

Efficacy of Acupuncture Combined with the Three-Step Analgesic Protocol in Treating Pain in Liver Cancer Pain: A Bayesian Network Meta-Analysis

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Background: Approximately 60–80% of patients with advanced liver cancer experience pain, significantly impairing quality of life. While the three-step analgesic regimen has limitations, acupuncture has gained attention for cancer pain management, though evidence for its combined use remains inconsistent. This Bayesian network meta-analysis evaluated the clinical value of acupuncture combined with the three-step regimen.

Methods: Randomized controlled trials on acupuncture combined with three-step analgesia for liver cancer pain were searched in Chinese and English databases up to August 2025. Bayesian network meta-analysis was performed using R software.

Results: Twenty-seven studies involving 2220 patients were included, covering six acupuncture modalities: Chinese herbal acupoint application, acupoint injection, acupuncture and moxibustion, acupuncture alone, heat-sensitive moxibustion, and floating acupuncture. For pain relief efficacy, SUCRA rankings were: acupuncture plus moxibustion combined with three-step therapy (0.96) > acupuncture plus herbal application combined with three-step therapy (0.65) > floating acupuncture plus herbal application combined with three-step therapy (0.64). For pain intensity (NRS), rankings were: herbal acupoint application combined with three-step therapy (0.72) > floating acupuncture plus herbal application combined with three-step therapy (0.70) > acupuncture combined with three-step therapy (0.63). For adverse events, rankings were: herbal acupoint application combined with three-step therapy (0.80) > acupuncture combined with three-step therapy (0.74) > heat-sensitive moxibustion combined with three-step therapy (0.72). CINeMA assessment indicated generally low evidence quality.

Conclusion: Current evidence suggests that herbal acupoint application and acupuncture combined with moxibustion may enhance the three-step analgesic regimen for liver cancer pain, but conclusions are limited by low evidence quality and require further high-quality trials for validation.

Keywords: acupuncture, three-step analgesic therapy, liver cancer pain, clinical efficacy, network meta-analysis

Introduction

Liver cancer is one of the malignant tumors with high morbidity and mortality rates worldwide, and the pain symptoms are prevalent among patients and can have a significant impact on their quality of life. Studies show that about 60% to 80% of patients with advanced liver cancer experience varying degrees of pain, with about 30% experiencing moderate to severe pain.¹ It is characterized by persistent pain accompanied by explosive pain episodes, which seriously affect the mobility and quality of life of patients. The impact of liver cancer pain on the quality of life of patients is multifaceted.



First, it leads to sleep disorders and loss of appetite in patients, which in turn exacerbates malnutrition and immune suppression. Secondly, it has been demonstrated to exert a substantial influence on the mental state of patients, leading to an augmentation in the prevalence of emotional disorders, including anxiety and depression. Research indicates that individuals diagnosed with liver cancer and depression exhibit a prevalence of depression that is two to three times higher compared to those with liver cancer alone.² In addition, pain limits patients' ability to perform daily activities, reduces their social engagement and quality of life. It is notable that the economic burden of liver cancer pain is also significant, with medical expenses for pain management amounting to billions of dollars in the United States each year.³

Since the World Health Organization (WHO) introduced the three-step analgesic therapy in 1986, it has become the cornerstone of cancer pain management. However, as clinical practice has evolved, the limitations of this traditional approach have become increasingly apparent. First, approximately 10% of patients exhibited an inadequate response to oral opioids, frequently accompanied by deleterious side effects.⁴ Secondly, the application of the three-step analgesic therapy in patients with advanced cancer is often too conservative, resulting in the delay of the use of interventional treatment measures and missing the optimal intervention time.⁵ Furthermore, despite the techniques such as nerve block, intrathecal drug infusion and spinal cord electrical stimulation have been incorporated into the fourth step, there remain challenges in the effective implementation of these methods in actual clinical practice.⁶ In recent years, with the renewal of the concept of pain management, the limitations of the three-step analgesic therapy have prompted scholars to propose some new treatment modalities. However, the implementation of these innovative approaches is still encumbered by numerous challenges.

While the limitations of the three-step analgesic therapy have become increasingly evident, acupuncture, a significant component of Chinese traditional medicine, has gradually garnered attention for its mechanism of action and clinical value in treating cancer pain. In recent years, a number of high-quality clinical studies have provided evidence-based evidence for the use of acupuncture to treat cancer pain. A meta-analysis of 78 randomized controlled trials⁷ demonstrated that a combination of acupuncture and three-step analgesic therapy yielded positive outcomes in enhancing patients' functional activity status and clinical efficacy. The combination of manual acupuncture and the three-step analgesic therapy exhibited the most optimal clinical response rate at the four-week intervention [OR = 5.42, 95% CI (1.99, 14.81)]. Additionally, a substantial improvement in KPS score was observed [SMD = 0.97, 95% CI (0.61, 1.33)]. In addition, external application of acupoints offers a distinct advantage in reducing pain scores [SMD = -1.14, 95% CI (-1.90, -0.93)]. Moxibustion on acupoints, in conjunction with the three-step analgesic therapy, was identified as the most effective approach to prolonging the duration of analgesia [SMD = 1.69, 95% CI (0.84, 2.54)] and shortening the onset of analgesia [SMD = -3.00, 95% CI (-4.54, -1.47)]. The potential advantages of acupuncture combined with the three-step analgesic therapy are mainly reflected in the following aspects: Firstly, acupuncture has been demonstrated to enhance the efficacy of the three-step analgesic therapy for certain patients, particularly those who are not susceptible to opioids. Secondly, acupuncture has been shown to have a reduced incidence of adverse effects, leading to a decrease in opioid dosage. Thirdly, acupuncture has been observed to not only alleviate pain but also enhance patients' overall functional status and quality of life, offering novel approaches to the comprehensive management of cancer pain.

In recent years, acupuncture combined with the three-step analgesic protocol has demonstrated unique therapeutic advantages. However, the clinical evidence still has problems such as large heterogeneity in research design and insufficient sample size. The effects of different acupuncture combined with three-step analgesic methods are controversial. Previously, there have been many meta-analyses on acupuncture for cancer pain, but there is a lack of network meta-analysis to systematically summarize different acupuncture methods. In the face of this situation, it is particularly necessary to conduct a network meta-analysis of acupuncture for liver cancer pain. Bayesian network meta-analysis, as an advanced data integration method, can simultaneously compare multiple intervention measures and improve statistical power by introducing prior information, providing a methodological basis for the comprehensive evaluation of acupuncture combined with the three-step protocol. These methodological advantages make Bayesian network meta-analysis an ideal tool for evaluating the clinical value of acupuncture combined with the three-step protocol, and are expected to provide high-quality evidence-based support for the optimization of treatment strategies for liver cancer pain.

Methods

Registration

This study was conducted in accordance with PRISMA's requirements. The present study has been registered with PROSPERO (ID: CRD420251128569).

Inclusion Criteria

Research subjects: Cases that were clearly identified in the study as meeting the diagnostic criteria for primary liver cancer and were confirmed as primary liver cancer by pathology/cytology, irrespective of the presence of metastasis. All patients had definite pain symptoms, with no restrictions on nationality, race, age or gender.

Intervention: Acupuncture-related therapies (acupuncture, needle-knife, floating needle, electroacupuncture, moxibustion, Chinese herbal acupoint application, Chinese herbal acupoint injection, etc) combined with three-step analgesic therapy.

Control group: Three-step analgesic therapy.

Outcome measures: Effective rate (= number of effective cases / total cases); Numerical Rating Scale (NRS):⁸ The degree of pain is divided into three levels, with a score of 0 to 10. Degree of pain: 0 (no pain), 1–3 (mild pain, less intense pain, normal work, no impact on sleep), 4–6 (moderate pain, unbearable pain, require painkillers, impact on sleep), 7–10 (severe pain, intense pain, may be accompanied by autonomic nerve dysfunction, severe impact on sleep, require painkillers). The pain is assessed by the patient themselves; Adverse reactions (AEs). Study type: Randomized controlled trials (RCTs), regardless of blinding status.

Exclusion Criteria

Duplicate publications; Reviews, animal experiments, cases, etc. There are no outcome indicators related to this study or no valid data can be extracted; Pain was caused by non-primary liver cancer; The sample size was small (less than 30 cases per group).

Literature Search Strategy

A comprehensive search was conducted on the following databases: The Cochrane Library, Web of Science, PubMed, EMbase, China BioMedical Literature Database (CBM), VIP, WanFang Database, and CNKI database. This search was conducted using a computerized platform until August 22, 2025. A comprehensive search strategy was employed, incorporating a combination of subject terms and free terms, along with manual retrieval of relevant literature citations. Search strategies are provided in [Supplementary material 1: Search strategies](#).

Literature Screening and Data Extraction

Two researchers independently screened the literature and extracted the data strictly in accordance with the inclusion and exclusion criteria, cross-checked them, discussed or consulted a third party in case of disagreement, and reached a consensus. The content that was extracted included the first author, the year of publication, the sample size, the intervention and control measures, the intervention time, the primary evaluation tools, and the outcome measures.

Risk of Bias Assessment

The risk of bias assessment for included studies was performed using the Cochrane Risk of Bias tool (ROB 2) as recommended in the Cochrane Handbook 5.3.0.⁹ The ROB 2 tool covers five key domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was rated as “low risk”, “some concerns”, or “high risk”. Two researchers independently conducted the assessments. Any discrepancies between evaluators were resolved through consultation with a third researcher or by discussion until consensus was reached.

Statistical Analysis

This study conducted a network meta-analysis using a random-effects model within the Bayesian framework. The analysis was implemented using the *gemtc* and *rjags* packages in R 4.3.0. For binary outcome variables, the relative risk (RR) was used as the effect size, and for continuous variables, the mean difference (MD) was used as the effect size. The corresponding 95% credibility intervals (CI) were also calculated. Heterogeneity was assessed using the Cochrane Q test and I² statistic. If $P > 0.1$ and $I^2 \leq 50\%$, indicating low heterogeneity among studies, a fixed-effects model was applied; otherwise, a random-effects model was used, and a sensitivity analysis was further conducted to infer the source of heterogeneity. Model fitting and evaluation: The Markov Chain Monte Carlo (MCMC) method was employed, with three chains run for 50,000 iterations, a burn-in period of 25,000 iterations, and a thinning interval of 10, resulting in 7500 posterior samples. All key parameters had Gelman-Rubin R values ≤ 1.05 , indicating good convergence. Results reporting: Based on the posterior samples, the median and 95% credibility intervals of the relative effects of each intervention were reported, and the efficacy ranking was conducted using the surface under the cumulative ranking curve (SUCRA) values. Node-splitting was used to test for inconsistency. Finally, publication bias was assessed using the Begg's test and a "comparison-adjusted" funnel plot was drawn using Stata 16 software.

Quality of Evidence Assessment

The quality of the evidence was assessed using CINeMA.¹⁰ The CINeMA scale encompasses six domains: intra-study bias, inter-study bias, indirectness, imprecision, heterogeneity, and inconsistency, which are used to assess the quality of evidence. Based on these assessments, the overall quality of evidence is categorized into four levels: high, moderate, low, or very low.

Results

Literature Search and Screening

A total of 1028 articles were retrieved in this study, 374 duplicate articles were excluded, 9 articles were excluded by reading the full text, and 27 articles were finally included.^{11–37} As illustrated in Figure 1, the process and results of literature screening are presented.

Basic Characteristics of the Literature

A total of 2220 patients were included in 27 articles,^{11–37} including 1113 in the intervention group and 1107 in the control group. Six acupuncture-related interventions were included: TCM acupoint application, TCM acupoint injection, needle and moxibustion, acupuncture, heat-sensitive moxibustion, and floating needle. The basic characteristics of the included literature are shown in Table 1.

Risk of Bias Assessment Results

Regarding bias in the randomization process, 13 references^{12–14,19,20,22,24,26,28,29,33,34,36} employed low-risk randomization methods, while 4 references^{11,16,25,35} utilized high-risk randomization methods. It is evident that none of the references under review have described allocation concealment and blinding. The challenge of blinding arises from the substantial disparities in intervention methodologies between the two groups. So the study data were complete and no obvious publication bias was observed. ROB2 rated four studies^{11,16,25,35} as "high risk" and the remaining 23 as "moderate risk". Figure 2 shows the risk of bias assessment results are presented.

Meta-Analysis

Efficacy

Efficacy outcomes were reported in 26 studies. The network structure did not form a closed loop (Figure 3). The most frequently studied intervention was acupoint patches combined with three-step analgesic therapy. The inconsistency test result was $P > 0.05$ under the consistency model. Heterogeneity was low ($I^2 = 4\%$). Direct meta-analysis showed that the following interventions were significantly more effective than three-step analgesic therapy alone ($P < 0.05$): TCM

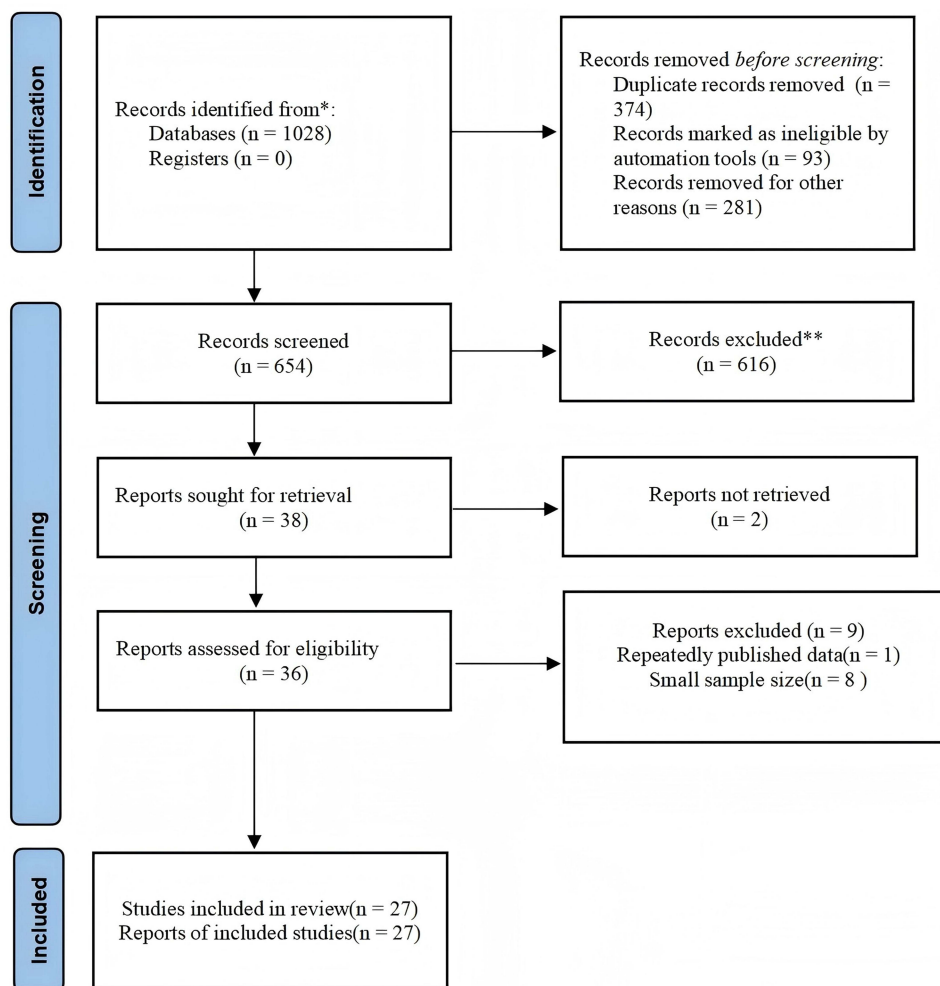


Figure 1 Flowchart of literature screening (*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers. **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools).

acupoint application combined with three-step analgesic therapy, TCM acupoint application plus TCM acupoint injection combined with three-step analgesic therapy, TCM acupoint injection combined with three-step analgesic therapy, and acupuncture-moxibustion combined with three-step analgesic therapy (Figure 4). Network meta-analysis indicated that the combination of acupuncture and moxibustion with three-step analgesic therapy was more effective than other acupuncture-related treatments (Supplementary material 2: League tables). According to the SUCRA rankings, the top three interventions were: acupuncture-moxibustion plus three-step analgesic therapy (0.96), followed by acupuncture combined with TCM acupoint application plus three-step analgesic therapy (0.65), and floating acupuncture plus TCM acupoint application combined with three-step analgesic therapy (0.64) (Table 2).

NRS

A total of eleven studies reported outcomes using the Numerical Rating Scale (NRS). No closed loop was present in the network diagram (Figure 5). The most frequently investigated intervention was acupoint patches combined with three-step analgesic therapy. The inconsistency test result was $P > 0.05$ under the consistency model. The heterogeneity test indicated low heterogeneity ($I^2 = 4\%$). Direct meta-analysis showed that Chinese herbal acupoint application (a therapy involving the external application of medicinal pastes or patches on specific acupoints) combined with three-step analgesic therapy was significantly more effective than three-step analgesic therapy alone ($P < 0.05$) (Figure 6). Network meta-analysis revealed no significant differences among all acupuncture-related interventions (Supplementary

Table 1 The Basic Characteristics of the Included Literature

Author	Year	Intervention	Samplesize	Age	Time	Outcomes
Zhang ZL ¹¹	2012	2 and 1/1	30/30	48.6±2.5	20d	Efficacy
Su C ¹²	2013	2 and 1/1	57/54	57.1/55.7	7d	Efficacy
Liu XF ¹³	2014	2 and 1/1	33/30	57.26±12.37/58.97±11.54	14d	Efficacy/AE
Shen LX ¹⁴	2014	3 and 1/1	45/45	52.1±6.6/49.8±5.7	28d	Efficacy
Tang H ¹⁵	2015	4 and 1/1	40/40	57.60±3.59	10d	Efficacy/AE
Sun XH ¹⁶	2016	2 and 1/1	44/44	43.2±2.5/49.2±2.6	28d	Efficacy
Zhou DQ ¹⁷	2016	2 and 1/1	32/33	49.66±8.50/51.27±8.89	14d	Efficacy
Wang BD ¹⁸	2017	4 and 1/1	30/30	40.21±1.6/42.21±1.58	10d	Efficacy/AE
Xuan J ¹⁹	2017	5 and 1/1	40/40	55.3±6.70/53.7±7.64	14d	Efficacy
Yu WF ²⁰	2018	2 and 1/1	51/51	65.51±8.68/65.30±8.55	28d	Efficacy/NRS/AE
Guo HL ²¹	2019	3 and 1/1	50/50	30±60/30±65	28d	Efficacy
Li ZJ ²²	2019	3 and 1/1	40/40	49.9±5.2/47.2±4.6	28d	Efficacy/NRS
Wu D ²³	2019	5 and 1/1	59/59	59.5±8.2/57.7±9.2	28d	Efficacy
Wu ZL ²⁴	2019	2 and 3 and 1/1	41/40	43.12±11.28/43.17±11.66	28d	Efficacy/NRS/AE
Zhang JW ²⁵	2019	2 and 1/1	46/46	58.78±10.4/57.34±9.96	7d	Efficacy/AE
Liu LX ²⁶	2020	6 and 1/1	30/30	53±9	14d	Efficacy/NRS/AE
Luan YH ²⁷	2020	2 and 1/1	30/30	45.0±±1.2/48.0±1.5	14d	NRS/AE
Yu XH ²⁸	2020	2 and 1/1	34/34	61.25±2.79/61.29±2.83	28d	Efficacy/AE
Ma J ²⁹	2021	5 and 1/1	34/34	54.29±5.91+5.87/54.02	14d	Efficacy/AE
Su YQ ³⁰	2021	2 and 1/1	38/38	60.57±6.58/61.46±5.72	28d	Efficacy/NRS
Wang LL ³¹	2021	5 and 1/1	40/40	59+10/60+9	10d	Efficacy/NRS/AE
Xu YJ ³²	2021	2 and 3 and 1/1	34/34	42.78±5.25/42.15±5.63	14d	Efficacy/AE
You Y ³³	2021	2 and 1/1	48/48	61.87±5.67/62.34±5.72	10d	Efficacy/NRS/AE
Jia LY ³⁴	2022	2 and 3 and 1/1	34/34	56.45±5.28/56.34±5.32	28d	Efficacy/NRS/AE
Chen Z ³⁵	2024	2 and 1/1	75/75			Efficacy
Feng Y ³⁶	2024	7 and 2 and 1/1	48/48	61.03±8.63/60.34±8.45	14d	Efficacy/NRS/AE
Zhao AJ ³⁷	2025	5 and 2 and 1/1	30/30	61.87±7.39/61.80±7.35	28d	Efficacy/NRS/AE

Notes: 1 = Three-step analgesic drugs, 2 = Chinese medicine acupoint application, 3 = Chinese medicine acupoint injection, 4 = Acupuncture and moxibustion, 5 = Acupuncture, 6 = Thermal sensitive moxibustion, 7 = Floating needle.

[material 2: League tables](#)). Based on SUCRA values, the top three treatments were: Chinese herbal acupoint application plus three-step analgesic therapy (0.72), followed by floating needle combined with Chinese herbal acupoint application plus three-step analgesic therapy (0.70), and acupuncture plus three-step analgesic therapy (0.63) (Table 2).

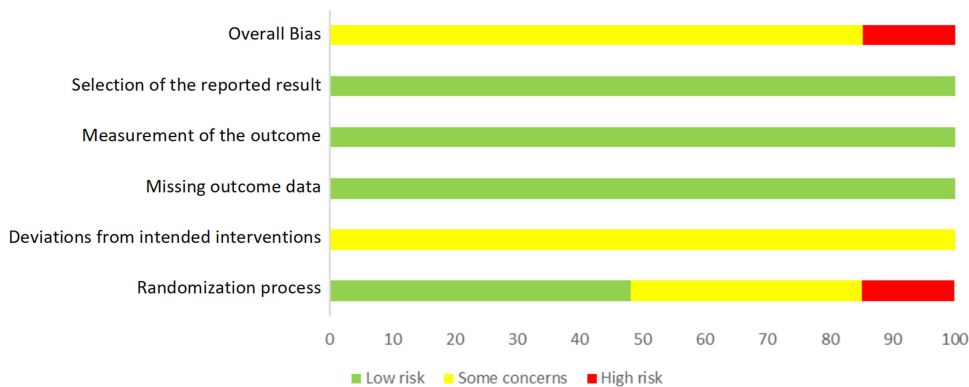


Figure 2 Risk of bias assessment results of included studies.

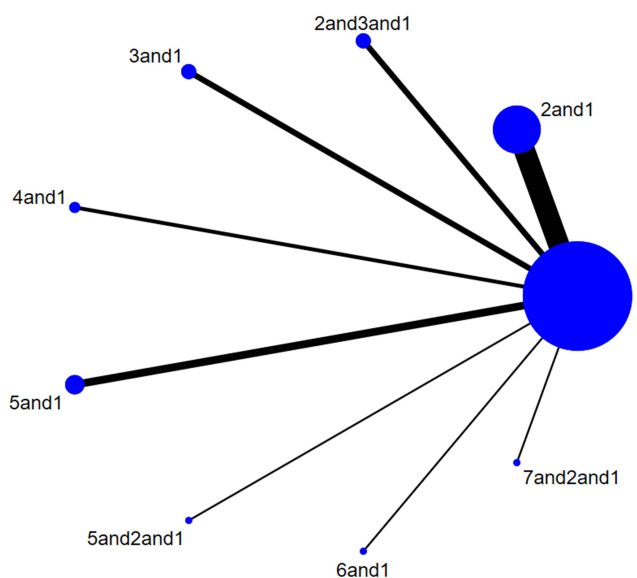


Figure 3 Network evidence structure diagram of pain relief efficacy (Efficacy).

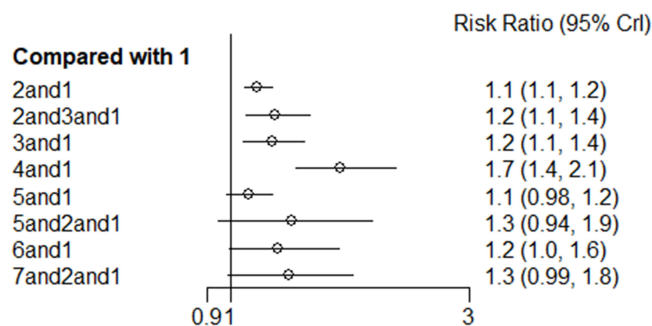


Figure 4 Forest plot of direct meta-analysis of pain relief efficacy (Efficacy).

Adverse Reactions

Adverse reactions were reported across 16 studies. It should be noted that Figure 7 does not form a closed loop (Figure 7). The most frequently studied intervention was the combination of acupoint patches with a three-step analgesic

Table 2 SUCRA Ranking

Intervention	Efficacy			NRS			Adverse Reaction		
	SUCRA	RR (95% CI)	No	SUCRA	MD (95% CI)	No	SUCRA	RR (95% CI)	No
2 and 1	0.32	1.13 (1.07, 1.22)	7	0.72	-1.81 (-2.92, -0.7)	1	0.80	0.32 (0.16, 0.61)	1
3 and 1	0.53	1.22 (1.06, 1.41)	6	0.46	-1.17 (-3.36, 1.02)	6			
2 and 3 and 1	0.56	1.23 (1.08, 1.44)	5	0.492	-1.24 (-2.84, 0.35)	5	0.416	0.71 (0.32, 1.09)	5
4 and 1	0.96	1.66 (1.36, 2.14)	1				0.411	0.7 (0.35, 1.31)	6
5 and 1	0.22	1.09 (0.98, 1.21)	8	0.63	-1.64 (-3.85, 0.58)	3	0.74	0.36 (0.13, 0.85)	2
6 and 1	0.57	1.25 (1.00, 1.65)	4	0.35	-0.83 (-3.07, 1.41)	7	0.72	0.19 (0.01, 1.69)	3
5 and 2 and 1	0.65	1.33 (0.94, 1.92)	2	0.498	-1.25 (-3.47, 0.99)	4	0.08	1.21 (0.49, 2.98)	8
7 and 2 and 1	0.64	1.31 (0.99, 1.76)	3	0.70	-2 (-4.21, 0.20)	2	0.58	0.51 (0.19, 1.32)	4
1	0.01	1	9	0.07	0	8	0.14	1	7

Notes: 1 = Three-step analgesic drugs, 2 = Chinese medicine acupoint application, 3 = Chinese medicine acupoint injection, 4 = Acupuncture and moxibustion, 5 = Acupuncture, 6 = Thermal sensitive moxibustion, 7 = Floating needle.

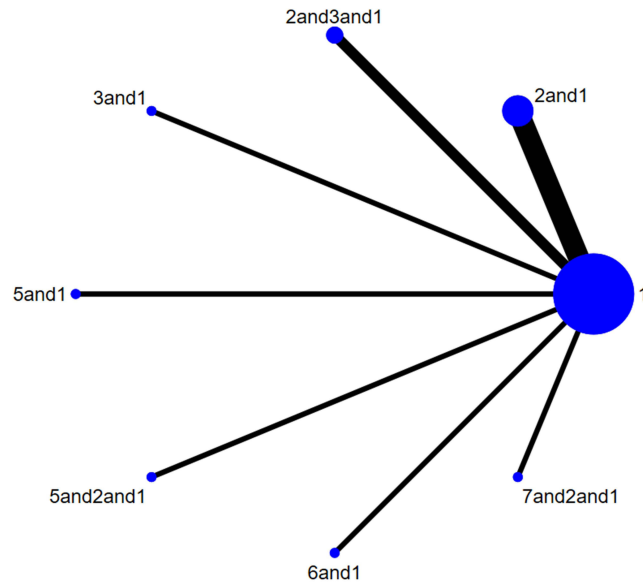


Figure 5 Network evidence structure diagram of pain intensity (NRS).

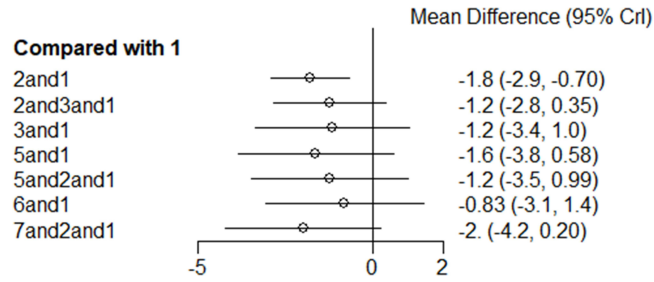


Figure 6 Forest plot of direct meta-analysis of pain intensity (NRS).

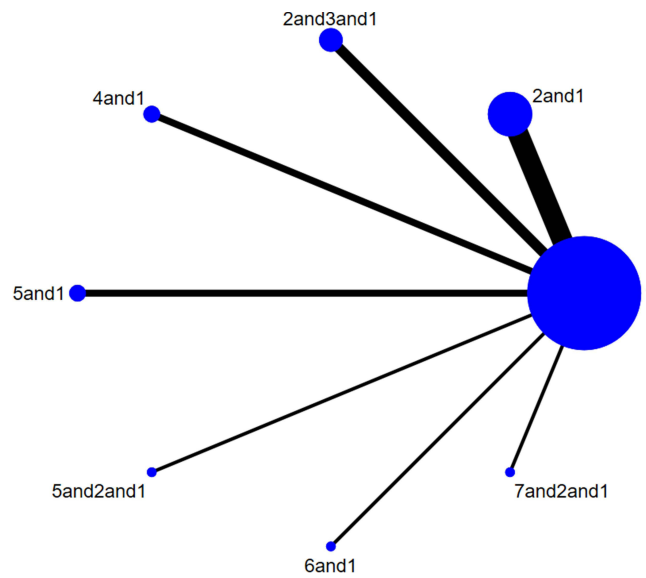


Figure 7 Network evidence structure diagram of adverse events (AE).

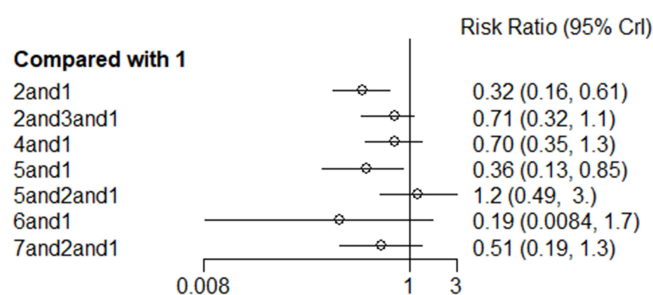


Figure 8 Forest plot of direct meta-analysis of adverse events (AE).

therapy. The consistency test yielded a result of $P > 0.05$, analyzed using a consistency model. Heterogeneity was low, with $I^2 = 4\%$. Direct meta-analysis indicated that both Chinese herbal acupoint application combined with three-step analgesic therapy and acupuncture combined with three-step analgesic therapy were significantly more effective than three-step analgesic therapy alone ($P < 0.05$) (Figure 8). Network meta-analysis revealed no statistically significant differences among various acupuncture-related interventions (Supplementary material 2: League tables). The top three treatments based on SUCRA rankings were: Chinese herbal acupoint application plus three-step analgesic therapy (0.80) > acupuncture plus three-step analgesic therapy (0.74) > heat-sensitive moxibustion plus three-step analgesic therapy (0.72). As shown in Table 2, the main adverse events reported included nausea and vomiting, constipation, and drowsiness, with constipation being the most frequently observed (Table 2). Table 3 summarizes the incidence rates of these adverse reactions.

Table 3 Adverse Reaction

Study	Intervention	Symptom	
		Intervention Group	Control Group
Liu XF ¹³	2 and I/I	Itching 2	Constipation 3, dizziness 2, nausea and vomiting 1
Tang H ¹⁵	4 and I/I	Nausea and vomiting 9, headache and dizziness 8, constipation 8, sleepiness 3	Nausea and vomiting 12, headache and dizziness 9, constipation 10, drowsiness 6
Wang BD ¹⁸	4 and I/I	Headache and dizziness 3, nausea and vomiting 3, drowsiness 2, constipation 2	Headache and dizziness 4, nausea and vomiting 5, drowsiness 4, constipation 4
Yu WF ²⁰	2 and I/I	Blister 1, mild infection 1	Blister 3, infection 2, stinging 2, allergy 3
Wu ZL ²⁴	2 and 3 and I/I	Nausea 10, constipation 18, fatigue 6, itchy skin 1	Nausea 11 Constipation 19 fatigue 7
Zhang JW ²⁵	2 and I/I	Rash 2	Itching 2
Liu LX ²⁶	6 and I/I	Vomiting 1	Drowsiness 2, constipation 2
Luan YH ²⁷	2 and I/I	Nausea and vomiting 3	Nausea and vomiting 5, liver and kidney function impairment 2, hemodynamic changes 1
Yu XH ²⁸	2 and I/I	Constipation 1, nausea and vomiting 1	Constipation 2, nausea and vomiting 3, itching 2, drowsiness 1
Ma J ²⁹	5 and I/I	Nausea and vomiting 1, dizziness 1	Nausea and vomiting 4, dizziness 3, low blood pressure 2
Wang LL ³¹	5 and I/I	Drowsiness 1, vomiting 1, nausea 2, constipation 2, urinary retention 1	Drowsiness 2, vomiting 3, nausea 4, constipation 4, urinary retention 2
Xu YJ ³²	2 and 3 and I/I	Nausea 1, constipation 1, difficulty breathing 1	Nausea 4, constipation 5, difficulty breathing 2
You Y ³³	2 and I/I	Nausea and vomiting 1 anorexia 2 headache 1	Nausea and vomiting 3 Diarrhea abdominal pain 2 anorexia 3 itching 1 headache 2
Jia LY ³⁴	2 and 3 and I/I	Nausea 3, fatigue 2, constipation 3, itchy skin 2	Nausea 6, fatigue 4, constipation 5, itchy skin 2, respiratory depression 1
Feng Y ³⁶	7 and 2 and I/I	Nausea and vomiting 5, constipation 9, respiratory depression 1, herpes 1, diarrhea 1	Nausea and vomiting 10, constipation 15, respiratory depression 2, urinary retention 2, herpes 1, diarrhea 3
Zhao AJ ³⁷	5 and 2 and I/I	Dizziness and drowsiness 6, nausea and vomiting 9, constipation 4, urinary retention 2, itching 8	Dizziness and sleepiness 4, nausea and vomiting 7, constipation 5, urinary retention 1, pruritus 7

Publication Bias Results

Publication bias was assessed for all primary outcome measures, and the results indicated a low probability of bias across the studies included. Statistical tests for funnel plot asymmetry did not yield significant values, supporting the absence of substantial publication bias. Specifically, the p-values for Egger’s regression test were as follows: for Efficacy outcomes, $P = 0.17$ (Figure 9); for the Numeric Rating Scale (NRS), $P = 0.81$ (Figure 10); and for Adverse Events (AE), $P = 0.78$ (Figure 11). These non-significant results (all $P > 0.05$) suggest that the meta-analytic findings are unlikely to have been substantially influenced by selective publication.

Quality of Evidence Evaluation Results

The CINeMA evaluation results indicated low evidence quality, with the main downgrading factors being Within-study bias and Incoherence (Table 4).

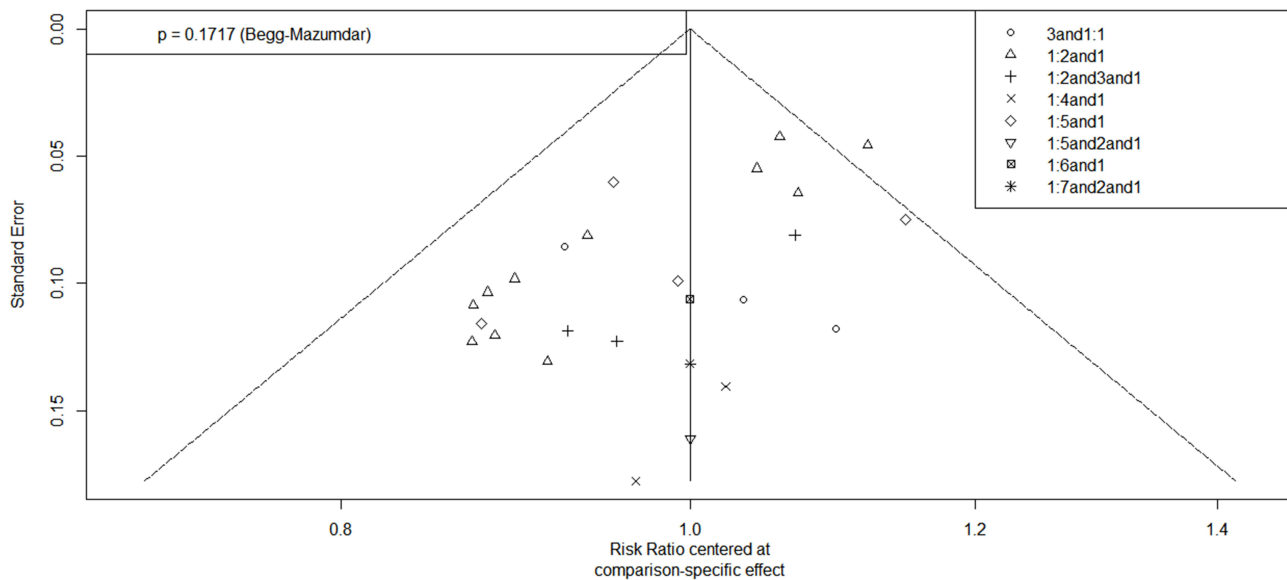


Figure 9 Funnel plot of publication bias (Efficacy).

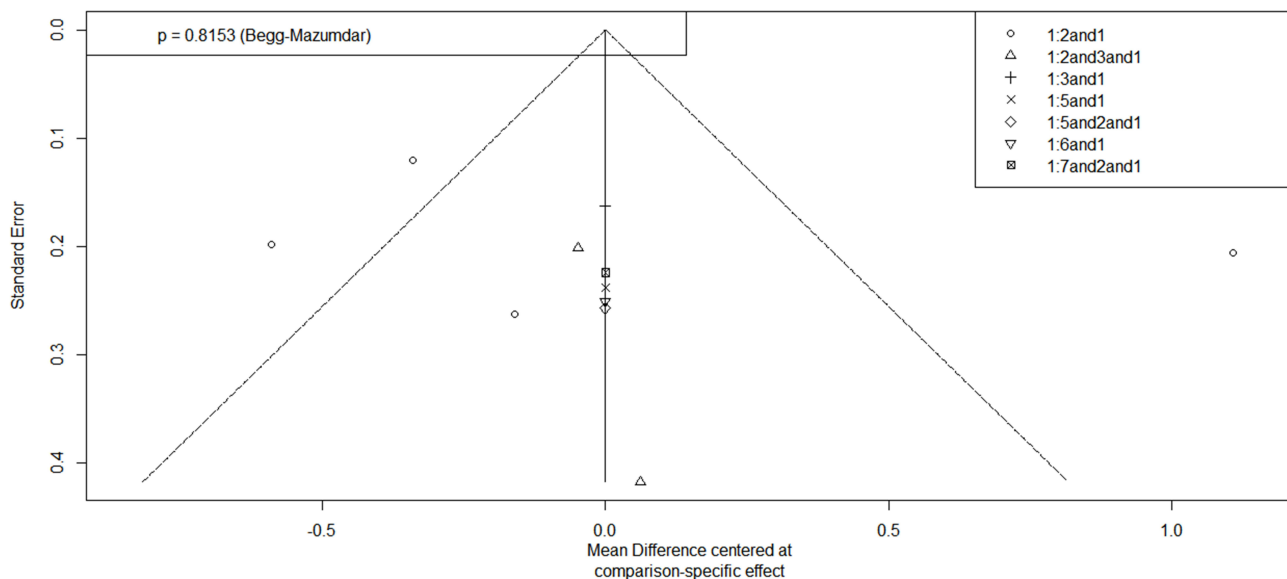


Figure 10 Funnel plot of publication bias (NRS).

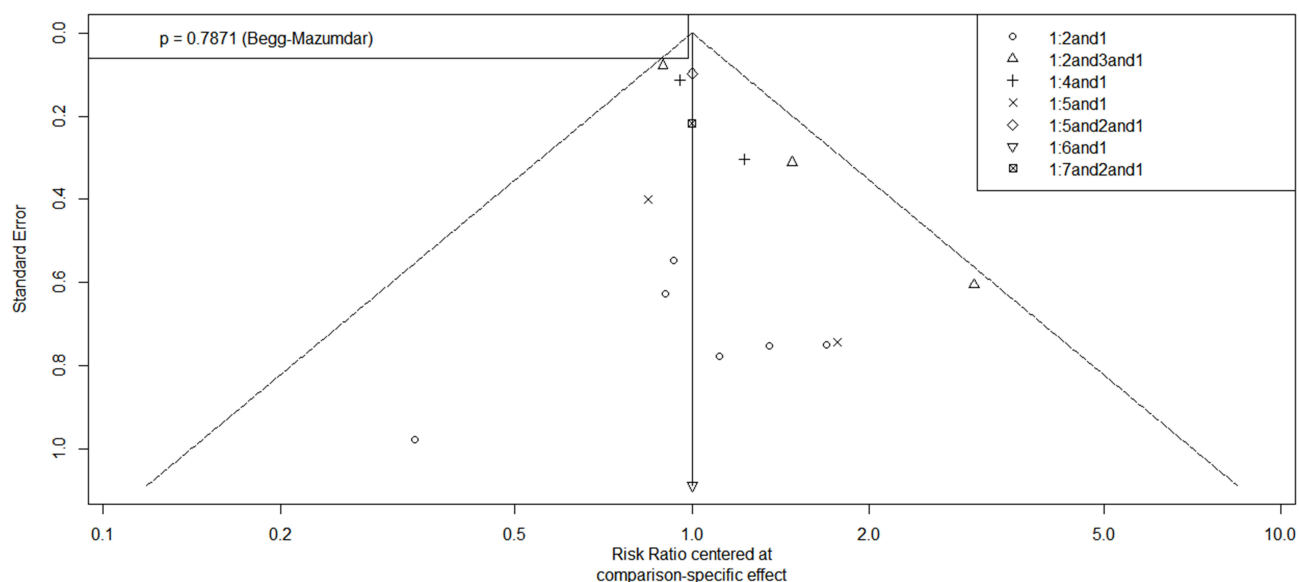


Figure 11 Funnel plot of publication bias (AE).

Sensitivity Analysis

We conducted a sensitivity analysis and found that the results were stable ([Supplementary material 3: Sensitivity analysis](#)).

Discussion

This study included 27 studies involving a total of 2220 patients, including six acupuncture methods: TCM acupoint application, TCM acupoint injection, acupuncture and moxibustion, acupuncture, heat-sensitive moxibustion, and floating acupuncture. Three outcome measures, namely efficacy, NRS and adverse reactions, were studied. In terms of efficacy: Compared with the three-step analgesic therapy, TCM acupoint application, TCM acupoint application combined with TCM acupoint, TCM acupoint injection, acupuncture and moxibustion combined with the three-step analgesic therapy had significant advantages. The top three SUCRA rankings are: acupuncture and moxibustion combined three-step analgesic therapy acupuncture combined with TCM acupoint application combined three-step pain relief therapy, floating needle combined with TCM acupoint application combined three-step analgesic therapy. In terms of NRS indicators: TCM acupoint application combined with three-step analgesic therapy has a significant advantage over three-step pain relief therapy. The top three SUCRA rankings are: TCM acupoint application combined with three-step pain relief therapy, floating needle combined with TCM acupoint application combined with three-step analgesic therapy acupuncture combined with three-step analgesic therapy. In AE: TCM acupoint application combined with three-step analgesic therapy. Acupuncture combined with three-step analgesic therapy has a significant advantage over the three-step analgesic therapy. The top three SUCRA rankings are: TCM acupoint application combined with three-step analgesic therapy, acupuncture combined with three-step analgesic therapy, and heat-sensitive moxibustion combined with three-step analgesic therapy. A comprehensive evaluation of the available evidence suggests that the integration of TCM acupoint application, acupuncture in conjunction with moxibustion, and a three-step pain relief therapy regimen yields optimal outcomes. The likelihood of publication bias influencing the results appears minimal. Nevertheless, given the potential inadequacy of the extant evidence, further substantiation is requisite to ensure the robustness of the conclusions.

In terms of adverse reactions, they are mostly symptoms such as constipation, nausea, and vomiting. Studies have demonstrated that three-step analgesic therapy frequently results in adverse reactions, including constipation, nausea, vomiting, drowsiness, and breathing difficulties.³⁸ Constipation, a prevalent adverse effect of opioid analgesics, has been reported in more than 90% of cases.³⁹ In cases of constipation induced by opioid analgesics, enemas and laxatives offer

Table 4 CINeMA Results

Outcomes	Comparison	Number of Studies	Within-Study Bias	Reporting Bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence Rating	Reason(s) for Downgrading
Efficacy	I:2 and I	11	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:2 and 3 and I	3	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:3 and I	3	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:4 and I	2	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:5 and I	4	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Very low	["Within-study bias", "Heterogeneity", "Incoherence"]
	I:5 and 2 and I	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low	["Within-study bias", "Imprecision", "Incoherence"]
	I:6 and I	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Very low	["Within-study bias", "Heterogeneity", "Incoherence"]
	I:7 and 2 and I	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Very low	["Within-study bias", "Heterogeneity", "Incoherence"]
NRS	I:2 and I	4	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:2 and 3 and I	2	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:3 and I	1	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:5 and I	1	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:5 and 2 and I	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	Some concerns	Very low	["Within-study bias", "Heterogeneity", "Incoherence"]
	I:6 and I	1	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
AE	I:7 and 2 and I	1	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:2 and I	6	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:2 and 3 and I	3	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:4 and I	2	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:5 and I	2	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]
	I:5 and 2 and I	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low	["Within-study bias", "Imprecision", "Incoherence"]
	I:6 and I	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low	["Within-study bias", "Imprecision", "Incoherence"]
	I:7 and 2 and I	1	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	["Within-study bias", "Incoherence"]

only transient relief, failing to address the underlying pathophysiology. These adverse reactions have the potential to impact the patient's quality of life and may also impose limitations on the continued utilization of the pharmaceutical agent. These findings underscore the limitations of the three-step analgesic therapy, and there is an urgent need to explore safer and more effective alternatives or adjuvant treatments.

As a traditional Chinese medical therapy, acupoint application has demonstrated unique therapeutic advantages in the management of liver cancer pain. First, it offers notable analgesic efficacy. Studies have confirmed that integrating acupoint application into standardized cancer pain management protocols significantly improves patients' quality of life scores, while effectively reducing pain levels measured by the Visual Analogue Scale (VAS) and alleviating negative emotional scores.⁴⁰ Feng et al further supported the role of this therapy in enhancing analgesic outcomes.⁴¹ The mechanism of action involves a dual effect: transdermal drug absorption and acupoint stimulation. By applying medication to specific acupoints, active ingredients penetrate the skin and directly target the affected area, while acupoint stimulation triggers neural reflexes that help regulate bodily functions. This combined approach not only increases drug bioavailability but also synergistically enhances pain relief. Second, the therapy exhibits a favorable safety profile. Wu et al⁴² reported a significantly lower incidence of adverse reactions (6.67%) in the acupoint application group compared to a Western medicine control group (23.33%). As an externally applied treatment that takes effect internally, it avoids gastrointestinal discomfort associated with oral medications and reduces the risk of injection-related pain. Third, acupoint application is well accepted among patients and demonstrates strong compliance. Its rapid onset, ease of operation, flexible acupoint selection based on syndrome differentiation, and suitability for repeated use contribute to its widespread cultural acceptance and clinical applicability in China. Furthermore, this method circumvents common concerns associated with Western analgesic drugs—such as dependency, addiction, and withdrawal reactions. Clinical practice has shown that acupoint application can significantly alleviate pain in liver cancer patients, reduce reliance on opioid dosages, and consequently lower the risks of drug dependence and adverse effects. Clinical practice has shown that acupoint application can significantly relieve pain symptoms in patients with liver cancer and reduce the dosage of opioid drugs, thereby lowering the risk of drug dependence and adverse reactions.

Acupuncture is a non-pharmaceutical therapy that has been demonstrated to rapidly alleviate pain, extend the duration of analgesia, and prevent the recurrence of pain. Currently, the international acceptance of acupuncture is growing steadily. In the 2016 practice guidelines proposed by the American Society of Clinical Oncology (ASCO), the use of acupuncture for the treatment of cancer-related pain is recommended. Recent studies have indicated that acupuncture treatment may enhance blood circulation and organ function, thereby reducing pain associated with cancer. The prevailing opinion among the scientific community is that acupuncture exerts its therapeutic effects by modulating the release of neurotransmitters, including endorphins, endogenous opioids (EOPs), 5-hydroxytryptamine (5-HT), and norepinephrine. A study has demonstrated that electroacupuncture and wrist-ankle acupuncture alleviate cancer-induced pain by modulating the expression of 5-HT and its receptors and increasing the secretion of opioid receptors, as well as by enhancing endorphins within the downstream pain regulation system. In addition, the combination of acupuncture and moxibustion has demonstrated distinctive therapeutic advantages in the management of liver cancer pain, with the underlying mechanism primarily attributed to the synergistic effect of neurotransmitter regulation and local microcirculation improvement. Research has demonstrated that acupuncture, through the stimulation of specific acupoints, can modulate the release of neurotransmitters such as serotonin and endorphins within the central nervous system, thereby inducing analgesic effects. Concurrently, the warming effect of moxibustion promotes local vasodilation, improves the tumor microenvironment, increases tissue oxygen supply, reduces inflammatory responses, and further alleviates pain symptoms. This combination therapy has been demonstrated to provide rapid pain relief and sustained analgesic effects, offering a more comprehensive pain management solution for patients with liver cancer. In the context of functional Magnetic Resonance Imaging (fMRI), researchers have identified a regulatory role for acupuncture in the thalamocortical circuit, thereby enhancing the functional connectivity (rsFC) between the thalamus and the default mode network (DMN) during rest periods. This regulatory mechanism, as evidenced by the observed analgesic effects, underscores the potential of acupuncture in addressing neurobiological processes associated with pain modulation.⁴³ A multitude of published meta-analyses have consistently demonstrated the efficacy of acupuncture in alleviating pain associated with liver cancer. For instance, a meta-analysis by Zhang et al⁴⁴ demonstrated that, in comparison with

Western medicine, Chinese herbal acupoint application in conjunction with analgesics or Chinese herbal acupoint application alone was capable of enhancing the efficacy of pain relief in patients diagnosed with primary liver cancer [RR=1.19, 95% CI (1.09, 1.30), $P<0.05$] and reducing the occurrence of adverse reactions [RR=0.30, 95% CI (0.20, 0.44), $P<0.05$]. A meta-analysis by He et al demonstrated that the combination of acupuncture and moxibustion exhibited a significant analgesic effect in patients suffering from PLC pain, when compared with the three-step analgesic therapy (1.69 [1.36, 2.10], $P < 0.05$).⁴⁵ In comparison with conventional analgesic methodologies, acupoint application and acupuncture boast a number of salient advantages. These modalities include simplicity of operation, a paucity of adverse effects, and a high degree of patient compliance. Consequently, they present a safe and effective complementary treatment option for the management of pain associated with liver cancer.

This study is the first to systematically summarize the differences in clinical efficacy between acupuncture combined with the three-step analgesic method and the three-step analgesic method alone in treating liver cancer pain. The research shows that acupuncture demonstrates potential as an alternative or complementary treatment option. However, this study also has several limitations. The CINeMA evaluation results indicate that the quality of evidence is low, with the main downgrading factors being within-study bias and incoherence. The main reason is that the methodology of the included studies is not rigorous. Although most of the studies included in this analysis claimed to have used randomization, the methods for generating the random sequence and the allocation concealment schemes were described vaguely or not reported at all. The lack of transparency in methodological reporting significantly increases the risk of potential selection bias, which is one of the main reasons for the downgrading of the “within-study bias” domain. Moreover, due to the nature of acupuncture intervention, blinding of the implementers and participants is difficult, and the blinding of outcome assessors is often not reported. The absence or insufficiency of blinding is a core factor in the high risk of “within-study bias” in this evaluation. Pain, as a subjective outcome, is susceptible to measurement bias. Some studies have limited sample sizes, and there are differences in intervention duration and treatment frequency, which may affect the stability and comparability of the effect size. There is also clinical heterogeneity and insufficient standardization of the intervention. The acupuncture intervention measures included in the study lack unified standards in terms of selection principles of acupoints and stimulation parameters (such as needling techniques, duration, and temperature), resulting in high clinical heterogeneity. Although the statistical heterogeneity test shows a low I^2 value, this method has limited ability to detect clinical heterogeneity, and the differences in actual intervention content between different studies may affect the reliability and generalizability of the results. There are also limitations in outcome indicators and follow-up duration. The studies mainly rely on short-term efficacy indicators (such as effective rate and NRS score), lacking dynamic assessment of long-term pain control, quality of life, functional status, and analgesic drug dosage. The reporting of adverse reactions is also brief, and the long-term safety has not been systematically evaluated. The design of such studies has limited ability to detect long-term or rare adverse events in combined therapy. Future research needs to integrate large-scale observational comparative studies or pharmacoepidemiological data to provide a more comprehensive and realistic long-term safety profile. Sparse network structure and uncertainty in indirect comparisons, the number of direct comparison studies between some intervention nodes is limited, mainly relying on indirect comparisons for effect inference, which may increase the uncertainty of the results. Although the node splitting method did not detect significant inconsistency, in the context of clinical heterogeneity, the evidence strength of indirect comparisons still needs to be interpreted with caution. Network meta-analysis may have significant inconsistency. We speculate that this may be due to the significant differences in acupuncture protocols among the included studies, which may make the estimates derived from indirect comparisons unreliable. This is a common problem in the current field of acupuncture RCTs.

Although this study provides evidence-based support for the application of acupuncture combined with a three-step analgesic therapy in the management of liver cancer pain, several critical issues remain to be addressed in future research. First, a multimodal efficacy evaluation system needs to be constructed, which integrates multi-dimensional indicators such as patient quality of life, functional status, and drug dosage. These indicators will be based on the traditional pain scores, and introduces objective biomarkers (such as serum endorphin levels, brain functional imaging changes) for comprehensive evaluation to fully reflect the clinical benefits of the combination therapy. Secondly, given the individual differences in pain mechanisms and the heterogeneity in treatment responses among patients with liver cancer, the design of future RCTs should focus on precise patient stratification strategies. It is recommended to establish predictive models

based on pain characteristics (such as neuropathic pain components), tumor stage, liver function reserve, psychosocial factors, etc, to achieve individualized optimization of treatment regimens. Furthermore, in the design of RCTs, the balance between standardization and individualization of the intervention plan should be fully considered, and key parameters of acupuncture intervention (such as acupoint selection, stimulation intensity, treatment frequency, etc) should be thoroughly defined, while reserving necessary individualized adjustment space to improve the clinical applicability and generalization value of the research findings.

Conclusions

Current evidence indicates that certain acupuncture combined with three-step analgesic drugs can increase the effective rate of pain relief in patients with primary liver cancer and reduce the incidence of adverse reactions. Overall, the combination of traditional Chinese medicine acupoint application, acupuncture and moxibustion with three-step analgesic drugs has the best effect. However, the limitations of the research mean that the research conclusions still need to be further verified by more high-quality randomized double-blind controlled trials. To enhance the level of evidence and promote clinical translation, future research should focus on the following aspects: In terms of trial design, large-sample, multi-center studies based on sample size calculation should be carried out; while taking into account the individualized treatment based on TCM syndrome differentiation, standardized core intervention protocols should be formulated and reported in accordance with the STRICTA guidelines. In terms of outcome evaluation, a multi-dimensional core indicator set including pain intensity, drug dosage, quality of life and safety should be constructed, and long-term follow-up of at least 3–6 months should be conducted. In terms of mechanism exploration, it is recommended to embed sub-studies in clinical trials to dynamically detect serum pain-related biomarkers (such as β -endorphin, inflammatory factors), and explore the differences in therapeutic effects based on pain types or TCM syndrome types. The baseline characteristics of patients (especially tumor stage, pain type and previous analgesic regimens) should be reported in a standardized manner, and future systematic reviews should actively plan and implement subgroup analysis and sensitivity analysis when data is available, to provide more stratified guidance significance evidence.

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Disclosure

The authors report no conflicts of interest in this work.

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