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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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META-ANALYSIS

Efficacy of hepatic arterial infusion chemotherapy and its combination strategies for advanced hepatocellular carcinoma: A network meta-analysis

Shun-An Zhou, Qing-Mei Zhou, Lei Wu, Zhi-Hong Chen, Fan Wu, Zhen-Rong Chen, Lian-Qun Xu, Bi-Ling Gan, Hao-Sheng Jin, Ning Shi

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Abstract

BACKGROUND

With the rapid progress of systematic therapy for hepatocellular carcinoma (HCC), therapeutic strategies combining hepatic arterial infusion chemotherapy (HAIC) with systematic therapy arised increasing concentrations. However, there have been no systematic review comparing HAIC and its combination strategies in the first-line treatment for advanced HCC.

AIM

To investigate the efficacy and safety of HAIC and its combination therapies for advanced HCC.

METHODS

A network meta-analysis was performed by including 9 randomized controlled trails and 35 cohort studies to carry out our study. The outcomes of interest comprised overall survival (OS), progression-free survival (PFS), tumor response and adverse events. Hazard ratios (HR) and odds ratios (OR) with a 95% confidence interval (CI) were calculated and agents were ranked based on their ranking probability.

RESULTS

HAIC outperformed Sorafenib (HR = 0.55, 95%CI: 0.42-0.72; HR = 0.51, 95%CI: 0.33-0.78; OR = 2.86, 95%CI: 1.37-5.98; OR = 5.45, 95%CI: 3.57-8.30; OR = 7.15, 95%CI: 4.06-12.58; OR = 2.89, 95%CI: 1.99-4.19; OR = 0.48, 95%CI: 0.25-0.92, respectively) and transarterial chemoembolization (TACE) (HR = 0.50, 95%CI: 0.33-0.75; HR = 0.62, 95%CI: 0.39-0.98; OR = 3.08, 95%CI: 1.36-6.98; OR = 2.07, 95%CI: 1.54-2.80; OR = 3.16, 95%CI: 1.71-5.85; OR = 2.67, 95%CI: 1.59-4.50; OR = 0.16, 95%CI: 0.05-0.54, respectively) in terms of efficacy and safety. HAIC + lenvatinib + ablation, HAIC + ablation, HAIC + anti- programmed cell death 1 (PD-1), and HAIC + radiotherapy had the higher likelihood of providing better OS and PFS outcomes compared to HAIC alone. HAIC + TACE + S-1, HAIC + lenvatinib, HAIC + PD-1, HAIC + TACE, and HAIC + sorafenib had the higher likelihood of providing better partial response and objective response rate outcomes compared to HAIC. HAIC + PD-1, HAIC + TACE + S-1 and HAIC + TACE had the higher likelihood of providing better complete response and disease control rate outcomes compared to HAIC alone.

CONCLUSION

HAIC proved more effective and safer than sorafenib and TACE. Furthermore, combined with other interventions, HAIC showed improved efficacy over HAIC monotherapy according to the treatment ranking analysis.

Key Words: Hepatic arterial infusion chemotherapy; Hepatocellular carcinoma; Network meta-analysis; Interventional therapy; Systemic treatment

Core Tip: Because there are not enough randomized controlled trials to demonstrate the efficacy and safety of hepatic arterial infusion chemotherapy (HAIC) in advanced hepatocellular carcinoma (HCC), HAIC has not yet been recognized in Western countries. Therefore, we conducted a network meta-analysis to compare the safety and efficacy of HAIC and its combination strategies for advanced HCC. Compared to sorafenib and transarterial chemoembolization, HAIC was found to be a better choice in terms of both efficacy and safety. Furthermore, interventions combined with HAIC showed marginally better efficacy compared to HAIC monotherapy.

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INTRODUCTION

Primary liver cancer ranks as the sixth most commonly diagnosed malignant tumor. It is the fourth leading cause of cancer-related mortality worldwide[1]. Its chief cause is liver cirrhosis, including alcoholic cirrhosis, virus-associated cirrhosis, cryptogenic cirrhosis, and other types[2]. Hepatocellular carcinoma (HCC) is the predominant liver cancer subtype[3]. Surgical resection is the leading curative treatment for patients with HCC. However, most patients are diagnosed with HCC at an advanced stage, thus precluding radical surgical resection[4,5]. Patients with advanced HCC demonstrate unsatisfactory outcomes, with a 5-year survival rate of only 5% to 36%[6].

Patients with early-stage HCC may be treated by surgical resection, liver transplantation, or ablation (A). However, locoregional therapies, including transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and systemic therapy are considered therapeutic options in patients with unresectable HCC. Systemic therapies, such as sorafenib, are primarily used for patients with unresectable HCC with distant metastases. However, many patients either reduce the dosage or discontinue the treatment because of adverse events (AEs) associated with long-term sorafenib use, limiting its therapeutic potential. Conversely, TACE is primarily administered to patients with unresectable HCC without distant metastases. One of its limitations is single-dose administration, which restricts the duration for high-concentration chemotherapy drugs to act on tumors. Japanese guidelines recommend HAIC combined with portal vein thrombosis as the first-line treatment for patients with HCC[7]. Owing to the blood supply characteristics of the liver and HCC cells, HAIC kills tumor cells by the continuous perfusion of cytotoxic drugs with high concentrations through the hepatic artery. Simultaneously, it does not considerably influence healthy liver tissues[8]. However, insufficient phase

3 randomized controlled trials (RCTs) have demonstrated that patients with HCC can benefit from HAIC. Therefore, HAIC has not been recognized in Western countries. Thus, we aimed to conduct a network meta-analysis of RCTs and cohort studies to compare the efficacy and safety of HAIC and its combination therapies with other interventions. We aimed to offer insights into evidence-based medicine for applying HAIC.

MATERIALS AND METHODS

Objective

To assess and compare the effectiveness of HAIC, both as a standalone treatment and combined with other strategies, in patients diagnosed with advanced HCC.

Search strategy and article selection criteria

Specific search terms were applied to the PubMed database to identify relevant RCTs and cohort studies assessing the efficacy of HAIC, either as a standalone treatment or combined with other therapies, published on or before July 10, 2023. Supplementary material describes the search strategy. Additionally, conference papers were manually searched to extract pertinent reference documents and abstracts. The screening process encompassed evaluating the titles, abstracts, and full texts to identify the studies that met the selection criteria.

The inclusion criteria were as follows: (1) RCTs and/or cohort studies; (2) Patients with unresectable HCC (including patients with Barcelona Clinic Liver Cancer stages B and C); (3) One study arm is HAIC or its combination, whereas the other arm is different treatment strategies or best supportive care (BSC); and (4) Overall survival (OS), progression-free survival (PFS), complete response (CR), partial response (PR), objective response rate (ORR), and disease control rate (DCR), AEs, or Kaplan-Meier curves are the outcome indicators. The exclusion criteria were as follows: (1) Articles without a study endpoint (PFS or OS); (2) Therapeutic strategies as a second-line treatment option for patients with unresectable HCC; and (3) Therapeutic strategies that could not be connected to the net graph in the network meta-analysis.

Data extraction

First, the titles and abstracts were read independently by two researchers and screened according to the selection criteria. Second, the full texts of the articles that met the inclusion criteria were read. Third, the articles were screened for network meta-analysis. Information on the pre-specified data, including baseline characteristics, sample size, tumor burden, AEs, and interventions, was extracted independently from each article by the two reviewers using a data form. A third reviewer resolved the disagreements. The outcomes included the OS, PFS, CR, PR, ORR, and DCR, AEs. We selected the data after propensity score matching.

Risk of bias and quality assessment

The quality of RCTs was assessed independently by the two reviewers using the Cochrane Risk of Bias assessment tool. This tool considers key criteria, including random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other biases. The methodological quality of cohort studies was assessed using the "star" rating system of the Newcastle-Ottawa Scale based on the following three factors: Selecting the research population, comparability of the study group, and evaluating the results.

Statistical analysis

R software version 4.2.3 (Mathsoft, Cambridge, United States) was used for the statistical analysis. Netmeta package was used to conduct the frequentist Network meta-analysis. The OS and PFS were estimated using hazard ratios (HR) with 95% confidence intervals (CI). The CR, PR, ORR, DCR, AE, and odds ratio (OR) with 95%CI were calculated. I^2 was calculated to assess the overall heterogeneity of the data model. For $I^2 > 50\%$, the random effects model was selected; conversely, the fixed effects model was selected. Additionally, the P-score was used to rank the treatments[9]. The network graph illustrates the indirect comparative associations among the interventions. Each node represents an intervention, and the node size represents the sample size of the intervention. The funnel plot depicts publication bias; $P > 0.05$ indicated no publication bias. The study has been registered on PROSPERO (ID: CRD42023463399). The manuscript was prepared and revised according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020[10] and Assessing the Methodological Quality of Systematic Reviews guidelines[11].

RESULTS

Study selection and baseline characteristics

Initially, we retrieved 1945 articles. Of them, 150 met the selection criteria for assessment based on their titles and abstracts. Subsequently, 105 articles were excluded after reading the full text, resulting in 45 articles. Additionally, we included 34 articles from the reference lists of other articles. We excluded 38 articles for various reasons, including duplicates, interventions unsuitable for the network graph, second-line therapies, and others. Finally, we included 44 articles, comprising 9 RCTs and 35 cohort studies[12-55]. Figure 1 presents the flow diagram. The 44 trials included 5789

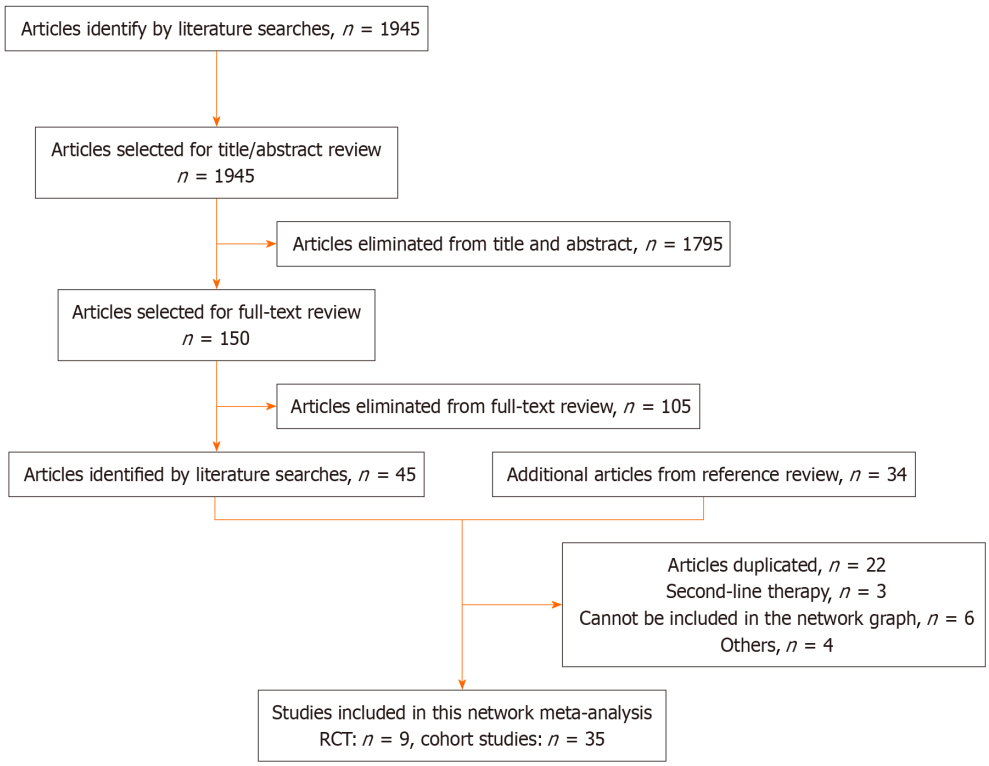

Figure 1 Flow diagram. RCTs: Randomized controlled trials.

patients. Supplementary Table 1 summarizes the baseline characteristics of the included studies. Figure 2 illustrates the network graph. Two nodes connected by a line indicate articles directly comparing the effectiveness of the two treatments, with the line thickness representing the article number available for comparison.

Network meta-analysis of clinical outcomes

Network meta-analysis of OS: OS data were extracted from 41 articles, including 9 RCTs and 32 cohort studies. They encompassed 5556 patients. Twelve interventions were compared (Figure 2). Patients receiving HAIC + lenvatinib (Lenv) + A (HR = 0.12; 95%CI: 0.03-0.57), HAIC + A (HR = 0.21; 95%CI: 0.07-0.67), HAIC + Lenv (HR = 0.29; 95%CI: 0.11-0.74), HAIC + sorafenib (Sora) (HR = 0.52; 95%CI: 0.33-0.81), and HAIC (HR = 0.55; 95%CI: 0.42-0.72) demonstrated significantly improved OS than patients receiving Sora (Figure 3). Furthermore, the most favorable OS outcomes were associated with HAIC + Lenv + A (P-score: 0.94), followed by HAIC + A (P-score: 0.85) and HAIC + Lenv (P-score: 0.77). Table 1 summarizes direct and indirect comparisons of the interventions for OS.

Network meta-analysis of PFS: PFS data were extracted from 30 articles, including 9 RCTs and 21 cohort studies. They encompassed 3742 patients. Eleven interventions were compared (Figure 2). Patients receiving HAIC + A (HR = 0.25; 95%CI: 0.08-0.77), HAIC + TACE (HR = 0.32; 95%CI: 0.14-0.75), and HAIC (HR = 0.51; 95%CI: 0.33-0.78) demonstrated significantly improved PFS outcomes than patients receiving Sora (Figure 3). Patients receiving HAIC + Lenv + A (HR = 0.26; 95%CI: 0.06-1.10) and HAIC + anti-programmed death 1 (PD-1) (HR = 0.33; 95%CI: 0.11-1.02) displayed marginally better PFS than patients receiving Sora, though insignificant. According to the treatment ranking analysis, HAIC + A (P-score: 0.79) was associated with the highest likelihood of favorable PFS outcomes, followed by HAIC + Lenv + A (P-score: 0.75) and HAIC + TACE + S-1 (S-1: A composite preparation of a 5-fluorouracil prodrug) (P-score: 0.71). Table 1 summarizes the direct and indirect comparisons of the interventions for PFS.

Network meta-analysis of CR: CR data were extracted from 35 articles, including 8 RCTs and 27 cohort studies. They encompassed 3867 patients. Nine interventions were compared (Figure 2). Patients receiving HAIC + Sora (OR = 7.62; 95%CI: 2.55-22.77) and HAIC (OR = 2.86; 95%CI: 1.37-5.98) demonstrated significantly improved CR outcomes (Figure 3). Patients receiving HAIC + TACE + S-1 (OR = 3.36; 95%CI: 0.42-26.67) and HAIC + TACE (OR = 3.06; 95%CI: 0.69-13.61) displayed marginally better CR outcomes than patients receiving to Sora, though insignificant. The most favorable CR outcomes were associated with HAIC + Sora (P-score: 0.86), followed by HAIC + PD-1 (P-score: 0.65). HAIC + TACE + S-1 (P-score: 0.62) and HAIC (P-score: 0.60) were positioned in fifth and sixth, respectively. The P-scores suggest better CR outcomes with BSC, compared with Sora. The small sample size for BSC may affect this statistically insignificant observation (BSC: OR = 1.48; 95%CI: 0.06-35.69). Table 1 summarizes direct and indirect comparisons of the interventions for CR.

Network meta-analysis of PR: PR data were extracted from 35 articles, including 8 RCTs and 27 cohort studies. They encompassed 3867 patients. Nine interventions were compared (Figure 2). Patients receiving HAIC + TACE + S-1 (OR =

Table 1 League table for clinical outcomes

League table											
OS											
HAIC + Lenv + A		0.42 (0.12; 1.44)									
0.58 (0.09; 3.84)	**HAIC + A**					0.38 (0.12; 1.17)					
0.42 (0.12; 1.44)	0.73 (0.17; 3.08)	**HAIC + Lenv**			0.52 (0.21; 1.28)						
0.36 (0.05; 2.31)	0.61 (0.13; 2.93)	0.84 (0.20; 3.46)	**HAIC + PD-1**		0.62 (0.21; 1.84)						
0.24 (0.05; 1.17)	0.41 (0.12; 1.39)	0.56 (0.20; 1.56)	0.66 (0.20; 2.20)	**HAIC + Sora**	0.43 (0.12; 1.47)	0.58 (0.36; 0.94)					
0.24 (0.04; 1.63)	0.42 (0.08; 2.09)	0.58 (0.13; 2.47)	0.68 (0.14; 3.32)	1.03 (0.31; 3.43)	**HAIC + RT**		0.50 (0.16; 1.52)				
0.22 (0.05; 1.01)	0.38 (0.12; 1.17)	0.52 (0.21; 1.28)	0.62 (0.21; 1.84)	0.94 (0.57; 1.55)	0.91 (0.29; 2.85)	**HAIC**	0.53 (0.40; 0.70)		0.50 (0.33; 0.75)	0.32 (0.11; 0.95)	
0.12 (0.03; 0.57)	0.21 (0.07; 0.67)	0.29 (0.11; 0.74)	0.34 (0.11; 1.05)	0.52 (0.33; 0.81)	0.50 (0.16; 1.52)	0.55 (0.42; 0.72)	**Sora**				
0.11 (0.01; 0.84)	0.18 (0.03; 1.10)	0.25 (0.05; 1.33)	0.30 (0.05; 1.76)	0.45 (0.10; 2.00)	0.44 (0.07; 2.66)	0.48 (0.12; 1.95)	0.88 (0.21; 3.63)	**HAIC + TACE + S-1**	1.00 (0.35; 2.86)		
0.11 (0.02; 0.63)	0.18 (0.04; 0.78)	0.25 (0.07; 0.91)	0.30 (0.07; 1.24)	0.45 (0.16; 1.29)	0.44 (0.10; 1.90)	0.48 (0.19; 1.21)	0.88 (0.34; 2.28)	1.00 (0.35; 2.86)	**HAIC + TACE**	1.03 (0.45; 2.34)	
0.11 (0.02; 0.53)	0.19 (0.06; 0.63)	0.26 (0.10; 0.70)	0.31 (0.10; 0.99)	0.47 (0.24; 0.90)	0.45 (0.13; 1.52)	0.50 (0.33; 0.75)	0.90 (0.55; 1.47)	1.03 (0.27; 3.91)	1.03 (0.45; 2.34)	**TACE**	
0.07 (0.01; 0.46)	0.12 (0.03; 0.58)	0.17 (0.04; 0.68)	0.20 (0.04; 0.92)	0.30 (0.09; 0.99)	0.29 (0.06; 1.40)	0.32 (0.11; 0.95)	0.58 (0.19; 1.77)	0.66 (0.11; 3.87)	0.66 (0.16; 2.73)	0.64 (0.20; 2.04)	**BSC**
PFS											
HAIC + A						0.49 (0.17; 1.39)					
0.96 (0.17; 5.46)	**HAIC + Lenv + A**						0.46 (0.16; 1.36)				
0.85 (0.16; 4.50)	0.89 (0.13; 5.94)	**HAIC + TACE + S-1**	0.90 (0.31; 2.59)								
0.77 (0.21; 2.77)	0.80 (0.17; 3.87)	0.90 (0.31; 2.59)	**HAIC + TACE**					0.39 (0.22; 0.70)			
0.75 (0.17; 3.29)	0.78 (0.14; 4.44)	0.88 (0.17; 4.61)	0.97 (0.27; 3.50)	**HAIC + PD-1**	0.65 (0.23; 1.85)						
0.53 (0.10; 2.70)	0.55 (0.09; 3.58)	0.62 (0.10; 3.73)	0.69 (0.16; 2.94)	0.71 (0.14; 3.61)	**HAIC + RT**					0.47 (0.14; 1.52)	
0.49 (0.17; 1.39)	0.51 (0.13; 2.04)	0.57 (0.16; 2.07)	0.63 (0.30; 1.32)	0.65 (0.23; 1.85)	0.92 (0.26; 3.21)	**HAIC**	0.91 (0.38; 2.16)	0.62 (0.39; 0.98)	0.51 (0.33; 0.78)		
0.44 (0.11; 1.72)	0.46 (0.16; 1.36)	0.52 (0.11; 2.45)	0.57 (0.18; 1.80)	0.59 (0.15; 2.30)	0.84 (0.18; 3.83)	0.91 (0.38; 2.16)	**HAIC + Lenv**				
0.39 (0.11; 1.32)	0.40 (0.09; 1.86)	0.45 (0.11; 1.91)	0.50 (0.19; 1.34)	0.52 (0.15; 1.76)	0.73 (0.20; 2.61)	0.79 (0.42; 1.51)	0.87 (0.30; 2.57)	**HAIC + Sora**	0.64 (0.40; 1.03)		
0.30 (0.10; 0.95)	0.31 (0.07; 1.36)	0.35 (0.11; 1.18)	0.39 (0.22; 0.70)	0.40 (0.13; 1.26)	0.57 (0.15; 2.16)	0.62 (0.39; 0.98)	0.68 (0.26; 1.82)	0.78 (0.36; 1.72)	**TACE**		
0.25 (0.08; 0.77)	0.26 (0.06; 1.10)	0.29 (0.07; 1.12)	0.32 (0.14; 0.75)	0.33 (0.11; 1.02)	0.47 (0.14; 1.52)	0.51 (0.33; 0.78)	0.56 (0.21; 1.47)	0.64 (0.40; 1.03)	0.82 (0.44; 1.53)	**Sora**	
CR											
HAIC + Sora			6.21 (0.28; 138.56)		6.77 (2.11; 21.68)						
1.46 (0.02; 90.79)	**HAIC + PD-1**		1.82 (0.04; 92.69)								

2.27 (0.22; 22.94)	1.55 (0.02; 123.86)	**HAIC + TACE + S-1**	1.10 (0.26; 4.62)					
2.49 (0.41; 15.27)	1.70 (0.03; 106.73)	1.10 (0.26; 4.62)	**HAIC + TACE**				3.30 (1.20; 9.03)	
2.66 (0.75; 9.46)	1.82 (0.04; 92.69)	1.17 (0.17; 8.14)	1.07 (0.29; 3.91)	**HAIC**	1.93 (0.09; 42.76)	2.13 (0.32; 14.10)	3.01 (1.41; 6.41)	3.08 (1.36; 6.98)
5.15 (0.18; 146.19)	3.52 (0.02; 524.16)	2.27 (0.06; 87.52)	2.07 (0.07; 59.37)	1.93 (0.09; 42.76)	**BSC**			
5.67 (0.58; 55.24)	3.87 (0.05; 303.50)	2.50 (0.17; 37.42)	2.27 (0.23; 22.55)	2.13 (0.32; 14.10)	1.10 (0.03; 41.42)	**HAIC + Lenv**		
7.62 (2.55; 22.77)	5.21 (0.10; 283.99)	3.36 (0.42; 26.67)	3.06 (0.69; 13.61)	2.86 (1.37; 5.98)	1.48 (0.06; 35.69)	1.35 (0.18; 10.25)	**Sora**	
8.21 (1.82; 37.10)	5.62 (0.10; 310.71)	3.62 (0.63; 20.94)	3.30 (1.20; 9.03)	3.08 (1.36; 6.98)	1.59 (0.06; 39.20)	1.45 (0.18; 11.38)	1.08 (0.36; 3.24)	**TACE**
PR								
HAIC + TACE + S-1		2.34 (0.86; 6.40)						
1.59 (0.42; 6.00)	**HAIC + Lenv**			1.54 (0.92; 2.56)				
1.72 (0.44; 6.65)	1.08 (0.50; 2.33)	**HAIC + PD-1**		1.42 (0.80; 2.51)				
2.34 (0.86; 6.40)	1.48 (0.62; 3.53)	1.36 (0.55; 3.37)	**HAIC + TACE**		2.16 (1.14; 4.08)			
2.42 (0.61; 9.51)	1.52 (0.69; 3.37)	1.41 (0.61; 3.23)	1.03 (0.41; 2.62)	**HAIC + Sora**	5.00 (1.19; 21.04)		4.50 (2.71; 7.48)	
2.44 (0.72; 8.32)	1.54 (0.92; 2.56)	1.42 (0.80; 2.51)	1.04 (0.51; 2.11)	1.01 (0.55; 1.85)	**HAIC**	2.07 (1.54; 2.80)	4.62 (0.24; 89.16)	6.32 (4.08; 9.80)
5.05 (1.54; 16.61)	3.18 (1.76; 5.76)	2.94 (1.55; 5.59)	2.16 (1.14; 4.08)	2.09 (1.06; 4.12)	2.07 (1.54; 2.80)	**TACE**		
11.28 (0.46; 277.69)	7.10 (0.35; 143.15)	6.56 (0.32; 133.57)	4.81 (0.23; 100.83)	4.67 (0.23; 95.70)	4.62 (0.24; 89.16)	2.23 (0.11; 43.69)	**BSC**	
13.29 (3.63; 48.61)	8.37 (4.32; 16.23)	7.73 (3.81; 15.68)	5.67 (2.49; 12.89)	5.50 (3.40; 8.89)	5.45 (3.57; 8.30)	2.63 (1.57; 4.41)	1.18 (0.06; 23.41)	**Sora**
ORR								
HAIC + TACE + S-1		1.99 (0.40; 9.99)						
1.28 (0.12; 14.33)	**HAIC + Lenv**			1.95 (0.51; 7.44)				
1.76 (0.15; 21.24)	1.37 (0.19; 10.05)	**HAIC + PD-1**		1.42 (0.33; 6.19)				
1.96 (0.21; 18.19)	1.53 (0.29; 7.97)	1.11 (0.19; 6.47)	**HAIC + Sora**	8.00 (1.08; 59.18)		6.08 (2.38; 15.59)		
1.99 (0.40; 9.99)	1.55 (0.26; 9.34)	1.13 (0.17; 7.53)	1.02 (0.22; 4.74)	**HAIC + TACE**		3.97 (1.43; 11.04)		
2.50 (0.34; 18.61)	1.95 (0.51; 7.44)	1.42 (0.33; 6.19)	1.28 (0.48; 3.37)	1.26 (0.38; 4.15)	**HAIC**	1.93 (0.07; 56.84)	3.16 (1.71; 5.85)	8.36 (4.66 15.01)
4.84 (0.09; 246.61)	3.77 (0.10; 143.00)	2.74 (0.07; 109.59)	2.47 (0.07; 83.18)	2.43 (0.07; 87.58)	1.93 (0.07; 56.84)	**BSC**		
7.91 (1.17; 53.36)	6.16 (1.41; 26.89)	4.48 (0.91; 22.12)	4.04 (1.28; 12.73)	3.97 (1.43; 11.04)	3.16 (1.71; 5.85)	1.63 (0.05; 50.80)	**TACE**	
17.88 (2.22; 143.80)	13.92 (3.25; 59.60)	10.14 (2.09; 49.09)	9.13 (3.87; 21.51)	8.97 (2.39; 33.65)	7.15 (4.06; 12.58)	3.70 (0.12; 113.89)	2.26 (0.98; 5.22)	**Sora**
DCR								
HAIC + TACE + S-1	2.04 (0.55; 7.61)							

1.17 (0.15; 9.35)	**HAIC + PD-1**	2.52 (0.72; 8.81)						
2.04 (0.55; 7.61)	1.74 (0.35; 8.65)	**HAIC + TACE**				3.87 (1.64; 9.11)		
2.95 (0.56; 15.45)	2.52 (0.72; 8.81)	1.45 (0.53; 3.94)	**HAIC**	1.40 (0.45; 4.37)	0.06 (0.00; 1.40)	1.71 (0.33; 8.88)	2.67 (1.59; 4.50)	3.02 (2.08; 4.40)
4.14 (0.56; 30.84)	3.53 (0.65; 19.15)	2.03 (0.45; 9.24)	1.40 (0.45; 4.37)	**HAIC + Lenv**				
4.38 (0.71; 26.90)	3.73 (0.87; 16.04)	2.15 (0.62; 7.49)	1.48 (0.70; 3.13)	1.06 (0.27; 4.11)	**HAIC + Sora**		1.68 (0.86; 3.29)	
5.05 (0.49; 52.13)	4.30 (0.54; 34.07)	2.47 (0.36; 17.01)	1.71 (0.33; 8.88)	1.22 (0.16; 9.01)	1.15 (0.19; 7.03)	**BSC**		
7.89 (1.64; 37.97)	6.73 (1.73; 26.11)	3.87 (1.64; 9.11)	2.67 (1.59; 4.50)	1.90 (0.55; 6.64)	1.80 (0.73; 4.48)	1.56 (0.28; 8.79)	**TACE**	
8.52 (1.56; 46.49)	7.26 (1.97; 26.84)	4.18 (1.43; 12.17)	2.89 (1.99; 4.19)	2.06 (0.62; 6.80)	1.95 (1.01; 3.75)	1.69 (0.31; 9.14)	1.08 (0.57; 2.05)	**Sora**

HAIC: Hepatic arterial infusion chemotherapy; Sora: Sorafenib; Lenv: Lenvatinib; TACE: Transarterial chemoembolization; RT: Radiotherapy; S-1: A composite preparation of a 5-fluorouracil prodrug; A: Ablation; PD-1: Programmed death 1; BSC: Best supportive care.

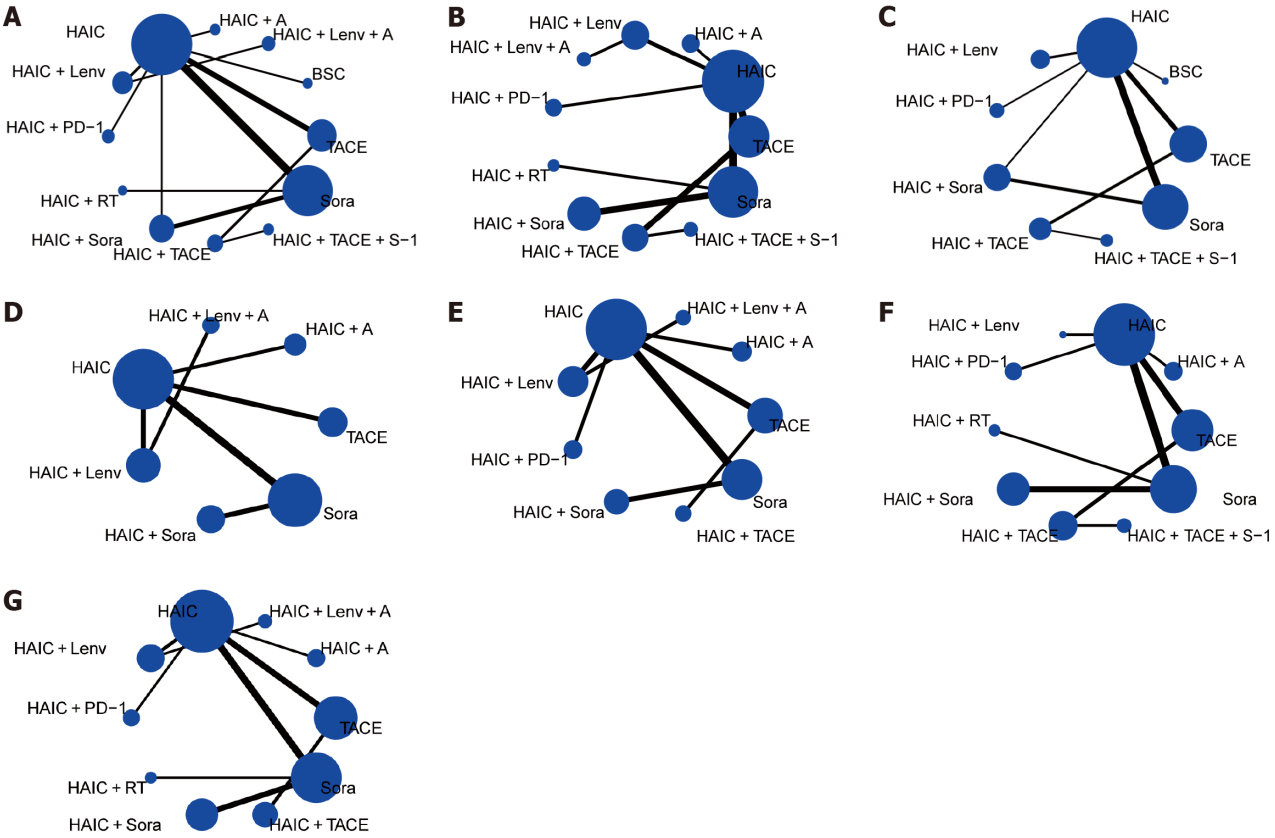

Figure 2 Network graph of the outcomes. A: Network graph of overall survival; B: Network graph of progression-free survival; C: Network graph of complete response, partial response, objective response rate, and disease control rate; D: Network graph of any grades adverse events (AEs); E: Network graph of 3-4 grades AEs; F: Network graph of 3-4 grades AEs for thrombocytopenia; G: Network graph of 3-4 grades AEs for elevated total bilirubin. HAIC: Hepatic arterial infusion chemotherapy; Sora: Sorafenib; Lenv: Lenvatinib; TACE: Transarterial chemoembolization; RT: Radiotherapy; S-1: A composite preparation of a 5-fluorouracil prodrug; A: Ablation; PD-1: Programmed death 1.

13.29; 95%CI: 3.63-48.61), HAIC + Lenv (OR = 8.37; 95%CI: 4.32-16.23), HAIC + PD-1 (OR = 7.73; 95%CI: 3.81-15.68), HAIC + TACE (OR = 5.67; 95%CI: 2.49-12.89), HAIC + Sora (OR = 5.50; 95%CI: 3.40-8.89), HAIC (OR = 5.45; 95%CI: 3.57-8.30), and TACE (OR = 2.63; 95%CI: 1.57-4.41) demonstrated significantly improved PR outcomes than patients receiving Sora (Figure 3). Furthermore, the most favorable PR outcomes were associated with HAIC + TACE + S-1 (P-score: 0.90), followed by HAIC + Lenv (P-score: 0.79) and HAIC + PD-1 (P-score: 0.74). Additionally, combination therapy for HAIC

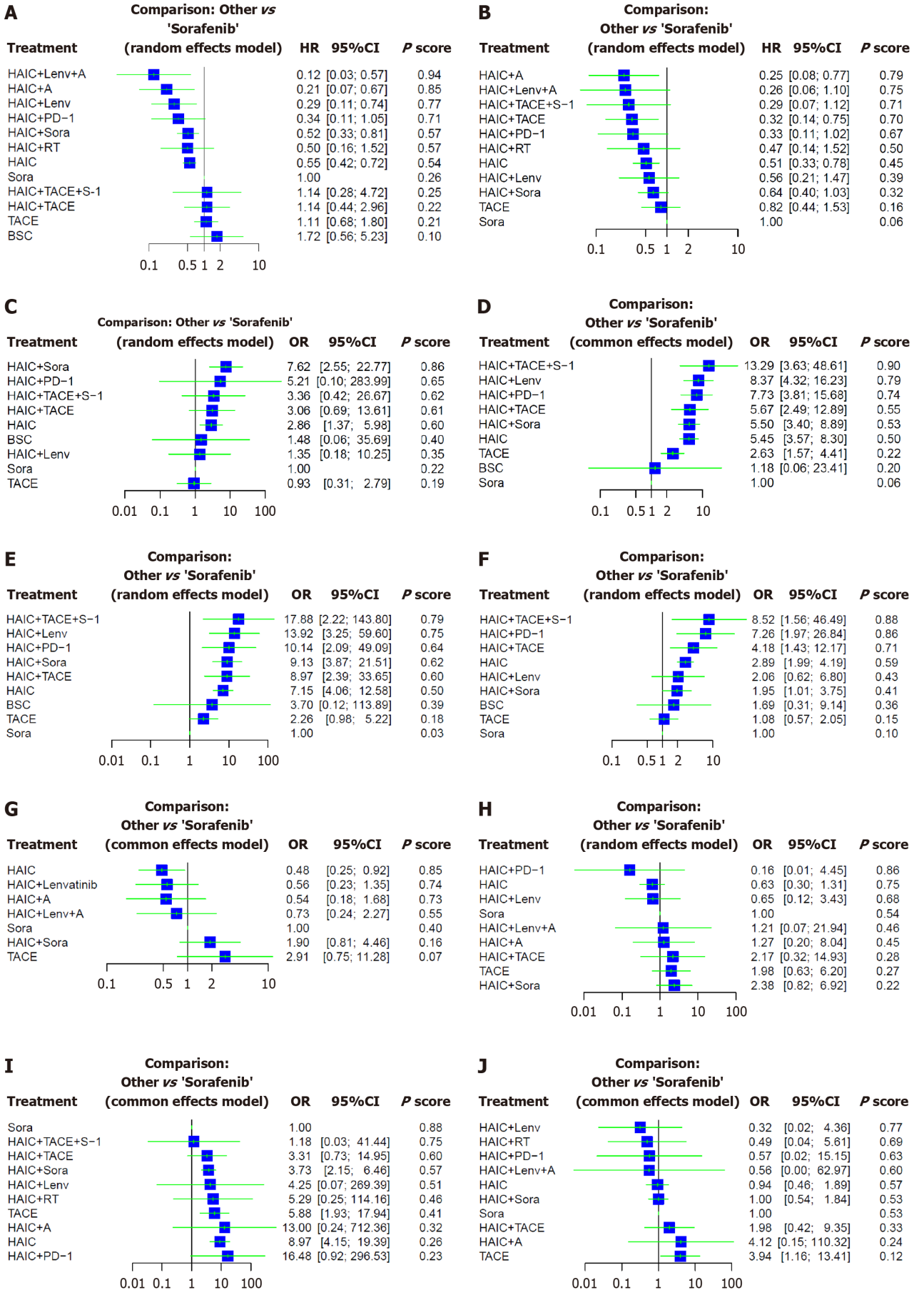

Figure 3 Forest plot of the outcomes and P score for treatment ranking. A: Forest plot of overall survival; B: Forest plot of progression-free survival; C: Forest plot of complete response; D: Forest plot of partial response; E: Forest plot of objective response rate; F: Forest plot of disease control rate; G: Forest plot of

any grades adverse events (AEs); H: Forest plot of 3-4 grades AEs; I: Forest plot of 3-4 grades AEs for thrombocytopenia; J: Forest plot of 3-4 grades AEs for elevated total bilirubin. HAIC: Hepatic arterial infusion chemotherapy; Sora: Sorafenib; Lenv: Lenvatinib; TACE: Transarterial chemoembolization; RT: Radiotherapy; S-1: A composite preparation of a 5-fluorouracil prodrug; A: Ablation; PD-1: Programmed death 1.

was highly ranked and generated statistically significant scores. Table 1 summarizes direct and indirect comparisons of the interventions for PR.

Network meta-analysis of ORR: ORR data were extracted from 35 articles, including 8 RCTs and 27 cohort studies. They encompassed 3867 patients. Nine interventions were compared (Figure 2). Patients receiving HAIC + TACE + S-1 (OR = 17.88; 95%CI: 2.22-143.80), HAIC + Lenv (OR = 13.92; 95%CI: 3.25-59.60), HAIC + PD-1 (OR =10.14; 95%CI: 2.09-49.09), HAIC + TACE (OR = 8.97; 95%CI: 2.39-33.65), HAIC + Sora (OR = 9.13; 95%CI: 3.87-21.51), and HAIC (OR = 7.15; 95%CI: 4.06-12.58) demonstrated significantly improved ORR outcomes than patients receiving Sora (Figure 3). Furthermore, the most favorable ORR outcomes were associated with HAIC + TACE + S-1 (P-score: 0.79), followed by HAIC + Lenv (P-score: 0.75) and HAIC + PD-1 (P-score: 0.64). Table 1 summarizes direct and indirect comparisons of the interventions for ORR.

Network meta-analysis of DCR: DCR data were extracted from 35 articles, including 8 RCTs and 27 cohort studies. They encompassed 3867 patients. Nine interventions were compared (Figure 2). Patients receiving HAIC + TACE + S-1 (OR = 8.52; 95%CI: 1.56-46.49), HAIC + PD-1 (OR = 7.26; 95%CI: 1.97-26.84), HAIC + TACE (OR = 4.18; 95%CI: 1.43-12.17), HAIC (OR = 2.89; 95%CI: 1.99-4.19), and HAIC + Sora (OR = 1.95; 95%CI: 1.01-3.75) demonstrated significantly improved DCR outcomes than patients receiving Sora (Figure 3). Furthermore, the most favorable DCR outcomes were associated with HAIC + TACE + S-1 (P-score: 0.88), followed by HAIC + PD-1 (P-score: 0.86) and HAIC + TACE (P-score: 0.71). The League Table summarizes direct and indirect comparisons of the interventions for DCR.

Network meta-analysis of any grade AEs: Any grade AE data were extracted from 12 articles, including 4 RCTs and 12 cohort studies. They encompassed 2095 patients. Seven interventions were compared (Figure 2). Patients receiving HAIC (OR = 0.48; 95%CI: 0.25-0.92) demonstrated a lower trend of any grade AEs than patients receiving Sora (Figure 3). Furthermore, HAIC (P-score: 0.85) generated the lowest incidence of any grade AEs (a higher ranking indicated a lower incidence). Table 2 summarizes direct and indirect comparisons of the interventions for any grade AEs. HAIC + A (OR = 0.19; 95%CI: 0.04-0.84), HAIC (OR = 0.16; 95%CI: 0.05-0.54), and HAIC + Lenv (OR = 0.19; 95%CI: 0.05-0.72) exhibited lower trends of any grade AEs, compared with TACE.

Network meta-analysis of grade 3 to 4 AEs: Data of grade 3 to 4 AEs were extracted from 16 articles, comprising 5 RCTs and 11 cohort studies. They encompassed 2449 patients. Seven interventions were compared (Figure 2). Patients receiving HAIC + PD-1 (OR = 0.16; 95%CI: 0.01-4.45), HAIC (OR = 0.63; 95%CI: 0.30-1.31), and HAIC + Lenv (OR = 0.65; 95%CI: 0.12-3.43) demonstrated marginally lower trends of grade 3 to 4 AEs than patients receiving Sora, though insignificant (Figure 3). Figure 3 illustrates the P-score for the treatment ranking analysis. Table 2 summarizes direct and indirect comparisons of the interventions for grade 3 to 4 AEs. HAIC demonstrated lower trends of grade 3 to 4 AEs than HAIC + Sora (OR = 0.26; 95%CI: 0.07-0.97) and TACE (OR = 0.32; 95%CI: 0.13-0.75).

Additionally, we examined thrombocytopenia and elevated total bilirubin, the most frequently reported AEs. Sora demonstrated lower trends of grade 3 to 4 AEs for thrombocytopenia than other interventions (Figure 3). TACE demonstrated higher trends of grade 3 to 4 AEs for elevated total bilirubin than Sora (OR = 0.25; 95%CI: 0.07-0.87) and HAIC (OR = 0.24; 95%CI: 0.09-0.65), consistent with the findings of a phase 3 study[48]. Table 2 summarizes direct and indirect comparisons of the interventions for any grade and grade 3 to 4 AEs.

Results of quality assessment, publication bias, inconsistency, and heterogeneity analyses

Supplementary material describes the results of quality assessment, publication bias, inconsistency, and heterogeneity analyses.

DISCUSSION

In this study, we incorporated direct and indirect evidence to compare the efficacy and safety of HAIC and combination therapy in patients with advanced HCC. HAIC was considered a better choice than Sora and TACE regarding efficacy and safety. Moreover, combined interventions displayed marginally better efficacy than HAIC monotherapy. HAIC and its combination are effective for advanced HCC[12,56,57]. The mechanism by which HAIC protects against HCC consists of the blood supply characteristics of the liver and HCC cells. The liver primarily receives its blood supply from the hepatic artery and portal vein, with only approximately 30% of the blood coming from the hepatic artery. In contrast, HCC cells receive approximately 90% of the blood supply from the portal vein[58]. Consequently, chemotherapeutic drugs administered into the hepatic artery predominantly reach the HCC cells, with only a fraction absorbed into the healthy liver tissues. This phenomenon allows HAIC to maintain a high concentration of chemotherapeutic drugs within the HCC cells and a low concentration in other tissues. Additionally, the liver is the primary metabolizing organ; thus, chemotherapeutic drugs reaching the healthy liver tissue can be metabolized to a limited extent, reducing the likelihood

Table 2 League table for adverse events

League table

Any grade AEs

HAIC	0.86 (0.47; 1.56)	0.88 (0.35; 2.22)		0.48 (0.25; 0.92)		0.16 (0.05; 0.54)		
0.86 (0.47; 1.56)	**HAIC + Lenv**		0.76 (0.38; 1.55)					
0.88 (0.35; 2.22)	1.03 (0.34; 3.09)	**HAIC + A**						
0.66 (0.26; 1.66)	0.76 (0.38; 1.55)	0.74 (0.20; 2.75)	**HAIC + Lenv + A**					
0.48 (0.25; 0.92)	0.56 (0.23; 1.35)	0.54 (0.18; 1.68)	0.73 (0.24; 2.27)	**Sora**	0.53 (0.22; 1.24)			
0.25 (0.09; 0.74)	0.29 (0.09; 1.00)	0.29 (0.07; 1.18)	0.38 (0.09; 1.59)	0.53 (0.22; 1.24)	**HAIC + Sora**			
0.16 (0.05; 0.54)	0.19 (0.05; 0.72)	0.19 (0.04; 0.84)	0.25 (0.06; 1.13)	0.34 (0.09; 1.33)	0.65 (0.13; 3.23)	**TACE**		

3-4 grade AEs

HAIC + PD-1	0.26 (0.01; 6.54)							
0.26 (0.01; 6.54)	**HAIC**	0.96 (0.22; 4.26)	0.63 (0.30; 1.31)		0.49 (0.09; 2.69)		0.32 (0.13; 0.75)	
0.25 (0.01; 8.71)	0.96 (0.22; 4.26)	**HAIC + Lenv**		0.54 (0.05; 5.76)				
0.16 (0.01; 4.45)	0.63 (0.30; 1.31)	0.65 (0.12; 3.43)	**Sora**					0.42 (0.14; 1.23)
0.13 (0.00; 9.57)	0.52 (0.03; 8.50)	0.54 (0.05; 5.76)	0.83 (0.05; 14.97)	**HAIC + LENV + A**				
0.13 (0.00; 4.90)	0.49 (0.09; 2.69)	0.51 (0.05; 4.89)	0.79 (0.12; 5.02)	0.96 (0.04; 25.23)	**HAIC + A**			
0.07 (0.00; 2.97)	0.29 (0.05; 1.70)	0.30 (0.03; 3.04)	0.46 (0.07; 3.16)	0.56 (0.02; 15.36)	0.58 (0.05; 6.78)	**HAIC + TACE**	1.10 (0.23; 5.19)	
0.08 (0.00; 2.32)	0.32 (0.13; 0.75)	0.33 (0.06; 1.84)	0.51 (0.16; 1.59)	0.61 (0.03; 11.50)	0.64 (0.10; 4.30)	1.10 (0.23; 5.19)	**TACE**	
0.07 (0.00; 2.21)	0.26 (0.07; 0.97)	0.27 (0.04; 1.97)	0.42 (0.14; 1.23)	0.51 (0.02; 11.17)	0.53 (0.06; 4.51)	0.91 (0.10; 8.28)	0.83 (0.17; 3.97)	**HAIC + Sora**

3-4 grade AEs for thrombocytopenia

Sora			0.27 (0.15; 0.46)		0.19 (0.01; 4.08)			0.11 (0.05; 0.24)
0.85 (0.02; 29.67)	**HAIC + TACE + S-1**	0.36 (0.01; 8.96)						
0.30 (0.07; 1.37)	0.36 (0.01; 8.96)	**HAIC + TACE**				0.56 (0.20; 1.55)		
0.27 (0.15; 0.46)	0.32 (0.01; 11.60)	0.89 (0.18; 4.42)	**HAIC + Sora**					
0.24 (0.00; 14.92)	0.28 (0.00; 58.91)	0.78 (0.01; 56.14)	0.88 (0.01; 57.66)	**HAIC + Lenv**				0.47 (0.01; 27.94)
0.19 (0.01; 4.08)	0.22 (0.00; 24.56)	0.63 (0.02; 19.15)	0.70 (0.03; 15.97)	0.80 (0.00; 140.28)	**HAIC + RT**			
0.17 (0.06; 0.52)	0.20 (0.01; 5.89)	0.56 (0.20; 1.55)	0.63 (0.18; 2.20)	0.72 (0.01; 46.14)	0.90 (0.03; 23.63)	**TACE**		0.66 (0.29; 1.47)
0.08 (0.00; 4.22)	0.09 (0.00; 17.21)	0.25 (0.00; 15.93)	0.29 (0.01; 16.31)	0.33 (0.00; 94.05)	0.41 (0.00; 63.25)	0.45 (0.01; 24.96)	**HAIC + A**	1.45 (0.03; 73.68)
0.11 (0.05; 0.24)	0.13 (0.00; 4.24)	0.37 (0.10; 1.35)	0.42 (0.16; 1.07)	0.47 (0.01; 27.94)	0.59 (0.02; 14.00)	0.66 (0.29; 1.47)	1.45 (0.03; 73.68)	**HAIC** 0.54 (0.03; 8.82)

0.06 (0.00; 1.09)	0.07 (0.00; 6.15)	0.20 (0.01; 4.33)	0.23 (0.01; 4.28)	0.26 (0.00; 35.95)	0.32 (0.00; 21.78)	0.36 (0.02; 6.48)	0.79 (0.01; 97.36)	0.54 (0.03; 8.82)	**HAIC + PD-1**
3-4 grade AEs for elevated total bilirubin									
HAIC + Lenv			0.57 (0.01; 29.09)	0.34 (0.03; 4.22)					
0.65 (0.02; 23.55)	**HAIC + RT**					0.49 (0.04; 5.61)			
0.56 (0.01; 33.37)	0.86 (0.01; 51.75)	**HAIC + PD-1**		0.60 (0.02; 14.98)					
0.57 (0.01; 29.09)	0.87 (0.00; 178.10)	1.01 (0.00; 293.95)	**HAIC + LENV + A**						
0.34 (0.03; 4.22)	0.52 (0.04; 6.61)	0.60 (0.02; 14.98)	0.60 (0.01; 63.73)	**HAIC**		0.94 (0.46; 1.89)		0.23 (0.01; 5.65)	0.24 (0.09; 0.65)
0.32 (0.02; 4.68)	0.49 (0.04; 6.06)	0.57 (0.02; 16.06)	0.56 (0.00; 65.61)	0.94 (0.37; 2.38)	**HAIC + Sora**	1.00 (0.54; 1.84)			
0.32 (0.02; 4.36)	0.49 (0.04; 5.61)	0.57 (0.02; 15.15)	0.56 (0.00; 62.97)	0.94 (0.46; 1.89)	1.00 (0.54; 1.84)	**Sora**			
0.16 (0.01; 2.86)	0.25 (0.01; 4.46)	0.29 (0.01; 9.46)	0.28 (0.00; 36.96)	0.47 (0.12; 1.90)	0.51 (0.10; 2.68)	0.51 (0.11; 2.39)	**HAIC + TACE**		0.50 (0.19; 1.30)
0.08 (0.00; 4.58)	0.12 (0.00; 7.10)	0.14 (0.00; 12.89)	0.14 (0.00; 39.31)	0.23 (0.01; 5.65)	0.24 (0.01; 6.87)	0.24 (0.01; 6.50)	0.48 (0.01; 15.85)	**HAIC + A**	
0.08 (0.01; 1.22)	0.12 (0.01; 1.90)	0.14 (0.00; 4.16)	0.14 (0.00; 16.88)	0.24 (0.09; 0.65)	0.25 (0.06; 1.00)	0.25 (0.07; 0.87)	0.50 (0.19; 1.30)	1.05 (0.04; 30.26)	**TACE**

AEs: Adverse events; HAIC: Hepatic arterial infusion chemotherapy; Sora: Sorafenib; Lenv: Lenvatinib; TACE: Transarterial chemoembolization; RT: Radiotherapy; S-1: A composite preparation of a 5-fluorouracil prodrug. A: Ablation; PD-1: Programmed death 1; BSC: Best supportive care; PR: Partial response; CR: Complete response; DCR: Disease control rate; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

of systemic AEs. These findings indicate that HAIC generated a lower incidence of any grade and grade 3 to 4 AEs than TACE. Moreover, HAIC generated a significantly lower incidence of any grade AEs than Sora. In a phase 3 trial, the TACE group exhibited a higher incidence of AEs than the HAIC group (30% *vs* 19%, $P = 0.03$)[13].

HAIC + Lenv + A, HAIC + A, HAIC + Lenv, HAIC + Sora, and HAIC outperformed Sora and TACE in improving OS. Additionally, HAIC + A, HAIC + TACE, and HAIC outperformed Sora and TACE in improving PFS. HAIC + Lenv + A and HAIC + A demonstrated better OS and PFS outcomes. This funding may be attributed to ablation that destroys tumors and generates an immune response with anti-tumor effects by activating tumor-specific antigens in the tumor microenvironment. Additionally, these tumor-specific antigens activate anti-tumor responses to vascular endothelial growth factor inhibitors[59]. Furthermore, HAIC combination therapy was superior to monotherapy, though insignificant. A phase 3 study indicated that HAIC + Sora demonstrated higher OS [HR = 0.35; 95%CI: 0.26-0.48, 13.37 (10.27-16.46) *vs* 7.13 (6.28-7.98) months, $P < 0.001$] and PFS [HR = 0.33; 95%CI: 0.25-0.43, 7.03 (6.05-8.02) *vs* 2.6 (2.15-3.05) months, $P < 0.001$] than HAIC alone[18]. Similarly, a phase 2 study demonstrated better OS and PFS outcomes for HAIC + Sora, compared with Sora for advanced HCC[16]. Furthermore, a phase 3 study indicated that HAIC was superior to TACE, resulting in longer OS [HR = 0.58; 95%CI: 0.45-0.75, 23.1 (18.5-27.7) *vs* 16.1 (14.3-17.9) months, $P < 0.001$] and PFS [HR = 0.57; 95%CI: 0.45-0.72, 9.6 (7.4-11.9) *vs* 5.4 (3.8-7.0) months, $P < 0.001$][13]. Similar trends can be observed for CR, PR, ORR, and DCR. HAIC resulted in better CR, PR, ORR, and DCR outcomes than Sora and TACE.

Furthermore, combination therapy was more effective than HAIC monotherapy. The statistical insignificance warrants additional clinical trials. You *et al*[41] reported significantly higher 1-, 2-, and 3-year OS and PFS rates in the HAIC + A group, compared with the HAIC group (OS: 64.3% *vs* 91.1%, 27.7% *vs* 74.3%, 16.0% *vs* 64.1%; PFS: 32.0% *vs* 61.2%, 16.1% *vs* 34.4%, 12.1% *vs* 29.5%; both $P < 0.001$). Long *et al*[37] reported significantly higher 1-, 2-, and 3-year cumulative OS rates in the HAIC + Lenv group, compared with the HAIC group ($P < 0.001$), without significant differences in the PFS, CR, PR, ORR, and DCR. Yuan *et al*[24] reported significantly increased ORR in the HAIC + Lenv group, compared with the HAIC group, despite no significant differences in the DCR, OS, and PFS between the groups. Mei *et al*[25] reported that the HAIC + PD-1 group achieved higher OS (HR = 0.62; 95%CI: 0.34-0.91), PFS (HR = 0.65; 95%CI: 0.43-0.87), and DCR (83% *vs* 66%; $P = 0.006$), compared with the HAIC group. Nagai *et al*[51] reported higher OS for HAIC + Sora than for HAIC.

This network meta-analysis has several limitations. First, we did not account for the impact of the HAIC dosing regimen and the dosage of other drugs on the efficacy. For instance, a phase 2 study demonstrated significantly better OS outcomes with Sora + HAIC using low-dose cisplatin than Sora[17]. By contrast, a phase 3 study demonstrated no significant difference in the OS between patients receiving Sora + HAIC using low-dose 5-fluorouracil[19]. This variation may have contributed to significant heterogeneity in some of the comparisons. Second, we included PD-1 without specifying the drug. Some relevant studies were not included because of their small number. For example, a cohort study demonstrated that HAIC + toripalimab was superior to Lenv, resulting in longer OS [17.13 (13.99-20.27) *vs* 10.1 (8.14-

12.06) months; HR = 0.50, 95%CI: 0.31-0.81; P = 0.005], higher DCR (86.8% *vs* 69.2%, P = 0.002), and higher ORR (47.2% *vs* 9.2%, P < 0.001)[60]. Third, Japanese guidelines recommend HAIC as a standard treatment for advanced HCC with portal vein tumor thrombus[7]. However, we could not conduct a subgroup network meta-analysis for portal vein tumor thrombus because of the limited number of studies reporting these outcomes.

CONCLUSION

HAIC is a relatively better choice for advanced HCC than Sora and TACE. It demonstrates a significantly lower trend of any grade AEs than Sora and TACE and of grade 3 to 4 AEs than TACE. Furthermore, combined interventions demonstrated modestly improved OS, PFS, CR, PR, ORR, and DCR, compared with HAIC alone, according to the treatment ranking analysis.

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FOOTNOTES

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