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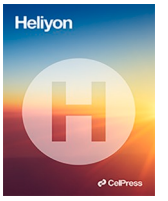

Research article

Evaluate the clinical efficacy of traditional Chinese Medicine as the neoadjuvant treatment in reducing the incidence of hepatocellular carcinoma in patients with hepatitis B-related cirrhosis: A systematic review and meta-analysis

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ABSTRACT

Background: Traditional Chinese Medicine (TCM), has been used for hepatocellular carcinoma (HCC) at every therapeutic stage, even before tumor formation. However, the efficacy of TCM in reducing the incidence of HCC in patients with chronic hepatitis B-related cirrhosis remains unclear. This study aims to address this gap.
Methods: Publications were collected from PubMed, EMBASE, Cochrane Library, Web of Science, CNKI, Sino Med, VIP, and Wan Fang Databases. Relative risk (RR) was calculated with a 95 % confidence interval (CI). Heterogeneity was assessed. The Cochrane Collaboration's tool was used to assess the risk of bias.
Results: 10 studies with 2702 patients showed that the combination therapy significantly reduced the incidence of HCC in patients with post-hepatitis B cirrhosis at 1, 3, and 5 years. However, the preventive effects of TCM were in compensated cirrhosis, but not the decompensated cirrhosis. Furthermore, TCM correlated with improved liver function and enhanced virological response.
Conclusion: Combination therapy with TCM demonstrated the certain potential in reducing the incidence of HCC in patients with hepatitis B cirrhosis. This is attrinuted to the improvement of liver function and enhancement of the viral response. However, the efficacy of TCM in the field still needs more high-quality RCTs to provide stronger evidence in the future.

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1. Introduction

Hepatitis B virus (HBV) infection is a major public health problem, with an estimated 296 million people chronically infected and 820,000 deaths worldwide in 2019 [1]. Hepatitis B-related cirrhosis is a common complication of HBV infection, and Hepatocellular carcinoma (HCC) is the main liver-related cause of death in patients with compensated cirrhosis [2]. The five-year survival rate of HCC is low due to the high rates of metastasis and recurrence [3,4]. It has been reported that patients with cirrhosis have a significantly higher risk of developing HCC than those without cirrhosis [5]. However, there are no established guidelines for reducing the incidence of HCC in patients with Hepatitis B-related cirrhosis. Therefore, it is necessary to identify effective intervention measures for decreasing the occurrence of HCC in patients with Hepatitis B-related cirrhosis.

Advanced HCC patients present a poor prognosis [6]. Commonly, advanced HCC is characterized by the manifestation of extra-hepatic spread or macrovascular invasion. At this stage of disease, systemic therapy represents the mainstay of treatment, if liver function is preserved and performance status appropriate [7]. In recent years, ground-breaking progress has been made in systemic therapy for HCC. Targeted therapy, immunotherapies, and their synergistic combinations greatly improve the survival of HCC patients and are widely applied in advanced-stage cases [8–10].

Concurrently, TCM has been widely used in the healthcare system for over three thousand years and offers comprehensive approaches including herbal medicine, acupuncture, moxibustion, cupping, massage, and physical exercise [11,12]. According to the TCM theories, the occurrence of illness is due to the disturbance of the body's each situation, such as the abnormal events in two opposing forces of energy, Yin and Yang. For alleviating symptoms of disease, Chinese medicine aims to restore the harmony of the body's situations by choosing different herbs combinations [13–15]. As complementary therapy, TCM was the one of important parts in the treatment of liver cirrhosis [16]. Several clinical studies have shown the combined TCM's beneficial effects in preventing HCC in patients with Hepatitis B-related cirrhosis [17,18], but the effect of TCM as the neoadjuvant treatment in preventing the incidence of HCC was still unclear.

To date, there has been a lack of consistency and comprehensive evaluation of the available research. This study aims to conduct a systematic review and meta-analysis to explore the clinical therapeutic effects of traditional Chinese medicine on hepatocellular carcinoma in patients with Chronic Hepatitis B-related cirrhosis and further explore its potential mechanisms.

2. Materials and methods

This study was guided by the Cochrane Handbook for Systematic Reviews of Interventions V5.1. The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023447915) [19].

2.1. Search strategy

The researchers in this paper searched electronic databases (PubMed, EMBASE, Cochrane Library, Web of Science, Sino Med, CNKI, VIP, and Wan Fang Data) from their creation to May 2023. The search strategy was constructed around the PICOS tool: (P) Population: people with liver fibrosis caused by HBV; (I) Intervention: TCMs compared with placebo or no treatment; in addition, any co-intervention had to be the same in both groups except for the TCM formulation; (C) Comparator: The control group received conventional Western medicine treatment, including antiviral, liver protection, supportive treatment and so on; (O) Outcomes: HCC incidence rate. (S) Study type: RCTs. The detailed search strategy is shown in Table 1 (Pubmed is used as an example).

2.2. Inclusion criteria

(1) Experimental group with traditional Chinese medicine treatment as an intervention for people with HBV-related liver cirrhosis, (2) Control group with conventional medicine treatment only (3) Clinical randomized controlled trial (4) Outcome included the occurrence of primary liver cancer.

Table 1
Search strategy on PubMed.

Search	PUBMED
#1	"hepatitis B virus" [All Fields] OR "cirrhosis" [All Fields] OR "liver cirrhosis" [All Fields] OR "hepatic cirrhosis" [All Fields] OR "hepatocirrhosis" [All Fields] OR "viral cirrhosis" [All Fields] OR "hepatitis B cirrhosis" [All Fields] OR "hepatitis b virus related cirrhosis" [All Fields] OR "hepatitis b virus related cirrhosis" [All Fields] OR "HBV - cirrhosis" [All Fields] OR "HBV - C" [Title/Abstract]
#2	"Liver cirrhosis" [All Fields] OR "hepatitis B virus" [MeSH Terms]
#3	#1 or #2
#4	((((((((((Medicine, Chinese Traditional [MeSH Terms]) OR (Traditional Chinese Medicine [Title/Abstract])) OR (Chung I Hsueh [Title/Abstract])) OR (Traditional Medicine, Chinese [Title/Abstract])) OR (Zhong Yi Xue [Title/Abstract])) OR (Chinese Traditional Medicine [Title/Abstract])) OR (Chinese Medicine, Traditional [Title/Abstract])) OR (Traditional Tongue Diagnosis [Title/Abstract])) OR (Tongue Diagnoses, Traditional [Title/Abstract])) OR (Traditional Tongue Diagnoses [Title/Abstract])) OR (Traditional Tongue Assessment [Title/Abstract])) OR (Tongue Assessment, Traditional [Title/Abstract])) OR (Traditional Tongue Assessments [Title/Abstract])
#5	#3 and #4

2.3. Exclusion criteria

(1) Studies with incomplete or unreported data (2) Studies from non-randomized Controlled trials, including quasi-randomized controlled trials, animal studies, Protocols, conference abstracts, case reports, or correspondence.

2.4. Study selection

The articles were screened and excluded using the literature management software Endnote. Two researchers (A. Tu and P. Zarghami) first screened the literature titles for duplication, non-randomized controlled trial studies, review papers, conference papers, protocols, and correspondence. The abstracts of the literature were then read by two researchers to identify literature for inclusion and to exclude literature. Finally, the remaining articles was read in full by both researchers and further identified for inclusion. During this process, both researchers independently screened the literature and finally compared the remaining articles; if it was the same, it was eventually included; if it was different, it was discussed and resolved by the third researcher (J. Wang).

2.5. Data extraction

The following data will be extracted from the selected studies by two independent reviewers using a standard data extraction sheet: (1) author, (2) country, (3) year of publication, (4) mean age, (5) sample size, (6) details of the intervention and (7) outcome.

2.6. Data analysis

Data analysis was conducted using the RevMan software V 5.4. In studies where traditional Chinese medicine was the intervention, all continuous data were presented as mean ± standard deviation (SD). Binary variables were reported as relative risk (RR), defined as the ratio of incidence in the treatment group to the incidence in the control group, along with 95 % confidence intervals (CI) in our analysis. For continuous variables, standardized mean difference (SMD) was used, which is calculated as the mean difference in

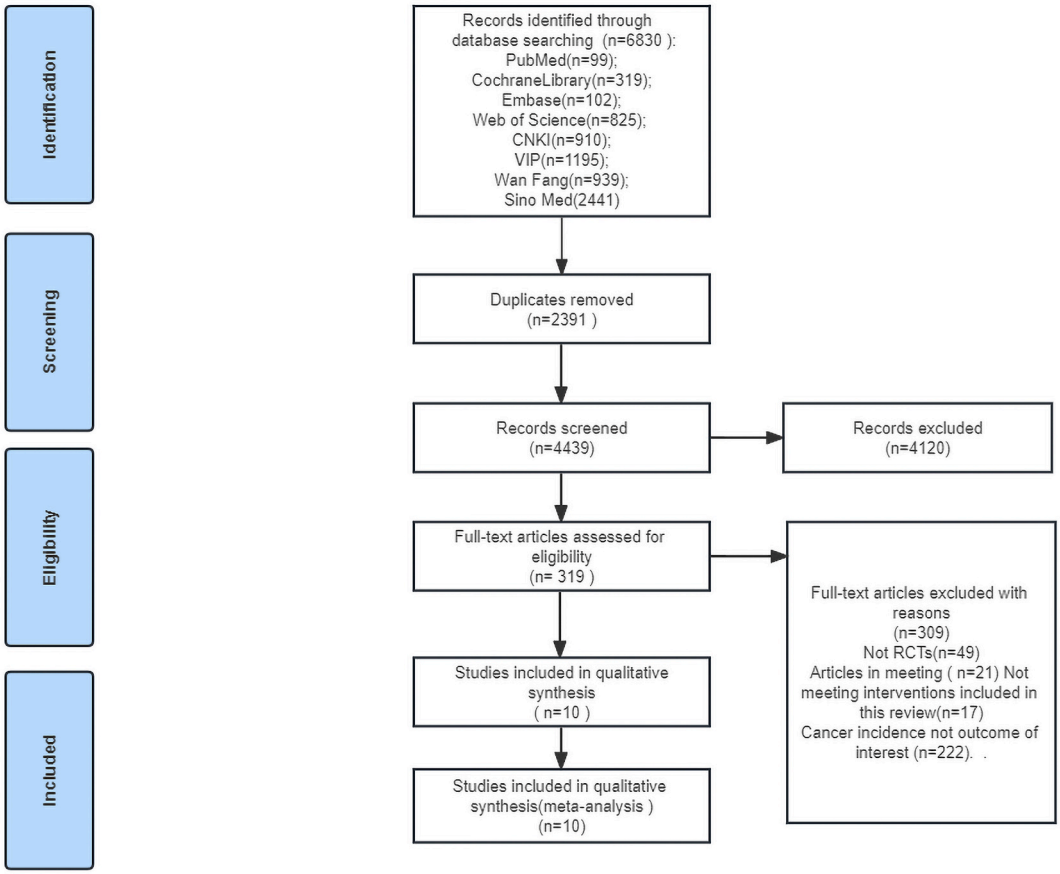


Fig. 1. Flow diagram for the selection process of the meta-analysis.

outcome between groups divided by the standard deviation of the outcome between subjects. SMD was also presented with 95 % confidence intervals (CI) in our analysis. Given the potential variability across studies, a random effects model for analysis when I2 > 50 % was employed. Conversely, when I2 < 50 %, a fixed effects model was used.

2.7. Risk of bias of individual studies

Two researchers independently assessed the risk of bias (ROB) [20], following the Cochrane Handbook version 5.1.0 tool for assessing ROB in RCTs. The following seven domains were considered: (1) randomized sequence generation, (2) treatment allocation concealment, (3) participants, (4) personnel, (5) incomplete outcome data, (6) selective reporting, and (7) other sources of bias. All domains were judged "low risk of bias," "high risk of bias," or "unclear risk of bias." Disagreements between the authors were resolved in a consensus meeting. If no consensus could be reached, a third author would decide.

3. Results

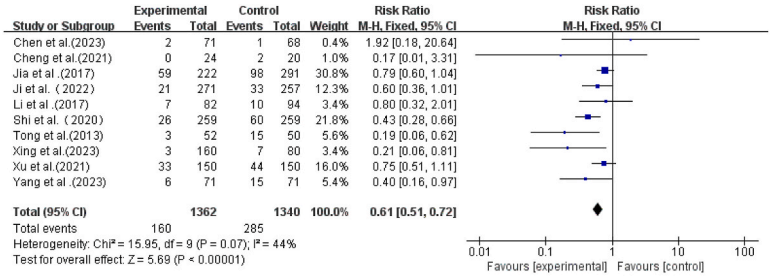
3.1. Retrieval results

The retrieval search identified 6830 relevant articles. Among them, 2391 articles were eliminated due to duplication, and 4120 articles were excluded after skimming through their titles or abstracts. Full-text assessment according to the inclusion and exclusion criteria led to the exclusion of 309 studies due to studies, not RCTs (n = 49) and meeting articles (n = 21), not meeting interventions included in this review (n = 17), and cancer incidence not outcome of interest (n = 222). Finally, 10 RCTs were included in this review [17,18,21–28]. The study selection process is illustrated in Fig. 1.

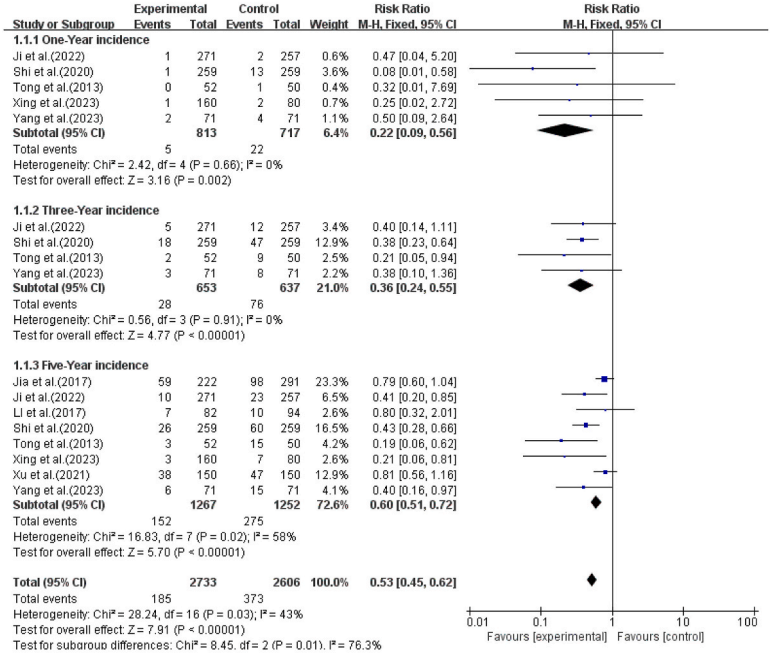
Table 2
Characteristics of the studies.

Author	Country	Year	Age [mean (SD)]	Total/male/female	Intervention	Outcome
Yang	China	2023	T:49.58 (14.07) C:49.65 (14.54)	T:71/53/18 C:71/57/14	Po. BLRG Tablet (tid) Length of Intervention: 5 years	IR
Xu	China	2021	T:53.2 (6.5) C:51.7 (6.8)	T: 150/88/62 C: 150/100/50	Po.FZHY Capsule (2g.tid).or ALHX Pills (6g.bid).or BJRG Tablets (2g.tid) Length of Intervention: 3 years	IR
Xing	China	2023	T: 49.37 (13.87) C: 49.06 (9.45)	T: 160/126/34 C: 80/58/22	Po.RG Granule (bid) Length of Intervention: 48 weeks	IR, istologic examination, liver function, and imageology examination
Tong	China	2013	T: 35–65 C: 36–65	T: 52/41/11 C: 50/40/10	Po.CPUL (100 ml bid) Length of Intervention: 3 years	IR,HBV - DNA, and antibodies
Shi	China	2020	T: 50.35 (12.67) C:49.7 (11.92)	T: 259/184/75 C: 259/168/91	Po.FZHY Capsule (1.5g.tid) Length of Intervention: At least 24 weeks	IR
Li	China	2017	T: 46.83 (12.62) C: 49.56 (14.82)	T: 82/69/13 C: 94/78/16	Po.BZYQ Pills (6g.bid) Length of Intervention:5 years	IR, liver function, complications, and safety assessment
Ji	China	2022	T: 42 (10.41) C: 42 (10.41)	T: 271/188/83 C: 257/178/79	Po.BJRG Tablets (2g.tid) Length of Intervention: At least 72 weeks	IR
Jia	China	2017	T: 55 (17) C: 55.2 (10)	T: 222/163/59 C: 291/194/97	Po.FZHY Capsule (1.5g.tid).or ALHX Pills (6g.bid). or BJRG Tablets (2g.tid). or HLSG Pills (2.2g.tid). Length of Intervention: At least 24 weeks	IR
Chen	China	2021	T: 54.3 (8.4) C: 55.3 (7.6)	T: 32/22/10 C: 30/19/11	Po.EZJD granule (bid) Length of Intervention: 48 weeks	IR, liver function, and liver fibrosis indicators
Chen	China	2023	T: 52.7 (9.61) C: 54.2 (9.41)	T: 71/54/17 C: 68/43/25	Po.YGJ (6.6g.tid) Length of Intervention: 24 weeks	IR, CTP, variceal bleeding liver function, mortality

Note: T: treatment group, C: control group, bid: bis in die, tid: ter in die, IR: HCC incidence rate, BLRG: Bielong Rugan tablet, FZHY: Fuzheng Huayu capsule, ALHX: Anluohuaxian pills, BJRG: Fufang Biejia Ruangan tablets, RG: Ruangan granule, CPUL: Compound Phyllanthus Urinaria L. HBV - DNA: Hepatitis B virus DNA, FZHY: Fuzheng Huayu capsule, BZYQ: Buzhong Yiqi pills, HLSG:Heluo Shugan pills. EZJD:Erzhu Jiedu Decoction granule, YGJ: Yanggan Jian, CTP: Child - Turcotte - Pugh class and score.



(A)



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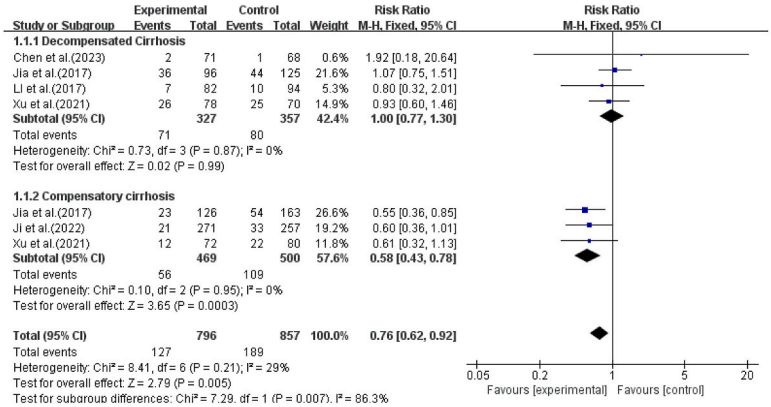
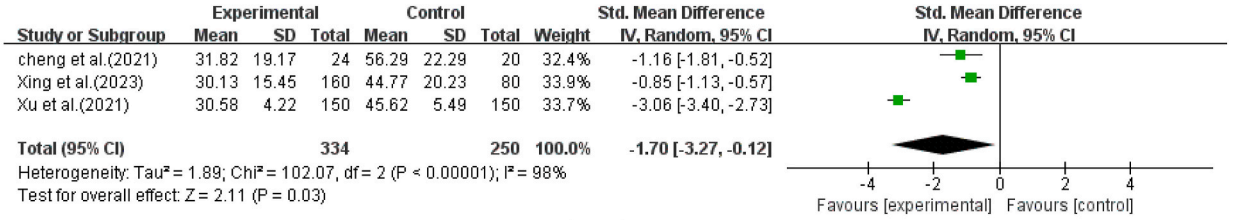


(C)

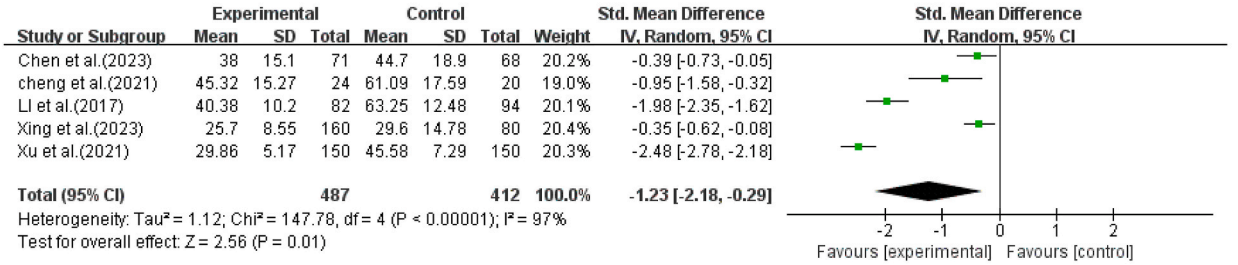
Fig. 2. Forest plots of the meta-analysis. (A) total HCC incidence, (B) 1-,3-, and 5-year HCC incidence, and (C) compensated group VS decompensated group.

3.2. Basic characteristics of included studies

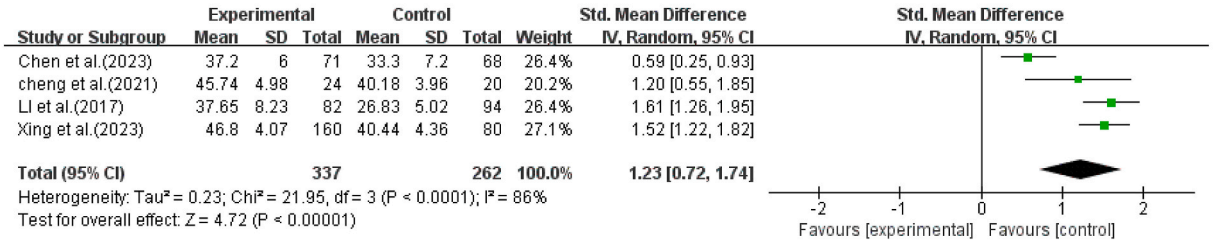
Ten RCTs published between 2013 and 2023, involved 2702 patients, of which 1340 were assigned to the control group, and 1362 patients were assigned to the experimental group. All patients were diagnosed with chronic hepatitis B liver fibrosis according to



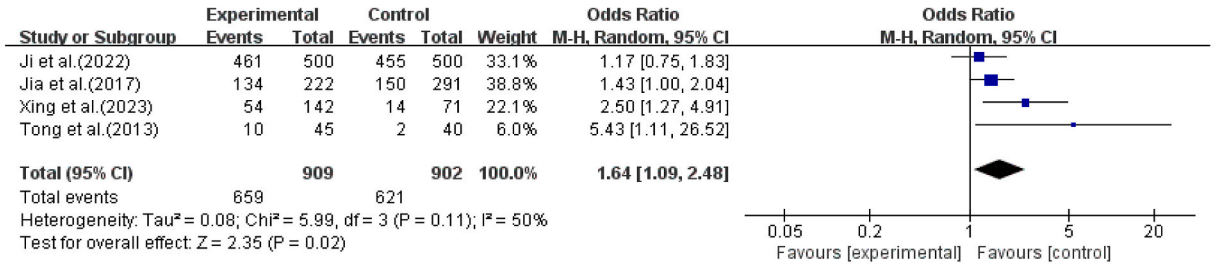
(A)



(B)



(C)



(D)

Fig. 3. Meta-analysis of ALT, AST, ALB, and Virological response.

definite diagnostic criteria and confirmed in regular hospitals. The control group was given conventional Western medicine treatment, and the experimental group received combined Western medicine treatment with traditional Chinese medicine based on the treatment strategy of the control group. Among the nineteen studies, five studies examined the efficacy of TCM in improving liver function [18, 23–25,27], and three studies investigated its impact on viral responses [22,23,28]. Detailed characteristics of included clinical trials are shown in Table 2.

3.3. Outcome measures

3.3.1. Incidence of hepatocellular carcinoma

The results showed that the incidence of HCC in patients with post-hepatitis B cirrhosis combined with traditional Chinese medicine was reduced by 39 % (RR = 0.61, 95 % CI [0.51–0.72], $P < 0.01$) compared with the control group (Fig. 2A). The heterogeneity was low ($I^2 = 44$ %).

In the sub-group analysis results showed the 1-year (RR = 0.22, 95 % CI [0.09–0.56], $P < 0.01$), 3-year (RR = 0.36, 95 % CI [0.24–0.55], $P < 0.01$) , and 5-year (RR = 0.60, 95 % CI [0.51–0.72], $P < 0.01$) outcomes, patients treated with a combination of TCM group with Western treatment, were significantly reduced the risk of HCC compared with the control group (Fig. 2B).

After classifying the population based on the stage of cirrhosis (compensated vs decompensated), TCM had obvious preventive effects in patients with compensatory cirrhosis (RR = 0.58,95 % CI [0.43–0.78], $P < 0.01$). However, for patients in the decompensated stage, the use of TCM has no preventive effect on the occurrence of HCC (RR = 1.0, 95 % CI [0.77–1.30], $P = 0.99$). The forest plots of compensated and decompensated are shown in Fig. 2C.

3.3.2. Liver function

Five trials [18,23–25,27], involving a total of 899 participants, provided available data showed that the values of ALT (SMD = −1.70 , 95 % CI [−3.27∼ −0.12], $P < 0.05$) and AST (SMD = −1.23 , 95 % CI [−2.18–0.29], $P = 0.01$) decreased significantly, and

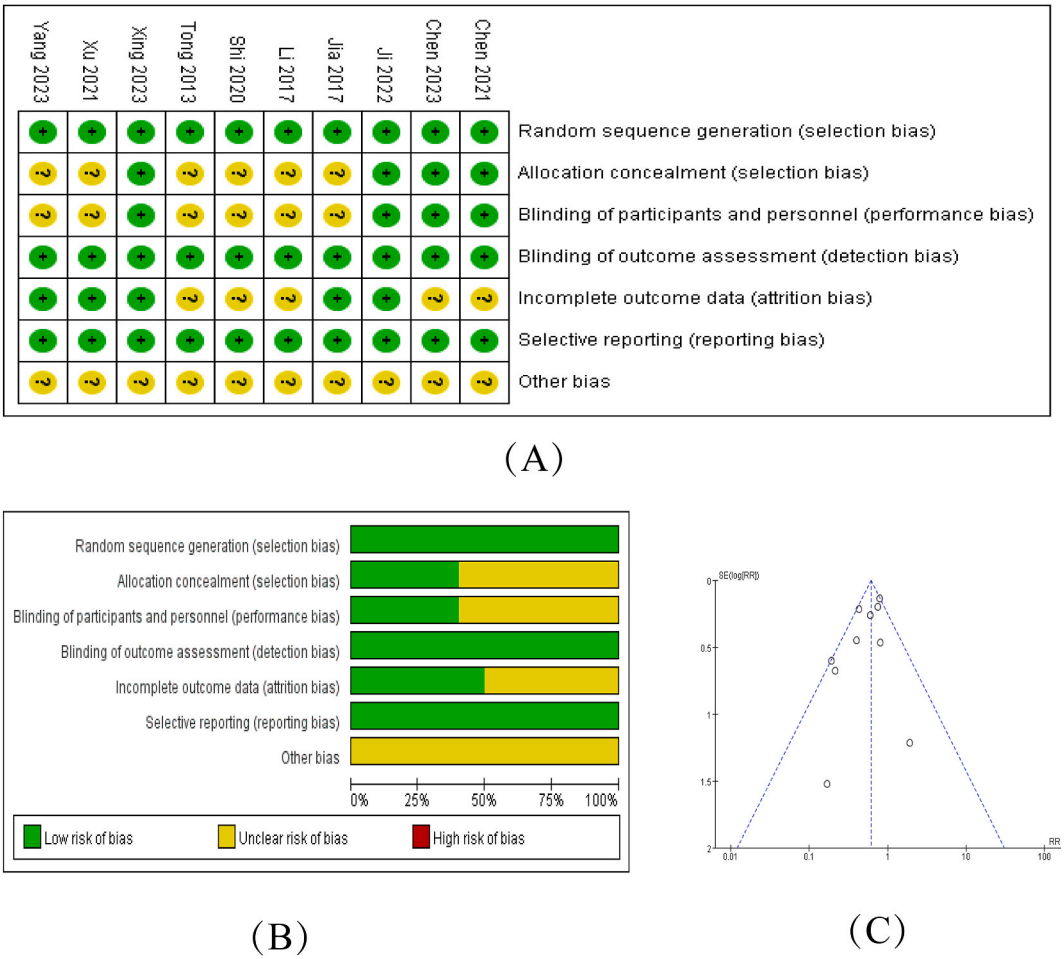


Fig. 4. Risk of bias in the included studies.

the ALB (SMD = 1.23 , 95 % CI [0.72–1.74], $P < 0.01$) value increased in the TCM group. The forest plots of ALT, AST, and ALB are shown in Fig. 3A, B, C.

3.3.3. Virological response

Four trials compared the post-treatment viral response. Briefly, among the 902 control cases [17,22,23,28], 621 showed HBV-DNA clearance after treatment, while 659 of the 909 intervention cases had a negative HBV-DNA status post-treatment. Thus, the combination treatment showed a greater antiviral effect than conventional Western medicine treatment (OR = 1.64,95 % CI [1.09–2.48], $P < 0.05$, Fig. 3D).

3.4. Assessment of risk of bias

The ROB results for each included RCT are presented in Fig. 4A and B. Regarding random sequence generation and blinding of outcome assessment, all studies were rated low-risk. Four studies were rated low-risk for the binding of participants and personnel and allocation concealment, while the remaining were rated unclear risk. Regarding incomplete outcome data, only one study was rated low-risk, and the remaining were rated unclear risk. All included studies were rated unclear risk for other biases.

3.5. Analysis of publication bias and sensitivity

Herein, publication bias was assessed using funnel plots. There was no publication bias among the included articles (Fig. 4C). The sensitivity analysis towards the primary indicators showed no significant changes after removing one study at a time, indicating that the results of this meta-analysis were stable and reliable.

4. Discussion

HBV-related cirrhosis is an independent risk factor for HCC, 70%–90 % of cases of HCC occur in patients with cirrhosis [29,30]. Hepatocellular carcinoma (HCC) represents the fifth most common malignancy and the third-leading cause of cancer-related death, worldwide, with more than 850,000 cases annually worldwide [31]. The complicated process that leads from cirrhosis to liver cancer can be caused by a variety of factors, such as the integration of viruses, modifications in cellular signaling, epigenetic modifications, and other intricate factors that result in the unchecked growth of hepatocytes that eventually develop into tumor cells [29,32–34]. In addition, inflammation, fibrosis, and microenvironment changes lead to immune tolerance and evasion of cancerous cells, and promote the development [35–37].

In recent years, numerous researchers have actively attempted to address the challenge of preventing HCC. The prevailing approaches mainly focus on managing chronic hepatitis through anti-viral therapy [38]. In this context, several researchers found that long-term Nucleoside analogues (NAs) therapy can reduce the risk of HCC [39–41]. Researchers believe that antiviral therapy can inhibit HBV replication, and improve liver inflammation activity. Consequently, this action alleviates cirrhosis and delays the progression from cirrhosis to HCC [41,42]. While NAs effectively inhibit HBV replication, long-term use often leads to drug resistance in many patients [43,44], and is potentially accompanied by adverse effects, particularly concerning bone and renal safety [45]. In addition, pure antiviral therapy alone may not entirely impede cirrhosis progression to HCC. In clinical practice, some patients may still develop hepatocellular carcinoma even if HBsAg is lost after treatment [46]. Therefore, there is an urgent need to discover and develop new medicines, especially nonnucleoside agents.

Our results show that TCM as the neoadjuvant treatment can be a promising candidate, as it can significantly reduce the risk of HCC. This corroborates with findings from previous studies, such as Tsai et al. a 15-year follow-up study involving 21,020 Taiwanese patients with chronic Hepatitis B, the results revealed those undergoing the combination of TCM and Western medicine had an approximately 37 % lower risk than those receiving solely Western medical treatment [47]. Our subgroup analysis uncovered significant effects of TCM in reducing HCC risk at 1, 3, and 5 years. Intriguingly, we noted an inverse relationship between the duration of TCM use and the magnitude of HCC risk reduction. This finding contrasts with previous studies and may be explained by differences in study populations, methodologies, or the intricate interplay of variables influencing TCM efficacy [21]. Furthermore, TCM demonstrated a significant capacity to lower HCC occurrence in compensated cirrhosis patients. However, this positive effect did not extend to decompensated cirrhosis patients. This discrepancy likely arises from the advanced disease status of decompensated cirrhosis, where factors like severe liver dysfunction and complications could differentially influence TCM's effectiveness.

Our results demonstrate a significant improvement in the ALT, AST, and ALB indicators within the combination therapy group compared to the control group. These crucial biochemical markers play an important role in assessing liver function, these findings strongly indicate a positive impact of TCM on mitigating liver function [48,49]. The analysis results reveal significant heterogeneity in our liver function indicators. The sensitivity analysis towards the primary indicators showed no significant changes after removing one study at a time, indicating that the results of this meta-analysis were stable and reliable. Heterogeneity may have resulted from different clinical baseline characteristics and intervention protocols among the included studies. Multiple clinical studies affirm its significant positive impact on improving liver function. A notable example is a systematic review conducted by Dai et al. synthesizing evidence from various clinical trials, and reported consistent improvements in serum markers of liver health following TCM administration field [50]. Emerging research highlights that Numerous herbal medicines have been demonstrated to have hepatoprotective effects [51], such as curcumin and tanshinone, that are known for their capability of mitigating oxidative stress and inflammatory responses, thereby alleviating hepatic injury [52–54]. Silymarin has membrane-stabilizing and antioxidant activity, it promotes

hepatocyte regeneration [55,56].

Additionally, our results show that TCM has benefits in assisting antiviral therapy. Some studies have suggested that the efficacy of combining traditional Chinese medicine with antiviral therapy surpasses that of antiviral therapy alone [57,58]. In addition, studies also suggested that treatment of TCM plus NAs may achieve viral suppression by regulating the host immunity [59,60]. It enhances the effectiveness of antiviral medications, mitigates liver inflammation, and alleviates accompanying symptoms [60]. This may be a crucial factor that could potentially role in slowing the progression of liver cirrhosis and reducing the incidence of HCC. In the progression of HCC patients with HBV, HBV-related liver inflammation was a pivotal factor contributing to fibrosis and cirrhosis [61,62]. Persistent virus infection can promote the advancement of liver inflammation, and then the long time of inflammation potentially resulting in extensive hepatocellular damage. This cascade of events leads to fibrosis and cirrhosis development, and the formation of HCC [63,64]. Based on the standard treatment including antivirus and antifibrosis medicine, the TCM can demonstrate a significant impact on improving liver function and enhancing antiviral responses, contributing to slowing the progression of liver diseases, thereby exhibiting significant potential in reducing the incidence of hepatocellular carcinoma [65,66]. Our research illuminates the potential of TCM in the management of Hepatitis B-related cirrhosis. The robust clinical evidence supporting the efficacy of TCM positions it as a promising intervention that is likely to garner increased attention in both research and clinical practice. Incorporating TCM into official recommendations for the management of Hepatitis B-related cirrhosis could optimize patient outcomes. The potential reduction in HCC incidence signifies a substantial public health benefit, considering the global burden of Hepatitis B-related diseases.

However, there were still several limitations in this meta-analysis. One key limitation is heterogeneity in the TCM interventions across different studies, including variations in the composition, dosage, and administration of herbal formulations. This heterogeneity poses challenges in drawing definitive conclusions on specific TCM components that produce the observed effects. Standardizing TCM interventions and using clearly defined herbal formulations are necessary. Another limitation is that TCM is mainly applied in China, and all studies included in this research originate from China. This could potentially lead to unavoidable regional bias. In addition, our results may have inherent bias due to unclear allocation concealment and blinding in some of the included trials. Finally, there were limited studies and sample sizes for liver function and virological response, which enhances the risk. Therefore, analytical bias. All these limitations may have resulted in insufficient evaluations of the outcome indicators. Future research endeavors should aim to address these limitations through standardized protocols, rigorous study designs, and broader patient populations to further enhance the validity and generalizability of the findings.

5. Conclusion

In conclusion, combination therapy with TCM as the neoadjuvant treatment showed the promising potential of reducing the incidence of HCC in patients with hepatitis B cirrhosis, by improving liver function and enhancing the viral response. The current study contributes valuable evidence for the integration of Traditional Chinese medicine into clinical practice for HCC prevention in hepatitis B-related cirrhosis patients however, the observed effects should be interpreted with caution and the limitations must be considered. It is essential to acknowledge that high-quality Randomized Controlled Trials can deepen knowledge and fill out the gaps in the future.

Authors' contributions

Encheng Wang: Formal analysis. Xiaodong Wang: Investigation, Data curation. Ding Zheng: Writing – original draft. Zhaoxuan Peng: Data curation. An Tu: Writing – original draft, Formal analysis, Data curation. Jing Wang: Writing – review & editing, Investigation, Conceptualization. Yue Yin: Formal analysis, Data curation. Mengyun Peng: Formal analysis, Data curation. Xiaoning Zhu: Writing – review & editing, Methodology, Conceptualization. Paniz Zarghami Dastjerdi: Writing – review & editing, Writing – original draft, Data curation.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University (KY2021056/FS-01).

Consent for publication

All authors approve publication.

Data availability statement

All the data was included in the article and supplements.

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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.

Acknowledgments

Not applicable.

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List of Abbreviations

TCM: Traditional Chinese Medicine
HCC: Hepatocellular Carcinoma
CI: Confidence Interval
RR: Relative Risk
CNKI: China National Knowledge Infrastructure
Sino Med: China Biological Medicine Database
VIP: Chinese Scientific Journal Database
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
ALB: Albumin
HBV-DNA: Hepatitis B Virus DNA
RCT: Randomized Controlled Trial
PROSPERO: International Prospective Register of Systematic Reviews
ROB: Risk of Bias
SD: Standard Deviation
I^2*:* Heterogeneity Measure (I-squared)
SMD: Standardized Mean Difference
Fig: Figure