that TCM combined with RFA significantly increased ORR and decreased AFP compared to RFA alone. These results were similar to those of the study by She et al. in which transcatheter arterial chemoembolization (TACE) combined with strengthening Qi and eliminating pathogens improved ORR in patients with PLC [42]. The subgroup analysis by Ma et al. showed that herbal medicine combined with RFA for hepatocellular carcinoma was effective in improving ORR in their study [41]. The ORR is a surrogate indicator of survival and is often used clinically to assess short-term efficacy [43]. It has been suggested that AFP may be a risk factor for tumor recurrence following RFA for liver cancer [44,45] and is mainly used to predict advanced disease and poor prognosis [43]. Studies have shown that the improvement of AFP may reduce the recurrence of postoperative RFA [44,46].

The immune system plays an important role in regulating tumor growth and metastasis [47]. Peripheral blood T lymphocyte subsets have become an important indicator for monitoring tumor progression and predicting outcome and prognosis in clinical treatment [48]. A previous study showed that Chinese herbs can modulate the immune system by suppressing the inflammatory response and enhancing immune function [49]. For example, the rebalancing of TGF-β/Smad7 signaling in hepatic stellate cells using bitter ginseng injection has a protective effect against liver fibrosis and hepatocarcinogenesis [50]. Additionally, ginger may inhibit tumor growth by promoting mitochondrial biogenesis and T-cell function [51]. Our findings confirmed that TCM combined with RFA significantly increased the percentage of $CD3^+$, $CD4^+$, and CD4+/CD8+ cells in the peripheral blood compared with RFA alone, suggesting an improvement in the function of the immune system.

Liver function indicators were often used to evaluate the safety of drugs. They also played an important role in the treatment and prognosis of the PLC [52]. Previous studies focused on adverse events and recurrence rates, lacking systematic summaries of liver function and immune function indicators [41,46]. Our study added to the evidence, and the results showed that TCM combined with RFA significantly improved ALT, AST, ALB, and TBIL levels, promoting the recovery of liver function. Furthermore, our study highlighted that TCM combined with RFA significantly improved the QOL of patients, which is an important secondary outcome measure.

We confirmed the positive effect of TCM on the ORR using TSA. Compared to previous studies, this study systematically evaluated the efficacy of TCM plus RFA in the treatment of PLC, bridging the gap in the systematic evaluation of immune and liver function. This study has several limitations. First, the participants in the included clinical studies were from China, which may have introduced regional and cultural biases. Second, our results may be inherently biased because some of the included trials were not described for randomization methods, allocation concealment, and blinding. Therefore, more high-quality randomized controlled clinical trials with larger sample sizes and multiple centers were required to provide more evidence.

5. Conclusion

TCM combined with RFA for PLC can effectively reduce AFP, and improve clinical efficacy, immune function, liver function, as well as QOL.

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Ethical approval

This article does not contain any studies with human participants or animals.

Informed consent

As this study was a systematic review and did not involve contact with patients or patient information, it was not applicable for obtaining informed consent.

Author contribution statement

Yuan Kong: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Xiaoning Zhu: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
Xue Zhang; Zetian Li: Performed the experiments; Contributed reagents, materials, analysis tools or data.
Yue Yin: Performed the experiments.
Jing Wang: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.
Hong Jia: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

The authors do not have permission to share data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] C.Y. Liu, K.F. Chen, P.J. Chen, Treatment of liver cancer, Cold Spring Harb Perspect Med 5 (2015) a021535, https://doi.org/10.1101/cshperspect.a021535.
[2] K.A. McGlynn, J.L. Petrick, H.B. El-Serag, Epidemiology of hepatocellular carcinoma, Hepatology 73 (Suppl 1) (2021) 4–13, https://doi.org/10.1002/hep.31288.
[3] Y. Jiang, Q.J. Han, J. Zhang, Hepatocellular carcinoma: mechanisms of progression and immunotherapy, World J. Gastroenterol. 25 (2019) 3151–3167, https://doi.org/10.3748/wjg.v25.i25.3151.
[4] M.S. Chen, J.Q. Li, Y. Zheng, et al., A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma, Ann. Surg. 243 (2006) 321–328, https://doi.org/10.1097/01.sla.0000201480.65519.b8.
[5] J. Huang, L. Yan, Z. Cheng, et al., A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria, Ann. Surg. 252 (2010) 903–912, https://doi.org/10.1097/SLA.0b013e3181efc656.
[6] K. Feng, J. Yan, X. Li, et al., A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma, J. Hepatol. 57 (2012) 794–802, https://doi.org/10.1016/j.jhep.2012.05.007.
[7] J.H. Kim, H.J. Won, Y.M. Shin, et al., Medium-sized (3.1-5.0 cm) hepatocellular carcinoma: transarterial chemoembolization plus radiofrequency ablation versus radiofrequency ablation alone, Ann. Surg Oncol. 18 (2011) 1624–1629, https://doi.org/10.1245/s10434-011-1673-8.
[8] M.M.A. Zaitoun, S.B. Elsayed, N.A. Zaitoun, et al., Combined therapy with conventional trans-arterial chemoembolization (cTACE) and microwave ablation (MWA) for hepatocellular carcinoma >3-<5 cm, Int. J. Hyperther. 38 (2021) 248–256, https://doi.org/10.1080/02656736.2021.1887941.
[9] W. Wang, J. Shi, W.F. Xie, Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis, Liver Int. 30 (2010) 741–749, https://doi.org/10.1111/j.1478-3231.2010.02221.x.
[10] X. Zeng, G. Liao, S. Li, et al., Eliminating METTL1-mediated accumulation of PMN-MDSCs prevents hepatocellular carcinoma recurrence after radiofrequency ablation, Hepatology (2022), https://doi.org/10.1002/hep.32585.
[11] M.C. Jansen, F.H. van Duijnhoven, R. van Hillegersberg, et al., Adverse effects of radiofrequency ablation of liver tumours in The Netherlands, Br. J. Surg. 92 (2005) 1248–1254, https://doi.org/10.1002/bjs.5059.
[12] P.K. Haber, M. Puigvehí, F. Castet, et al., Evidence-based management of hepatocellular carcinoma: systematic review and meta-analysis of randomized controlled trials (2002-2020), Gastroenterology 161 (2021) 879–898, https://doi.org/10.1053/j.gastro.2021.06.008.
[13] W.Z. Wang, M.H. Lin, Y.J. Li, Cfw, C.H. Ma, A randomized double-blind prospective study of radiofrequency combined with Pingxiao capsule in the treatment of 40 cases of liver cancer, Fujian Journal of Traditional Chinese Medicine 41 (3) (2010).
[14] S.W. Wang, Progress in the treatment of mycoplasma pneumoniae in children with integrated Chinese and Western medicine, Contemporary Medicine Forum 18 (2020) 201–203.
[15] Q.A. Jia, Z.G. Ren, Y. Bu, et al., Herbal compound "songyou Yin" renders hepatocellular carcinoma sensitive to oxaliplatin through inhibition of stemness, Evid Based Complement Alternat Med 2012 (2012), 908601, https://doi.org/10.1155/2012/908601.
[16] X. Liao, Y. Bu, Q. Jia, Traditional Chinese medicine as supportive care for the management of liver cancer: past, present, and future, Genes Dis 7 (2019) 370–379, https://doi.org/10.1016/j.gendis.2019.10.016.
[17] X. Wang, N. Wang, F. Cheung, L. Lao, C. Li, Y. Feng, Chinese medicines for prevention and treatment of human hepatocellular carcinoma: current progress on pharmacological actions and mechanisms, J Integr Med 13 (2015) 142–164, https://doi.org/10.1016/S2095-4964(15)60171-6.
[18] Y. Wang, Q. Zhang, Y. Chen, et al., Antitumor effects of immunity-enhancing traditional Chinese medicine, Biomed. Pharmacother. 121 (2020), 109570, https://doi.org/10.1016/j.biopha.2019.109570.
[19] C.G. Hou, L. Xu, Clinical evaluation on fushengkang capsules combined with radiofrequency ablation guided by real-time virtual navigation system in treating primary liver cancer, China Pharmaceuticals 27 (2018) 44–47.
[20] W.L. Li, Y.Q. Xu, , HLY, X. Wang, Z. Fang, Y. Xu, Effects of qinggan huayu decoction combined with radiofrequency ablation on quality of life, immune function and tumor metastasis of hepatocellular carcinoma patients, Anti-tumor Pharmacy 10 (2020) 225–231.
[21] Y.G. Liu, R. Nan, J.T. Li, et al., Clinical study of yipi yanggan decoction combined with percutaneous radiofrequency ablation in treating hepatitis B-related small liver cancer, Journal of Guangzhou University of Traditional Chinese Medicine 38 (2) (2021) 223–229, https://doi.org/10.13359/j.cnki.gzxbtcm.2021.02.001.
[22] Z.X. Li, L.J. Xu, X.Y. Wen, H.Y. Sun, M. Xia, The efficacy of Jiawei Xiaoyao Powder combined with radiofrequency ablation in the treatment of liver cancer, The Journal of Medical Theory and Practice 35 (5) (2022) 794–796, https://doi.org/10.19381/j.issn.1001-7585.2022.05.027.
[23] M. Cumpston, T. Li, M.J. Page, J. Chandler, V.A. Welch, J.P. Higgins, J. Thomas, Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions, Cochrane Database Syst. Rev. 10 (2019), Ed000142, https://doi.org/10.1002/14651858.ED000142.
[24] J. Brok, K. Thorlund, J. Wetterslev, C. Gluud, Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses, Int. J. Epidemiol. 38 (2009) 287–298.
[25] J.J. Lin, C.N. Jin, J.X. Zeng, X.H. Dai, Clinical observation of kangai injection combined with radiofrequency ablation for primary liver cancer, Guangming Journal of Chinese Medicine 24 (2009) 1887–1889.
[26] Y.L. Tang, T. Han, Efficacy observation of strengthening vital qi, reliving toxin and dredging collaterals method combined with radiofrequency ablation in treatment of primary liver cancer, Liaoning Journal of Traditional Chinese Medicine 49 (2022) 78–82, https://doi.org/10.13192/j.issn.1000-1719.2022.02.023.
[27] S. Wang, Z. Guo, Effects of self-made xiaoji huoxue Kang'Ai formula combined with initial experience of real time virtual sonography navigation system guided radiofrequency ablation in treatment of primary hepatic carcinoma, Chinese Archives of Traditional Chinese Medicine 37 (2019) 2381–2384.
[28] C. Yang, Clinical Study on 42 Cases of PHC (Stagnation and Spleen Deficiency Card) Treated by the Modified Xiaoyaosan Combined with RFA, vol. 2, Hubei University of Chinese Medicine, 2012, p. 47.

[29] H.Y. Zhang, H.B. Wang, Clinical observation of radiofrequency ablation combined with Jiawei Sijunzi Decoction in the treatment of primary liver cancer, Journal of Practical Traditional Chinese Medicine 35 (2019) 549–550.
[30] H. Zou, Short-term Efficacy and Major Complications of Modified Chaishao Liujunzi Decoction Combined with Radiofrequency Ablation in the Treatment of Primary Liver Cancer, vol. 4, Hubei University of Chinese Medicine, 2017, p. 61.
[31] X.H. ShangGuan, S.D. Duan, Observation on short - term and long - term effect of shenling baizhu powder combined with western medicine in treating primary liver cancer with spleen deficiency syndrome, J. Sichuan Tradit. Chin. Med. 34 (2016) 95–97.
[32] H.Z. Lou, H.M. Pan, W. Jin, Clinical study on treatment of primary liver cancer by Aidi injection combined with cool-tip radiofrequency ablation, Zhongguo Zhong Xi Yi Jie He Za Zhi 27 (2007) 393–395.
[33] X.P. Xie, P. Chen, , HJZ, H.B. Lu, D.B. Zhuo, Clinical study of primary liver cancer by Aidi Injection combined with radiofrequency ablation, China J. Mod. Med. 20 (2010) 1857–1859+1862.
[34] Y.W. Zhang, Analysis of 90 cases of small hepatocellular carcinoma treated with ultrasound-guided percutaneous radiofrequency minimally invasive technique combined with Tianzhi Cao capsules, Contemp. Med. (9) (2010).
[35] Z.D. Yue, L. Zhou, F.Q. Liu, , HWZ, L. Wang, Clinical study on treatment of primary liver cancer by aidi injection combined with radiofrequency ablation, Pharmacol. Clin. Chin. Mater. Med. 26 (2010) 77–79.
[36] Y.J. Lin, , ALW, Y.Q. Zhang, , ZMZ, H.S. Lu, Clinical efficacy of radiofrequency ablation combined with aitongxiao granule in improving the quality of life of patients with advanced primary liver cancer, Lishizhen Medicine and Materia Medica Research 26 (2015) 909–910.
[37] W.R. Wang, , SDC, L.M. Zeng, Clinical observation on treatment of mid-advanced patients with hepatocarcinoma by xiao'aiping combined with ultrasound guided percutaneous radio-frequency, Chinese Journal of Integrated Traditional and Western Medicine (1) (2003) 19–21.
[38] Y.F. Liu, H.B. Han, Clinical observation on the treatment of liver cancer by percutaneous radiofrequency ablation guided by Chinese medicine ailiyou combined with ultrasound, J. Tradit. Chin. Med. (2005) 123–124.
[39] J. Zheng, J. Cai, L. Tao, et al., Comparison on the efficacy and prognosis of different strategies for intrahepatic recurrent hepatocellular carcinoma: a systematic review and Bayesian network meta-analysis, Int. J. Surg. 83 (2020) 196–204, https://doi.org/10.1016/j.ijsu.2020.09.031.
[40] J.L. Tang, B.Y. Liu, K.W. Ma, Traditional Chinese medicine, Lancet 372 (9654) (2008) 1938–1940, https://doi.org/10.1016/S0140-6736(08)61354-9.
[41] L. Ma, B. Wang, Y. Long, H. Li, Effect of traditional Chinese medicine combined with Western therapy on primary hepatic carcinoma: a systematic review with meta-analysis, Front. Med. 11 (2) (2017) 191–202, https://doi.org/10.1007/s11684-017-0512-0.
[42] Y. She, Q. Huang, Z. Ye, et al., The therapeutic principle of combined strengthening qi and eliminating pathogens in treating middle-advanced primary liver cancer: a systematic review and meta-analysis, Front. Pharmacol. 12 (2021), 714287, https://doi.org/10.3389/fphar.2021.714287.
[43] Y.Z. He, K. He, R.Q. Huang, et al., A clinical scoring system for predicting tumor recurrence after percutaneous radiofrequency ablation for 3 cm or less hepatocellular carcinoma, Sci. Rep. 11 (2021) 8275, https://doi.org/10.1038/s41598-021-87782-y.
[44] H. Kun, H. Yongzhu, H. Zemin, et al., Analysis of risk factors for recurrence after radiofrequency ablation of liver cancer and preoperative prediction score, Chin. J. Hepatobiliary Surg. 27 (2021) 169–174, https://doi.org/10.3760/cma.j.cn113884-20200506-00246.
[45] Z. Shi, T. Song, Y. Wan, et al., A systematic review and meta-analysis of traditional insect Chinese medicines combined chemotherapy for non-surgical hepatocellular carcinoma therapy, Sci. Rep. 7 (2017) 4355, https://doi.org/10.1038/s41598-017-04351-y.
[46] Z. Wang, X.L. Yu, J. Zhang, et al., Huaier granule prevents the recurrence of early-stage hepatocellular carcinoma after thermal ablation: a cohort study, J. Ethnopharmacol. 281 (2021), 114539, https://doi.org/10.1016/j.jep.2021.114539.
[47] R.N. Hanna, C. Cekic, D. Sag, et al., Patrolling monocytes control tumor metastasis to the lung, Science 350 (2015) 985–990, https://doi.org/10.1126/science.aac9407.
[48] X. Meng, Y. Gao, L. Yang, et al., Immune microenvironment differences between squamous and non-squamous non-small-cell lung cancer and their influence on the prognosis, Clin. Lung Cancer 20 (2019) 48–58, https://doi.org/10.1016/j.cllc.2018.09.012.
[49] K. Fu, C. Wang, C. Ma, H. Zhou, Y. Li, The potential application of Chinese medicine in liver diseases: a new opportunity, Front. Pharmacol. 12 (2021), 771459, https://doi.org/10.3389/fphar.2021.771459.
[50] Y. Yang, M. Sun, W. Li, et al., Rebalancing TGF-β/Smad7 signaling via Compound kushen injection in hepatic stellate cells protects against liver fibrosis and hepatocarcinogenesis, Clin. Transl. Med. 11 (2021), e410, https://doi.org/10.1002/ctm2.410.
[51] X. Deng, D. Chen, X. Sun, J. Dong, J. Huang, Effects of ginger extract and its major component 6-gingerol on anti-tumor property through mitochondrial biogenesis in CD8(+) T cells, J. Food Sci. 87 (2022) 3307–3317, https://doi.org/10.1111/1750-3841.16228.
[52] European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer, EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma, J. Hepatol. 56 (2012) 908–943, https://doi.org/10.1016/j.jhep.2011.12.001.