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REVIEW

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Potential of neoadjuvant hepatic artery perfusion chemotherapy in improving surgical outcomes in hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract

Background The purpose of this study was to assess the effectiveness of adjuvant treatment with new hepatic arterial infusion chemotherapy (HAIC) prior to hepatic resection in patients with resectable hepatocellular carcinoma (HCC).

Methods A systematic review was conducted utilizing established databases and registries as of January 15, 2025, without imposing restrictions based on language, publication date, or status. The inclusion criteria were met by studies that examined the effects of HAIC, with or without surgical intervention, in comparison to surgical treatment alone. The primary outcomes encompassed overall survival (OS) and disease-free survival (DFS), while secondary outcomes included recurrence rate and adverse events. A random effects model was employed to analyze the data.

Results A total of 10 studies involving 1,014 patients were included. The results showed that preoperative HAIC improved patient survival (OS), disease-free survival (DFS), and recurrence rates compared with surgical treatment alone. The most common grade 3 and higher adverse reactions in patients treated with preoperative HAIC included vomiting, leukopenia, neutropenia, hypothyroidism, and diarrhea.

Conclusion Preoperative HAIC has been demonstrated to enhance survival outcomes in patients with resectable HCC; however, the clinical efficacy of this approach requires further validation through large-scale design studies.

Keywords Primary liver cancer, Hepatic artery infusion chemotherapy, Neoadjuvant therapy, Hepatectomy

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Introduction

Primary hepatocellular carcinoma (HCC) is the most widespread form of cancer worldwide, approximately 700,000 deaths per year [1, 2]. According to the latest data released by the National Cancer Centre of China in 2024, the number of new cases of liver cancer in China reached 368,000, ranking fourth in the number of new cancer cases. The number of deaths from liver cancer was 317,000, the second highest mortality rate in the country [3, 4]. The common therapeutic methods of HCC include hepatectomy, ablation, radiotherapy and systemic antitumor therapy [5, 6]. Based on data from previous studies, although Overall Survival after surgery for (China Liver Cancer Staging, CNLC) intermediate and advanced HCC (stages CNLC IIb, IIIa, IIIb) in the staging program of HCC in China is not satisfactory, the effect of local treatment and/or systemic antineoplastic therapy on tumor control may provide more possibilities for improving resection rate, reducing postoperative recurrence and metastasis, and improving prognosis in patients with intermediate and advanced HCC [7].

Hepatic arterial infusion chemotherapy (HAIC), as a local-regional chemotherapy technique, has gradually gained attention in the field of liver cancer treatment in recent years. In terms of evidence-based medicine, the standard treatment options for early-stage hepatocellular carcinoma (BCLC stage 0/A) are mainly surgical resection, liver transplantation, and local ablation, and its efficacy has been fully validated by several level I evidence studies [8]. Regarding the clinical value of surgery and local regional chemotherapy, surgical resection is still the curative treatment for early-stage hepatocellular carcinoma, with a 5-year survival rate of 60-70%; for some high-risk patients with large tumour loads or microvascular invasion, local treatments such as adjuvant postoperative transarterial chemoembolization (TACE) can reduce the risk of recurrence, but the evidence is mostly of grade II-III, and higher-quality studies are needed to support it [9]. Direct infusion of chemotherapeutic agents through the hepatic artery by HAIC significantly increases local drug concentrations in the tumour while reducing toxicity in the body circulation [10]. Although most of the current studies of HAIC are focused on intermediate and advanced hepatocellular carcinoma, the value of its precision delivery properties in the adjuvant treatment of early hepatocellular carcinoma is being explored [11].

There is a lack of consensus on whether patients with HCC (stage CNLC I b~IIa and some stages CNLC IIb and IIIa) who are suitable for surgical resection but at high risk of recurrence and metastasis after surgery can benefit from neoadjuvant HAIC therapy in terms of disease recurrence and long-term survival after surgery [12, 13]. Therefore, the purpose of this study is to provide evidence-based evidence for future scientific research and clinical diagnosis and treatment by evaluating the value of neoadjuvant HAIC in improving the effect of surgical treatment of HCC.

Materials and methods

Literature retrieval strategy

This study was searched in the following electronic databases: PubMed, Embase, Cochrane Library and Web of Science. The search strategies employed in the article included the following search terms: ("HAIC" or "Hepatic Arterial Infusion Chemotherapy") and ("Hepatocellular Carcinoma" or "Hepatocellular Carcinoma" or "Hepatocellular Carcinoma" or "Hepatocellular Carcinoma") and ("Resection" or "Surgical Resection" or "Rescue Resection" or "Rescue Resection"). A list of references to the retrieved study reports was manually consulted to obtain a selection of articles that met the inclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria for this systematic review and meta-analysis were as follows: (1) HCC patients with a diagnosis clearly suitable for surgical resection but with a high risk of postoperative recurrence and metastasis (CNLC stages Ib to IIa, and CNLC stages IIb and IIIa) [11]; (2) age ≥ 18 years (adult studies only), with exclusion of cases in children and adolescents; (3) HCC patients in the study group who received neoadjuvant HCC patients treated with neoadjuvant HAIC prior to hepatectomy in the study group; (3) Included studies must be original, including observational studies (OBS) or randomized controlled trials (RCTs); and (4) at least information on OS, DFS, or PFS in relation to prognosis should be reported (5). There was no time limit for publication; (6) The language was limited to Chinese and English, and other languages were excluded.

The exclusion criteria for this meta-analysis included studies that were (1) not related to the efficacy of neoadjuvant HAIC in improving HCC; (2) Review, conference abstract, case report and other documents; (3) animal experiment; (4) There were no relevant prognostic studies.

Data extraction and quality evaluation

The objective of the present study was to ascertain the primary outcomes of interest, which were OS and PFS. The secondary outcomes of interest included adverse events (AEs) and recurrence rate. Following a thorough evaluation of the included studies, the two authors independently assessed the studies and retrieved the relevant information using a standardized data extraction protocol. Disagreements between the two researchers regarding the data extraction process were resolved through discussion or by a third investigator ruling. The

information extracted from the included studies included details on the authors, year of publication, country, demographic characteristics of patients, in addition to long-term outcomes of OS and DFS.

The Newcastle-Ottawa Scale was utilized to evaluate the quality of the included studies across three domains: patient selection, comparability between groups, and outcome assessment. Literature score > 6 is considered a high quality study [14]. The quality evaluation shall be conducted by two researchers independently, and if there is disagreement on the evaluation results, the third researcher shall be asked for adjudication.

Data synthesis and analysis

For binary data (e.g. recurrence rates, adverse events), risk ratios (RRs) and their 95% confidence intervals (CIs) were employed. Time-to-event data (including OS and DFS) were subsequently summarized using risk ratios (HRs) and their 95% CIs. The presence of heterogeneity across studies was evaluated through the utilization of the I^2 statistic. The overlap of CIs was examined visually using forest plots. When heterogeneity was detected, possible causes were explored by assessing the individual study characteristics and subgroup characteristics. The data were synthesized using a random effects model, and the results were interpreted.

Results

Article filtering results

The PRISMA flowchart in Fig. 1 shows which studies were eligible. A sum of 4,975 database results were identified. After removing duplicates, the review authors screened 2,533 records. The automated tool excluded one record and looked for 101 reports to search, of which 2,432 reports were not searched due to the exclusion of animal studies or the application of the established exclusion criteria. Fifty-six studies were evaluated for eligibility, and 46 studies were excluded on the basis that they were unable to obtain the required data ($n = 6$), while the other 40 reports were excluded because of inconsistent study design ($n = 21$), or inconsistent measurements ($n = 19$). Finally, 10 studies were eligible for inclusion in this analysis [15–24].

Clinicopathological characteristics of included studies

Table 1 summarizes the clinicopathological characteristics of cases receiving preoperative adjuvant therapy. Of the 10 studies included in this study, four were conducted in China [15, 18, 22, 24], three in Japan [16, 19, 20], two in Korea [21, 23], and one in Germany and Switzerland [17]. The sample size of the study ranged from 30 to 220 participants. Of the included studies, seven compared HAIC combined with surgery and surgery alone for resection, and the remaining three studies summarized the adverse events associated with HAIC treatment. The majority of patients were male (707/1014, 69.7%), predominantly elderly (mean age 53.0-61.8 years), and had a maximum tumor diameter of 11.6 cm (range 6.7–11.6) 0.35.2% of patients (357/1014) had multiple tumors.

Risk of bias of the included studies

As demonstrated in Table 2, the risk of bias in the included studies is summarized and presented. It is evident that the risk of bias was low in all of the included studies.

Overall survival

In this Meta-analysis, a total of six follow-up studies involving 762 patients were included in the analysis. Of these patients, 395 received preoperative HAIC, while 367 only underwent surgical resection. These studies reported overall survival (OS) and based on the available data, assessed the effect of preoperative HAIC on OS. The results of the analyses showed that preoperative HAIC treatment may significantly increase patients' OS compared with surgical resection alone. Specifically, patients with preoperative HAIC significantly improved their survival prognosis compared to the surgical resection alone group (HR:0.76, 95% CI:0.64–0.90). (Fig. 2)

Disease-free survival

Six cohort studies with 659 patients (preoperative HAIC = 207, surgical resection alone = 452) reported DFS. preoperative HAIC treatment may increase PFS compared to surgical resection only patients (HR: 0.65, 95%CI: 0.46 to 0.91). This result suggests that preoperative HAIC may prolong disease-free survival by improving local control and early micro metastasis suppression in patients. (Fig. 3)

Recurrence rate

Four follow-up studies involving 629 subjects were included, in which 305 subjects underwent preoperative HAIC and 324 underwent surgical resection alone. These studies reported recurrence in patients with hepatocellular carcinoma and analyzed the effect of preoperative HAIC treatment on recurrence. The results of the analyses suggest that preoperative HAIC treatment may significantly reduce the risk of recurrence of hepatocellular carcinoma compared to patients who received surgical resection only. Specifically, the risk ratio (RR) of recurrence in the preoperative HAIC group was 0.90, with a 95%CI of 0.76 to 1.06. This result suggests that preoperative HAIC may reduce the recurrence rate of hepatocellular carcinoma by effectively reducing the tumor load and controlling micro metastases. (Fig. 4)

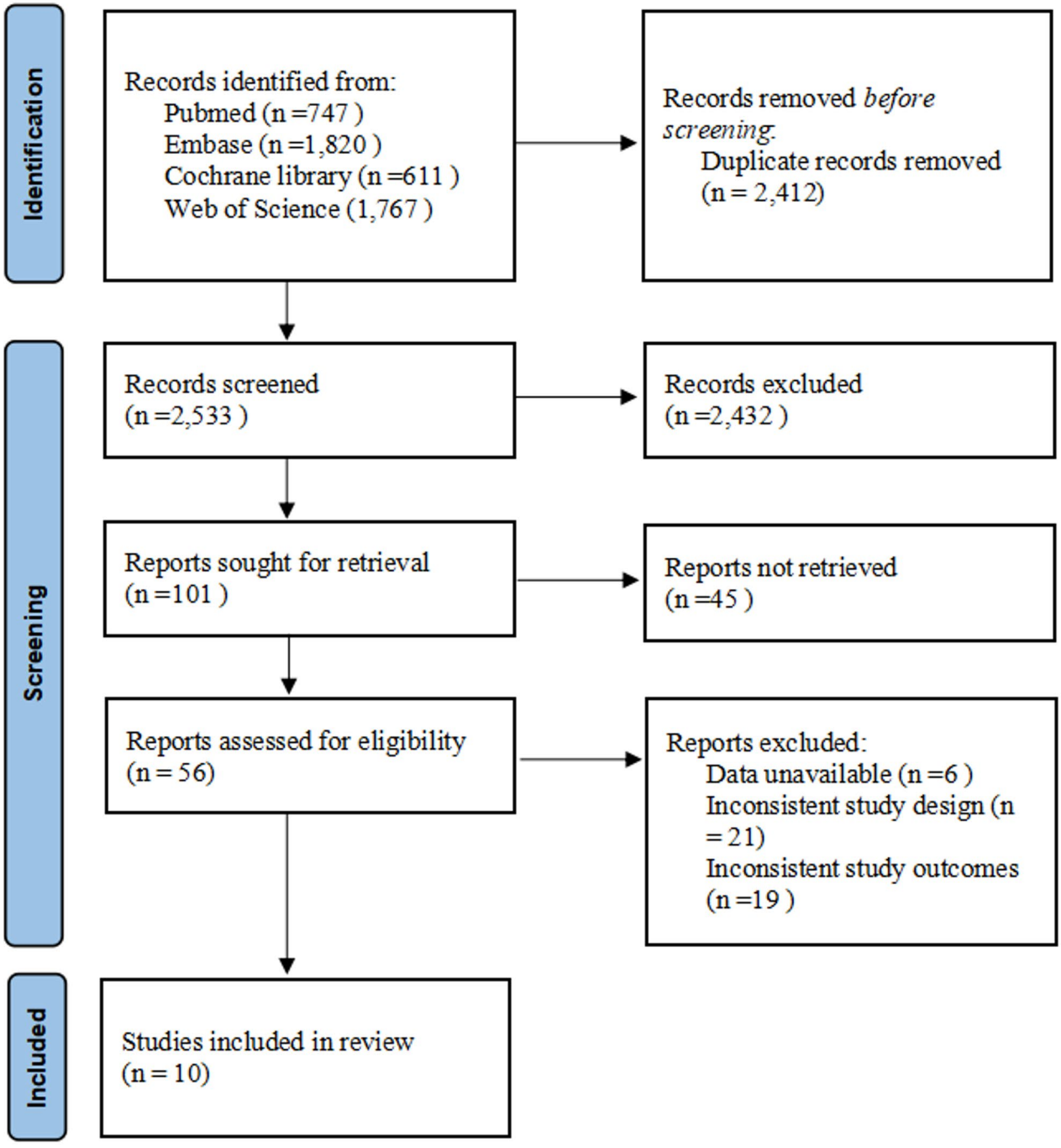

Fig. 1 Literature screening flow chart

Adverse events of neoadjuvant therapy

Adverse events were reported in 4 studies of 253 patients treated with preoperative HAIC. The majority of grade 3 and higher AEs were vomiting, Leukopenia, Neutropenia, Hypothyrea and Diarrhea. (Table 3).

Discussion

HAIC has unique advantages in the management of patients with progressive unresectable liver malignancies due to its blood supply and insensitivity to systemic chemoradiotherapy [25]. Studies have shown that, unlike other adjuvant therapies, HAIC improves prognosis in patients with advanced liver cancer [26]. However, for resectable liver cancer patients, recurrence is still a key

Table 1 Clinicopathological characteristics of patients undergoing neoadjuvant therapy

Study	Country	Study Design	Risk of Bias	No. Cases	Mean or Median Age	Sex	Chemotherapy Protocol	Number of Cirrhosis [*n* (%)]	Mean or Maximum Tumor Size (cm)	Number of Tumours [*n* (%)]
Wei, 2023	China	Cohort study	Low	HAIC + Surgical Resection (39) Surgical Resection (78)	53. 4	M (105), F (12)	mFOLFOX continuous infusion	NR	NR	1: 79(67.5) ≥ 2: 38(32.5)
GOTO, 2021	Japan	Cohort study	Low	HAIC + Surgical Resection (24) Surgical Resection (56)	NR	NR	CDDP、5-fluorouracil、Lipiodol continuous infusion	NR	NR	NR
Lorenz,1998	Germany, Switzerland	Cohort study	Low	HAIC + Surgical Resection (108) Surgical Resection (111)	61.0	M (127), F (92)	5-fluorouracil、FA continuous infusion	NR	7.0	NR
Hsiao, 2017	China	Cohort study	Low	HAIC + Surgical Resection (61) Surgical Resection (160)	58.0	M (177), F (44)	Cisplatin、5-fluorouracil、Epirubicin continuous infusion	86 (38.9)	NR	1: 117(52.9) ≥ 2: 104(47.1)
Nitta, 2013	Japan	Cohort study	Low	HAIC + Surgical Resection (38) Surgical Resection (35)	61.8	M (62), F (11)	Cisplatin、5-fluorouracil continuous infusion	NR	6.7	1: 25(34.2) ≥ 2: 48(65.8)
Kojima, 2015	Japan	Cohort study	Low	HAIC + Surgical Resection (27) Surgical Resection (25)	61.0	M (40), F (12)	5-fluorouracil and cisplatin (FP) and epirubicin (Epi-ADM) intermittent administration	29 (55.8)	7.0	1: 18(34.6) ≥ 2: 34(65.4)
Chong, 2018	Korea	Cohort study	Low	HAIC + Surgical Resection (98) Surgical Resection (18)	54.3	M (78), F (14)	5-fluorouracil and cisplatin continuous infusion	116 (100)	9.0	1: 85(73.3) ≥ 2: 31(26.7)
He, 2017	China	Cohort study	Low	HAIC (38)	NR	M (30), F (8)	NR	18 (47.4)	NR	< 3: 20(52.6) ≥ 3: 18(47.4)
Hyun, 2009	Korea	Cohort study	Low	HAIC (68)	53.0	M (60), F (8)	5-fluorouracil and cisplatin continuous infusion	NR	NR	1: 8(11.8) ≥ 2: 60(88.2)
Cai, 2023	China	Cohort study	Low	HAIC (30)	55.5	M (28), F (2)	mFOLFOX continuous infusion	NR	11.6	< 3: 6(20.00) ≥ 3: 24(80.00)

NR = not reported

Table 2 Risk of bias assessment of non-randomized comparative studies included in the systematic review

S. No	Study	Study Design	Selection Domain	Comparability Domain	Outcome Domain	Overall Score	Risk of Bias[#]
1	Wei, 2023	Cohort study	4	1	1	6	Low
2	GOTO, 2021	Cohort study	4	1	1	6	Low
3	Lorenz,1998	Cohort study	4	1	2	7	Low
4	Hsiao, 2017	Cohort study	4	1	2	7	Low
5	Nitta, 2013	Cohort study	4	1	1	6	Low
6	Kojima, 2015	Cohort study	4	1	1	6	Low
7	Chong, 2018	Cohort study	4	1	2	7	Low
8	He, 2017	Cohort study	4	1	2	7	Low
9	Hyun, 2009	Cohort study	4	1	2	7	Low
10	Cai, 2023	Cohort study	4	1	2	7	Low

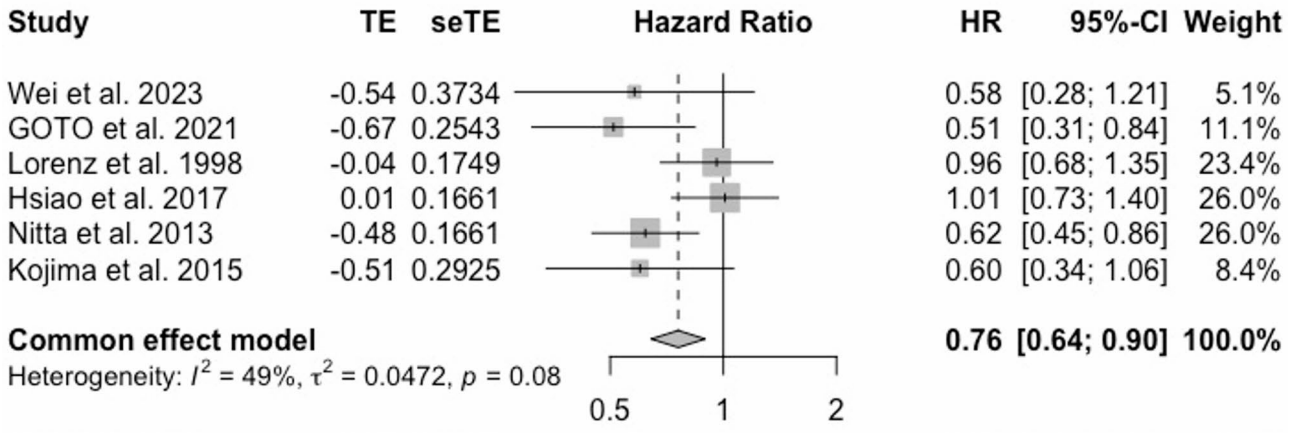

Fig. 2 Long-term survival forest map of liver cancer patients after preoperative HAIC neoadjuvant chemotherapy (OS)

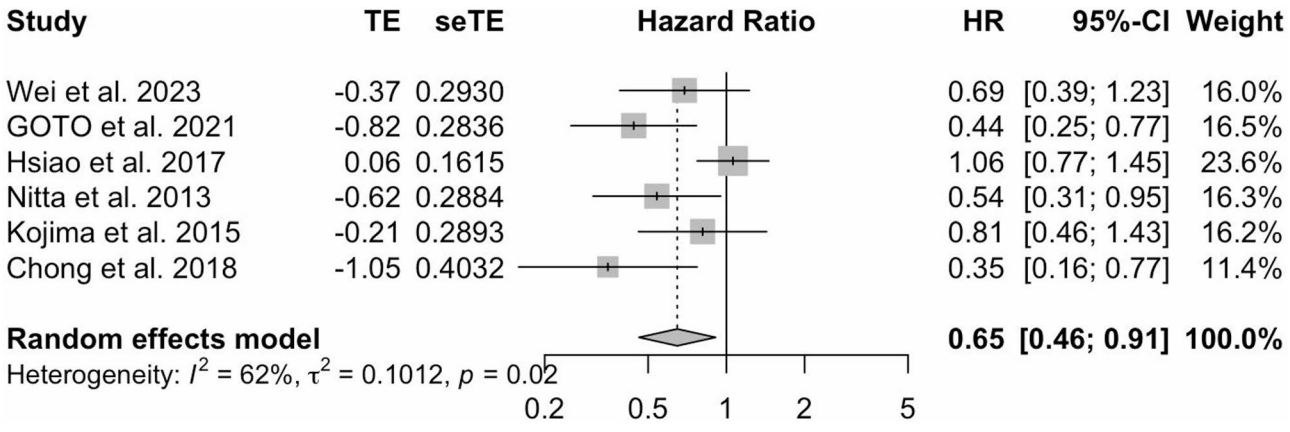

Fig. 3 Long-term survival forest map of liver cancer patients after preoperative HAIC neoadjuvant chemotherapy (DFS)

factor affecting postoperative survival [27]. Especially for patients who are suitable for surgical resection but are in stage CNLC I b~IIa and some stage CNLC IIb and IIIa, the risk of recurrence and metastasis is very high. Early recurrence is closely related to the survival time of patients [28].

The findings of this comprehensive review demonstrated that patients with resectable hepatocellular carcinoma treated with neoadjuvant HAIC were superior to those treated with surgical resection alone in terms of OS and DFS, and the difference was statistically significant. The 1-, 3-, and 5-year survival rates and the 1-, 3-, and 5-year disease-free survival rates of patients treated with HAIC were higher than those who underwent surgical resection alone. Neoadjuvant HAIC for resectable liver cancer patients may be of great benefit in improving prognosis and prolonging survival. Studies have been conducted on various treatment regimens to prevent recurrence of HCC. In 2015, a systematic treatment of 230 patients showed that mDFS was prolonged

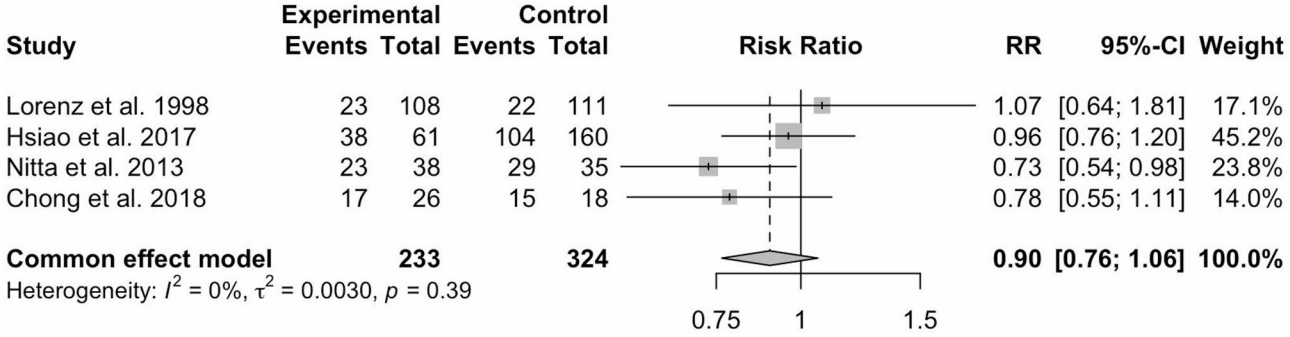

Fig. 4 Long-term survival forest map of liver cancer patients after preoperative HAIC neoadjuvant chemotherapy (Recurrence rate)

14 months by injection of activated cytokines into patients to induce killer cells, Cytokine-induced Killer [29]. Another multicenter, large-sample study showed that mDFS was only 0.1 months longer in patients treated with sorafenib [30]. A 2018 study of 250 patients with HCC showed that patients with HCC who had moderate to high risk factors for recurrence were treated with Transarterial Chemoembolization after hepatectomy to prolong their mDFS by 8 months [31]. This meta-analysis shows that the application of HAIC to adjuvant treatment before resection of liver cancer can effectively improve the survival prognosis of patients and provide more adjuvant treatment options for resectable liver cancer patients.

The results analyzed in this study showed that preoperative HAIC in patients with HCC led to a significant reduction in the risk of recurrence. This result suggests that preoperative HAIC may significantly reduce the recurrence rate of hepatocellular carcinoma by reducing tumor load and controlling micro metastases. This result is consistent with previous studies, many of which have found that neoadjuvant HAIC may enhance survival outcomes and diminish the likelihood of tumor recurrence in individuals diagnosed with hepatocellular carcinoma by reducing tumor size and micro metastases [32, 33].

The efficacy of preoperative HAIC is mainly due to its ability to act directly on the tumor vasculature and micrometastases. HAIC enables chemotherapeutic agents to reach higher concentrations in the hepatic region through local arterial perfusion, which significantly improves the efficiency of tumour treatment [34]. In addition, preoperative HAIC is able to improve the microcirculation of the liver and increase the sensitivity of the tumor to chemotherapeutic agents, thus inhibiting micro metastasis [34]. Compared with surgical resection alone, HAIC provided a stronger local therapeutic effect and significantly reduced the risk of postoperative recurrence. Although this study showed that HAIC treatment had a positive impact on recurrence, due to some heterogeneity between studies, follow-up is needed to further validate the long-term efficacy of HAIC treatment in different patient populations, especially in high-risk patients (e.g., patients with poorer liver function or more comorbidities).

However, although preoperative HAIC therapy has demonstrated significant results in recurrence control, the incidence of adverse events cannot be ignored. Data from this study showed that the most common grade 3 and higher adverse reactions in patients receiving preoperative HAIC therapy included vomiting, leukopenia, neutropenia, hypothyroidism, and diarrhea. These adverse reactions are common problems in HAIC therapy and may have an impact on patients' quality of life. Vomiting and diarrhea are common gastrointestinal reactions to chemotherapy, while leukopenia and neutropenia increase the risk of infection. Although these adverse reactions are usually manageable, close monitoring of the patient's clinical condition during treatment and adjustment of the treatment regimen according to the response are required. Particularly in elderly patients and those with underlying medical conditions, these adverse reactions may be more severe, affecting the continuity and efficacy of treatment.

This meta-analysis is subject to certain limitations. Firstly, due to the low focus on preoperative neoadjuvant HAIC therapy and lack of large cohort studies, and the short follow-up time of preoperative neoadjuvant HAIC therapy, there are relatively few included articles, and more high-quality clinical studies are needed to make the results more convincing. Second, none of the included literatures mentioned the description of blind evaluation of research results, which may be biased. However, the meta-analysis has a large sample size and a certain representativeness through the establishment of perfect search strategy and literature screening criteria, and unlimited publication year.

In conclusion, the strategy of preoperative neo-adjuvant HAIC sequential hepatectomy prolongs the survival time of resectable HCC patients, improves the prognosis and benefits the survival time of HCC patients with high postoperative risk of recurrence and metastasis.

Table 3 Adverse events (> = grade 3) related to presurgical HAIC therapy

Study	No. Cases	Fever	Pain	Vomiting	Leukopenia	Anemia	Thrombocytopenia	Diarrhea	Infection	Hypothyrea	Gastrointestinal bleeding	Neutropenia	Emesis/Hematemesis	All
Wei, 2023	39	0	0	0	0	1	1	0	1	0	0	0	0	3
He, 2017	38	0	1	4	3	1	2	1	0	0	1	1	0	14
Hyun, 2009	68	0	0	0	0	0	0	0	2	2	0	2	0	6
Cai, 2023	30	2	0	0	0	0	0	2	0	1	0	0	1/1	7

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03859-2.

Supplementary Material 1

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None.

Author contributions
Zi-Kui Shanga and Jian-Hua Zhang of the study and participated in its design. Jian-Hua Zhang and Xi-Yuan Chen conducted the systematic literature review. Ran-Xia and Chuan-Sen Deng performed data analyses. Zi-Kui Shanga and Jian-Hua Zhang drafted the article. Chun-Quan Suna and Jia-Hai Zhua critically revised the article. All authors have read and approved the final version of the article. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate
Not applicable.

Consent to participate
All authors have participated and provided consent for publication.

Competing interests
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