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ORIGINAL RESEARCH

Transcatheter hepatic arterial infusion chemotherapy vs sorafenib in the treatment of patients with hepatocellular carcinoma of Barcelona Clinic Liver Cancer stage C: a meta-analysis of Asian population

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Objective: To compare the clinical efficacy and safety of transcatheter hepatic arterial infusion chemotherapy (HAIC) with those of sorafenib in the treatment of patients with hepatocellular carcinoma (HCC) of Barcelona Clinic Liver Cancer (BCLC) stage C.

Methods: Potentially relevant studies comparing the clinical efficacy and safety of HAIC with those of sorafenib were searched using Medline, PubMed, Embase, Cochrane Library, and Chinese databases (Wanfang Data and China National Knowledge Infrastructure). Overall survival rate (OSR), tumor response rate, disease control rate (DCR), and serious adverse events (SAEs) were compared and analyzed. Pooled ORs with 95% CIs were calculated using either the fixed-effects model or the random-effects model. All statistical analyses were conducted using Review Manager (version 5.3) from the Cochrane Collaboration.

Results: A total of 1,264 patients were included in this meta-analysis. The results of this study showed that HAIC was associated with significantly higher 1-, 2-, and 3-year OSRs than sorafenib (OR 1.88, 95% $CI_{1\text{-year}}$: [1.27–2.78], $P_{1\text{-year}}$=0.002; OR 2.15, 95% $CI_{2\text{-year}}$: [1.06–4.37], $P_{2\text{-year}}$=0.03; OR 7.90, 95% $CI_{3\text{-year}}$: [2.12–29.42], $P_{3\text{-year}}$=0.002). Compared to sorafenib, HAIC was associated with superior complete response (CR), partial response (PR), and objective response rate (ORR) (OR 3.90, 95% CI_{CR}: [1.89–8.03], P_{CR} =0.0002; OR 3.47, 95% CI_{PR}: [2.31–5.24], P_{PR} <0.00001; OR 3.02, 95% CI_{OR}: [2.05–4.45], P_{OR} <0.0001). There was no statistically significant difference between HAIC and sorafenib in stable disease (SD), progressive disease (PD), DCR, and SAEs (OR 0.86, 95% CI_{SD}: [0.51–1.45], P_{SD} =0.56; OR 0.62, 95% CI_{PD}: [0.35–1.11], P_{PD} =0.11; OR 0.53, 95% CI_{SAE}: [0.14–1.92], P_{SAE} =0.33).

Conclusion: This study showed that HAIC was associated with better efficacy than sorafenib in terms of OSR and tumor response. Therefore, HAIC can be considered as an alternative treatment option for patients with HCCs of BCLC stage C.

Keywords: HCC, HAIC, targeted therapy, BCLC, prognosis, meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is a serious health problem, which accounts for more than 700,000 new cases worldwide annually.[1,2] HCC is the second leading cause of cancer-related death in many countries and regions.[3] The Barcelona Clinic Liver Cancer (BCLC) staging system has been widely accepted as a treatment guideline that comprehensively considers tumor burden, hepatic function, and performance status of

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patients with HCC.[4,5] Sorafenib is a multikinase inhibitor that targets raf kinase, which participates in the proliferation of tumor cells, and vascular endothelial growth factor (VEGF) receptor-2, VEGF receptor-3, and platelet-derived growth factor receptor, which contribute to angiogenesis of tumor cells. In clinical practice, according to the current guidelines, including the BCLC staging classification, sorafenib is the standard treatment modality for patients with advanced HCC in many countries. In previous studies, sorafenib was proved to prolong overall survival by 2.3–2.8 months and improve the response rate by 2.0%–3.3%, compared to placebo.[6,7] However, because of the comprehensive consideration of limited efficacy, adverse events, and high cost, the clinical benefits of sorafenib were still unsatisfying.

In the last decade, epirubicin-, cisplatin-, interferon-, or 5-fluorouracil-based transcatheter hepatic arterial infusion chemotherapy (HAIC) was widely used for patients with BCLC stage C HCCs in Asian countries. HAIC was suggested as a promising treatment as it can inhibit tumor growth through antiangiogenic mechanisms with less toxicity and fewer systemic side effects than the maximum tolerated dose therapy. Several studies have reported the clinical effectiveness of HAIC for BCLC stage C HCCs, with response rates ranging from 20.8% to 52%, and the median survival time in complete and partial responders is approximately 40 and 17 months, respectively.[8–10] Some previous studies comparing the clinical efficacy of HAIC with that of sorafenib suggested that HAIC was superior to sorafenib for patients with BCLC stage C HCCs.[8,12–14] However, some other studies reported conflicting results.[10,11,15]

To the best of our knowledge, no meta-analysis studies have been performed to compare the clinical benefits and safety of HAIC with those of sorafenib in the treatment of patients with BCLC stage C HCCs. In this study, we designed a meta-analysis to compare comprehensively the efficacy and safety of HAIC with those of sorafenib for BCLC stage C HCCs. We hope that the comparison of these treatments could help stratify the benefits of treatment choices for patients with HCC.

Methods

Search strategy

In this meta-analysis, Medline, PubMed, Embase, Cochrane Library, and Chinese databases (Wanfang Data and China National Knowledge Infrastructure) were searched for studies comparing the clinical efficacy and safety of HAIC with those of sorafenib in the treatment of patients with BCLC stage C HCCs from January 2007 to June 2017. The study search used the following MeSH search headings: "hepatocellular carcinoma" or "primary liver cancer", "BCLC stage C", "transcatheter", "hepatic arterial infusion chemotherapy", and "sorafenib". A limit was set on clinical studies that were designed to compare the clinical effectiveness and adverse events of HAIC with those of sorafenib in BCLC stage C HCCs. There was no language restriction in this search.

Inclusion criteria of published trials

To be considered as eligible in this meta-analysis, the enrolled studies were required to have comparative data on clinical efficacy (overall survival rate [OSR], tumor response rate, disease control rate [DCR]) and adverse events of HAIC and sorafenib in patients with BCLC stage C HCCs. The inclusion criteria were as follows: 1) trial design: the trials must be designed as clinical studies with comparative data on clinical effectiveness and adverse events of HAIC and sorafenib for BCLC stage C HCCs; 2) clear document indications for use of HAIC and sorafenib; 3) treatment design: HAIC vs sorafenib; 4) characteristics of patients: the studies were required to have relatively integrated basic characteristics of enrolled patients, such as average age, percentage of male, Child–Pugh class, tumor size, portal vein tumor thrombosis (PVTT), and virus infection; 5) time of publication: from January 2007 to June 2017; and 6) study results: at least one item of results on OSR, tumor response rate, DCR, or adverse event was applicable.

Reviews without abstracts, original data, editorials, expert opinions, letters, case reports, and studies lacking control groups were excluded from the analysis.

Evaluation strategy

Data extraction was independently conducted by two reviewers using the standardized methods, with any disagreements being settled by discussion of the respective study data and adjudicated by an experienced reviewer. From each study, the following data were abstracted: data for publication details (name of the first author and year of publication) and study characteristics (study design, age, gender of patients, study design, tumor size, tumor number, Child–Pugh class, OSR, tumor response rate, incidence of adverse events, etc.).

Statistical analysis

Statistical analyses were performed on dichotomous outcomes, and standard meta-analytical techniques were used in this study. Pooled ORs with 95% CIs were calculated using either the fixed-effects model or the random-effects model. For each meta-analysis, the χ^2 and I^2 statistics were

first calculated to assess the heterogeneity of the included studies. $P<0.1$ and $I^2>50\%$ were considered significant. For $P<0.1$ and $I^2>50\%$, the random-effects model was used; otherwise, data were assessed using the fixed-effects model. The risk of publication bias in this study was assessed by visual inspection of the symmetry of the funnel plot. All statistical analyses were performed using Review Manager (version 5.3) from the Cochrane Collaboration. The significance of the pooled ORs was assessed by the *Z*-test. $P<0.05$ was considered significant.

Results

Search results

This study found a total of 86 potentially relevant studies. On the basis of the inclusion and exclusion criteria of this study, 10 retrospective cohort studies comparing the clinical efficacy and adverse events of HAIC with those of sorafenib for the treatment of BCLC stage C HCCs were finally included.[8–17] The flowchart of the search strategy for included studies is shown in Figure 1. A total of 1,264 patients were included in the study, of whom 505 patients underwent sorafenib treatment and 759 patients underwent HAIC treatment. The basic characteristics, OSR, tumor response rate, and DCR of patients in enrolled trials are summarized in Tables 1 and 2. The quality of the included studies was assessed using the Cochrane Collaboration's tool.

Meta-analysis results

OSR

Six, four, and four studies reported the comparative data for OSR at 1, 2, and 3 years, respectively. From the results of tests for heterogeneity between trials ($\chi^2_{1\text{-year}}=7.16$, $P_{1\text{-year}}=0.21$, $I^2_{1\text{-year}}=30\%$; $\chi^2_{2\text{-year}}=1.15$, $P_{2\text{-year}}=0.77$, $I^2_{2\text{-year}}=0\%$; $\chi^2_{3\text{-year}}=1.70$, $P_{3\text{-year}}=0.64$, $I^2_{3\text{-year}}=0\%$), the fixed-effects model was used to pool the results in the analysis of the effects of OSR. Compared to sorafenib, the data and forest plots of our study showed that HAIC was associated with significantly higher 1-, 2-, and 3-year OSR in the treatment of patients with BCLC stage C HCC (OR 1.88, 95% $CI_{1\text{-year}}$: [1.27–2.78], $P_{1\text{-year}}=0.002$; OR 2.15, 95% $CI_{2\text{-year}}$: [1.06–4.37], $P_{2\text{-year}}=0.03$; OR 7.90, 95% $CI_{3\text{-year}}$: [2.12–29.42], $P_{3\text{-year}}=0.002$) (Figure 2 and Table 3).

Tumor response to therapy

Nine, nine, nine, nine, and ten studies reported the comparative data for tumor response rate in terms of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and objective response rate (ORR), respectively. From the results of tests for heterogeneity between trials ($\chi^2_{CR}=7.76$, $P_{CR}=0.26$, $I^2_{CR}=23\%$; $\chi^2_{PR}=14.95$, $P_{PR}=0.06$, $I^2_{PR}=46\%$; $\chi^2_{SD}=29.72$, $P_{SD}=0.0002$, $I^2_{SD}=73\%$; $\chi^2_{PD}=34.62$, $P_{PD}\leq0.0001$, $I^2_{PD}=38\%$; $\chi^2_{OR}=12.73$, $P_{OR}=0.08$, $I^2_{OR}=45\%$), either the random-effects model or the fixed-effects model was used to pool the results in the analysis of the effects of CR, PR, SD, PD, and OR. The data and forest plots of our study revealed that HAIC was associated with obviously better CR, PR, and OR than sorafenib (OR 3.90, 95% CI_{CR}: [1.89–8.03], $P_{CR}=0.0002$; OR 3.47, 95% CI_{PR}: [2.31–5.24], $P_{PR}<0.00001$; OR 3.02, 95% CI_{OR}: [2.05–4.45], $P_{OR}<0.0001$). There was no statistically significant difference between HAIC and sorafenib in stable SD and PD (OR 0.86, 95% CI_{SD}: [0.51–1.45], $P_{SD}=0.56$; OR 0.62, 95% CI_{PD}: [0.35–1.11], $P_{PD}=0.11$) (Figure 3 and Table 3).

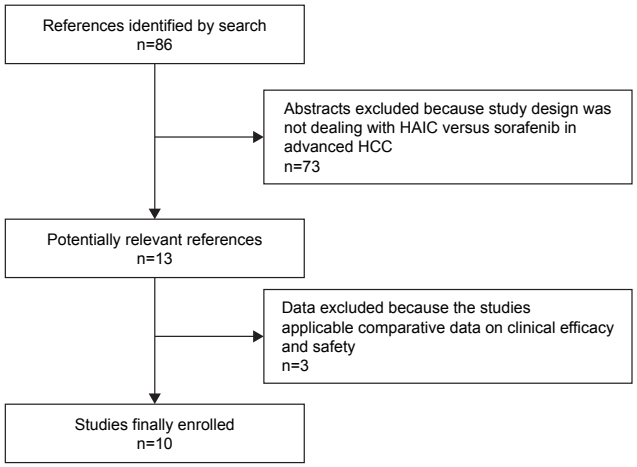


Figure 1 The flowchart of the search strategy for study inclusion.
Abbreviations: HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma.

Table 1 Baseline characteristics of the included trials

Study (year)	Country	Design	Treatment	No of pts	Age (years)	Sex (M/F)	Tumor size (cm)	Tumor number (solitary/multiple)	Child–Pugh class (A/B/C)	Virus infection (HBV/HCV)	PVTT (%)	Extrahepatic metastasis (%)
Yang et al (2017)[8]	Korea	RCS	Sorafenib	53	58.0±9.2	39/14	9.2±5.1	17/36	34/19/0	43/4	53 (100)	35 (66.0)
			HAIC	54	54.4±11.0	50/4	12.5±4.6	8/46	25/29/0	44/6	54 (100)	28 (51.9)
Terashima et al (2017)[9]	Japan	RCS	Sorafenib	51	69 (median)	45/6	NA	NA	51/0/0	16/24	NA	25 (49.0)
			HAIC	139	69 (median)	111/28	NA	NA	139/0/0	36/75	NA	24 (17.3)
Hatooka et al (2016)[10]	Japan	RCS	Sorafenib	58	70 (50–88)	43/15	3.2 (0.5–19)	24/34	NA	13/40	58 (100)	6 (10.3)
			HAIC	65	67 (46–84)	59/6	4.0 (1.5–14)	17/48	NA	15/43	65 (100)	34 (52.3)
Fukubayashi et al (2015)[11]	Japan	RCS	Sorafenib	72	68.9±9.84	51/21	NA	NA	61/11/0	15/36	21 (29.2)	33 (45.8)
			HAIC	128	65.5±9.32	113/15	NA	NA	79/49/0	33/77	64 (50.0)	33 (25.8)
Kawaoka et al (2015)[12]	Japan	RCS	Sorafenib	41	69 (30–81)	29/12	4.0 (1.0–19)	NA	NA	15/24	14 (34.1)	14 (34.1)
			HAIC	136	67 (30–85)	123/13	4.5 (1.0–18)	NA	NA	33/75	92 (67.6)	92 (67.6)
Kondo et al (2015)[13]	Japan	RCS	Sorafenib	83	70 (37–88)	74/9	NA	NA	78/5/0	15/52	20 (24.0)	NA
			HAIC	44	71 (54–84)	32/12	NA	NA	31/13/0	1/33	24 (54.5)	NA
Song et al (2015)[14]	Korea	RCS	Sorafenib	60	55.8±9.0	44/16	NA	NA	47/13/0	41/5	60 (100)	21 (35)
			HAIC	50	54.3±9.9	38/12	NA	NA	45/5/0	44/2	50 (100)	12 (24)
Shiozawa et al (2014)[17]	Japan	RCS	Sorafenib	47	69.4±8.2	43/4	NA	NA	39/8/0	8/27	NA	8 (17.0)
			HAIC	77	67.3±6.8	64/13	NA	NA	49/26/2	14/47	NA	3 (3.8)
Jeong et al (2012)[16]	Korea	RCS	Sorafenib	20	59.5 (49–75)	11/9	3.0±0.9	NA	NA	13/NA	NA	10 (50)
			HAIC	21	51 (33–75)	21/0	3.4±0.2	NA	NA	18/NA	NA	7 (33)
Hiramine et al (2011)[15]	Japan	RCS	Sorafenib	20	69.6 (44–83)	17/3	NA	NA	14/18/0	5/10	NA	6 (30)
			HAIC	45	69.6 (47–84)	32/13	NA	NA	26/24/0	11/2	NA	5 (25)

Note: Data presented in Age and Tumor size as mean±SD and median (range A to B).

Abbreviations: F, female; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; M, male; NA, not available; pts, patients; PVTT, portal vein tumor thrombosis; RCS, retrospective cohort study.

Table 2 The prognosis of patients reported in the included trials

Study (year)	Treatment	No of pts	1-year OSR	2-year OSR	3-year OSR	5-year OSR	CR	PR	SD	PD	ORR	DCR
Yang et al (2017)[8]	Sorafenib	53	5.6% (3/53)	3.8% (2/53)	0% (0/53)	0% (0/53)	0% (0/41)	0% (0/41)	22% (9/41)	78% (32/41)	0% (0/41)	22% (9/41)
	HAIC	54	22.2% (12/54)	7.4% (4/54)	3.7% (2/54)	1.9% (1/54)	0% (0/54)	7% (4/54)	39% (21/54)	54% (29/54)	7% (4/54)	46% (25/54)
Terashima et al (2017)[9]	Sorafenib	51	4% (2/51)	0% (0/51)	0% (0/51)	0% (0/51)	0% (0/51)	6% (3/51)	45% (23/51)	45% (23/51)	5.9% (3/51)	51% (26/51)
	HAIC	139	15% (21/139)	4% (5/139)	2% (3/139)	1% (2/139)	9% (12/139)	27% (37/139)	32% (45/139)	29% (41/139)	35% (49/139)	68% (94/139)
Hatooka et al (2016)[10]	Sorafenib	58	NA	NA	NA	NA	2% (1.2/58)	4% (2.3/58)	60% (35/58)	27% (16/58)	6% (3.5/58)	NA
	HAIC	65	NA	NA	NA	NA	0% (0/65)	12% (21/65)	54% (35/65)	27% (17/65)	12% (7.8/65)	NA
Fukubayashi et al (2015)[11]	Sorafenib	72	NA	NA	NA	NA	4.2% (3/72)	11.1% (8/72)	59.7% (43/72)	25% (18/72)	15.3% (11/72)	NA
	HAIC	128	NA	NA	NA	NA	3.9% (5/128)	22.7% (29/128)	41.4% (53/128)	32% (41/128)	26.6% (34/128)	NA
Kawaoka et al (2015)[12]	Sorafenib	41	NA	NA	NA	NA	2.4% (1/41)	2.4% (1/41)	43.9% (18/41)	41.5% (17/41)	4.8% (2/41)	NA
	HAIC	136	NA	NA	NA	NA	5.9% (8/136)	25% (34/136)	40% (55/136)	21.3% (29/136)	30.9% (42/136)	NA
Kondo et al (2015)[13]	Sorafenib	83	42% (35/83)	17% (14/83)	0% (0/83)	NA	3.6% (3/83)	13.2% (11/83)	36.1% (30/83)	39.7% (33/83)	16.9% (14/83)	53.0% (44/83)
	HAIC	44	46% (20/44)	24% (11/44)	15% (7/44)	NA	6.8% (3/44)	11.3% (5/44)	16.0% (7/44)	59.1% (26/44)	18.1% (8/44)	34.1% (15/44)
Song et al (2015)[14]	Sorafenib	60	8.3% (5/60)	1.7% (1/60)	1.7% (1/60)	NA	0% (0/60)	13.3% (8/60)	31.7% (19/60)	55.0% (33/60)	13.3% (8/60)	45.0% (27/60)
	HAIC	50	2.4% (12/50)	8.0% (4/50)	8.0% (4/50)	NA	2% (1/50)	22% (11/50)	66% (33/50)	10.0% (5/50)	24.0% (12/50)	90.0% (45/50)
Shiozawa et al (2014)[17]	Sorafenib	47	38.2% (18/47)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	HAIC	77	47% (36/77)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jeong et al (2012)[16]	Sorafenib	20	32.5% (7/20)	NA	NA	NA	0% (0/20)	10% (2/20)	25% (5/20)	65% (13/20)	NA	35% (7/20)
	HAIC	21	38.1% (8/21)	NA	NA	NA	0% (0/21)	19% (4/21)	23.8% (5/21)	57.1% (12/21)	NA	38.1% (8/21)
Hiramine et al (2011)[15]	Sorafenib	20	NA	NA	NA	NA	0% (0/20)	0% (0/20)	65% (13/20)	35% (7/20)	0% (0/20)	65% (13/20)
	HAIC	45	NA	NA	NA	NA	4.4% (2/45)	17.8% (8/45)	46.7% (21/45)	31.1% (14/45)	22.2% (10/45)	68.8% (31/45)

Abbreviations: CR, complete response; DCR, disease control rate; HAIC, hepatic arterial infusion chemotherapy; NA, not available; ORR, objective response rate; OSR, overall survival rate; PD, progressive disease; PR, partial response; pts, patients; SD, stable disease.

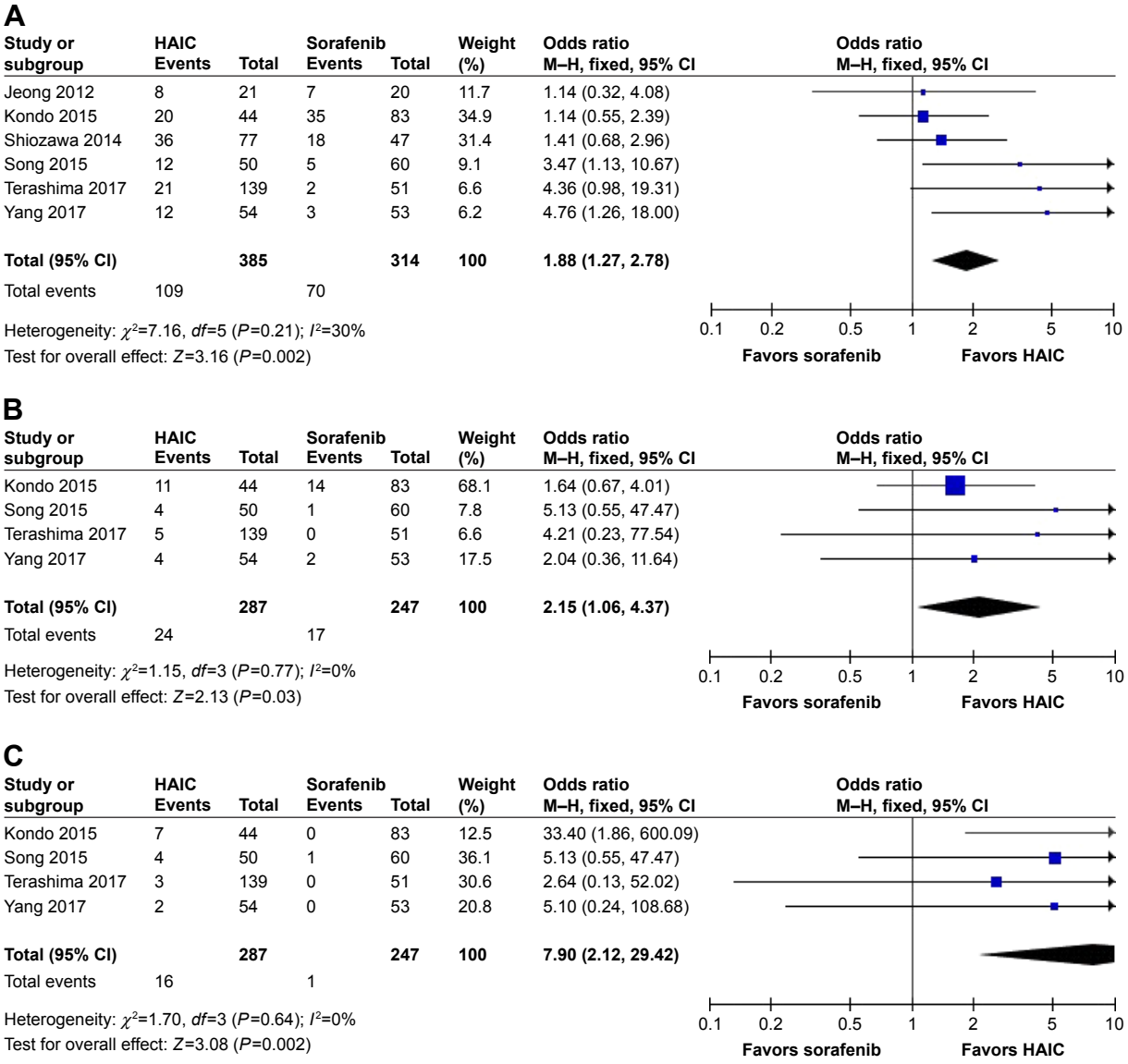


Figure 2 HAIC vs sorafenib for BCLC stage C HCCs in terms of overall survival rates.
Notes: (**A**) Meta-analysis of 1-year results. (**B**) Meta-analysis of 2-year results. (**C**) Meta-analysis of 3-year results.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma.

Table 3 Summary of the results in this meta-analysis

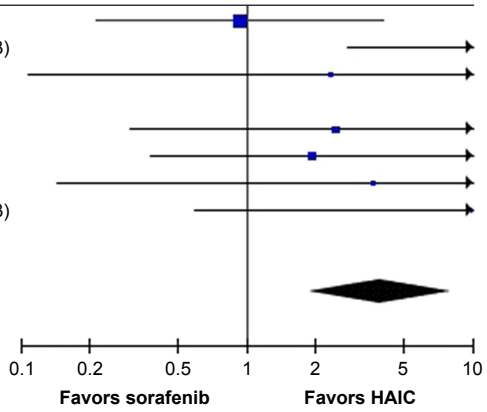
Variables	No of studies furnishing data	Results of HAIC and sorafenib		OR (95% CI)	*Z* (*Z*-test)	*P*-value
Clinical efficacy						
Overall survival rate						
1-year	6	28.3%	22.2%	1.88 (1.27–2.78)	3.16	0.002
2-year	4	8.3%	6.8%	2.15 (1.06–4.37)	2.13	0.03
3-year	4	5.5%	0.4%	7.90 (2.12–29.42)	3.08	0.002
Tumor response rate						
CR	9	7.1%	1.7%	3.90 (1.89–8.03)	3.68	0.0002
PR	9	22.4%	7.8%	3.47 (2.31–5.24)	5.95	<0.00001
SD	9	40.3%	43.7%	0.86 (0.51–1.45)	0.58	0.56
PD	9	31.3%	43.0%	0.62 (0.35–1.11)	1.61	0.11
ORR	8	25.2%	9.8%	3.02 (2.05–4.45)	5.6	<0.00001
DCR	6	61.7%	45.8%	1.84 (0.78–4.36)	1.39	0.16
Serious adverse events	7	13.1%	20.4%	0.53 (0.14–1.92)	0.97	0.33

Abbreviations: CR, complete response; DCR, disease control rate; HAIC, hepatic arterial infusion chemotherapy; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

A

Study or subgroup	HAIC Events	Total	Sorafenib Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Fukubayashi 2015	5	128	3	72	38.5	0.93 (0.22, 4.03)
Hatooka 2016	18	65	1	58	8.0	21.83 (2.81, 169.63)
Hiramine 2011	2	45	0	20	6.8	2.36 (0.11, 51.34)
Jeong 2012	0	21	0	20		Not estimable
Kawaoka 2015	8	136	1	41	15.1	2.50 (0.30, 20.60)
Kondo 2015	3	44	3	83	20.2	1.95 (0.38, 10.10)
Song 2015	1	50	0	60	4.6	3.67 (0.15, 92.01)
Terashima 2017	12	139	0	51	6.9	10.10 (0.59, 173.73)
Yang 2017	0	54	0	41		Not estimable
Total (95% CI)		**682**		**446**	**100**	**3.90 (1.89, 8.03)**
Total events	49		8			

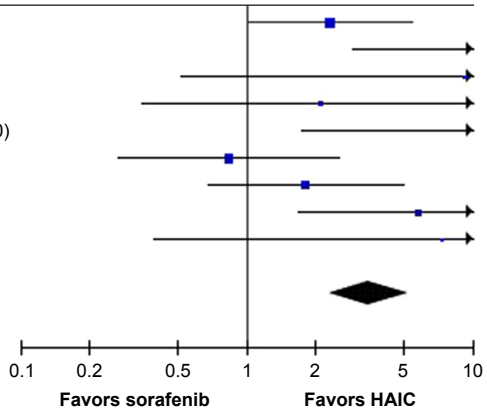
Heterogeneity: χ^2=7.76, *df*=6 (*P*=0.26); I^2=23%
Test for overall effect: *Z*=3.68 (*P*=0.0002)



B

Study or subgroup	HAIC Events	Total	Sorafenib Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Fukubayashi 2015	29	128	8	72	27.4	2.34 (1.01, 5.45)
Hatooka 2016	21	65	2	58	5.0	13.36 (2.97, 60.08)
Hiramine 2011	8	45	0	20	1.9	9.29 (0.51, 169.33)
Jeong 2012	4	21	2	20	5.7	2.12 (0.34, 13.10)
Kawaoka 2015	34	136	1	41	4.0	13.33 (1.77, 100.70)
Kondo 2015	5	44	11	83	23.4	0.84 (0.27, 2.59)
Song 2015	11	50	8	60	19.6	1.83 (0.67, 4.99)
Terashima 2017	37	139	3	51	11.1	5.80 (1.70, 19.77)
Yang 2017	4	54	0	41	1.8	7.40 (0.39, 141.37)
Total (95% CI)		**682**		**446**	**100**	**3.47 (2.31, 5.24)**
Total events	153		35			

Heterogeneity: χ^2=14.95, *df*=8 (*P*=0.06); I^2=46%
Test for overall effect: *Z*=5.95 (*P*<0.00001)



C

Study or subgroup	HAIC Events	Total	Sorafenib Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Fukubayashi 2015	53	128	43	72	13.2	0.48 (0.26, 0.86)
Hatooka 2016	35	65	35	58	12.2	0.77 (0.37, 1.57)
Hiramine 2011	21	45	13	20	9.4	0.47 (0.16, 1.40)
Jeong 2012	5	21	5	20	7.3	0.94 (0.23, 3.90)
Kawaoka 2015	55	136	18	41	12.3	0.87 (0.43, 1.76)
Kondo 2015	7	44	30	83	10.6	0.33 (0.13, 0.84)
Song 2015	33	50	19	60	11.6	4.19 (1.88, 9.31)
Terashima 2017	45	139	23	51	12.7	0.58 (0.30, 1.12)
Yang 2017	21	54	9	41	10.7	2.26 (0.90, 5.68)
Total (95% CI)		**682**		**446**	**100**	**0.86 (0.51, 1.45)**
Total events	275		195			

Heterogeneity: τ^2=0.45; χ^2=29.72, *df*=8 (*P*=0.0002); I^2=73%
Test for overall effect: *Z*=0.58 (*P*=0.56)

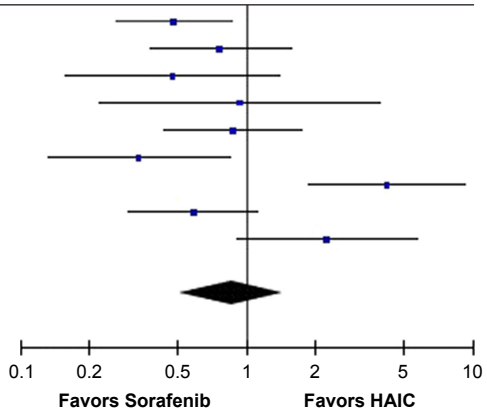
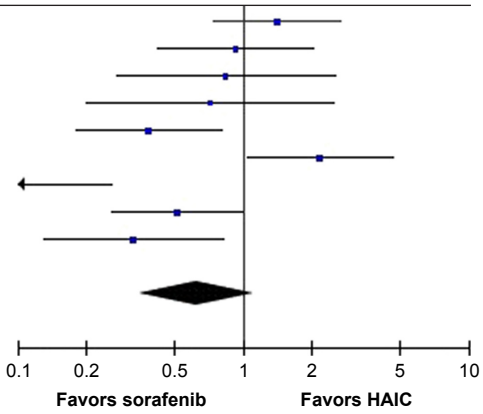


Figure 3 (*Continued*)

D

Study or subgroup	HAIC Events	Total	Sorafenib Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Fukubayashi 2015	41	128	18	72	12.6	1.41 (0.74, 2.71)
Hatooka 2016	17	65	16	58	11.6	0.93 (0.42, 2.07)
Hiramine 2011	14	45	7	20	9.6	0.84 (0.28, 2.56)
Jeong 2012	12	21	13	20	8.8	0.72 (0.20, 2.53)
Kawaoka 2015	29	136	17	41	12.0	0.38 (0.18, 0.81)
Kondo 2015	26	44	33	83	12.0	2.19 (1.04, 4.61)
Song 2015	5	50	33	60	10.0	0.09 (0.03, 0.26)
Terashima 2017	41	139	23	51	12.5	0.51 (0.26, 0.99)
Yang 2017	29	54	32	41	10.9	0.33 (0.13, 0.81)
Total (95% CI)		**682**		**446**	**100**	**0.62 (0.35, 1.11)**
Total events	214		192			

Heterogeneity: τ^2=0.60; χ^2=34.62, *df*=8 (*P*<0.0001); I^2=77%
Test for overall effect: *Z*=1.61 (*P*=0.11)



E

Study or subgroup	HAIC Events	Total	Sorafenib Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Fukubayashi 2015	34	128	11	72	30.8	2.01 (0.95, 4.26)
Hatooka 2016	8	65	4	58	11.1	1.89 (0.54, 6.66)
Hiramine 2011	10	45	0	20	1.6	12.13 (0.67, 217.91)
Kawaoka 2015	42	136	2	41	6.3	8.71 (2.01, 37.77)
Kondo 2015	8	44	14	83	23.7	1.10 (0.42, 2.85)
Song 2015	12	50	8	60	16.5	2.05 (0.76, 5.51)
Terashima 2017	49	139	3	51	8.5	8.71 (2.58, 29.42)
Yang 2017	4	54	0	41	1.6	7.40 (0.39, 141.37)
Total (95% CI)		**661**		**426**	**100**	**3.02 (2.05, 4.45)**
Total events	167		42			

Heterogeneity: χ^2=12.73, *df*=7 (*P*=0.08); I^2=45%
Test for overall effect: *Z*=5.60 (*P*<0.00001)

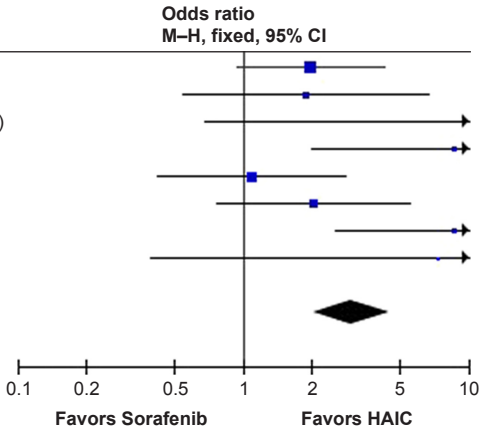


Figure 3 HAIC vs sorafenib for BCLC stage C HCCs in terms of tumor response rates.
Notes: (**A**) Meta-analysis of CR results. (**B**) Meta-analysis of PR results. (**C**) Meta-analysis of SD results. (**D**) Meta-analysis of PD results. (**E**) Meta-analysis of ORR results.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CR, complete response; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

DCR

Six studies reported the comparative data on DCR of HAIC and sorafenib for patients with BCLC stage C HCC. From the results of tests for heterogeneity between trials (χ^2_{DCR}=26.21, P_{DCR} ≤0.0001, I^2_{DCR} =83%), the random-effects model was used to pool the results in the analysis of the effects of DCR. The data and forest plot of our study showed no statistically significant difference in DCR between HAIC and sorafenib

Study or subgroup	HAIC Events	Total	Sorafenib Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Hiramine 2011	31	45	13	20	15.6	1.19 (0.39, 3.63)
Jeong 2012	8	21	7	20	14.4	1.14 (0.32, 4.08)
Kondo 2015	15	44	44	83	18.1	0.46 (0.21, 0.98)
Song 2015	45	50	27	60	16.0	11.00 (3.83, 31.58)
Terashima 2017	94	139	26	51	18.8	2.01 (1.04, 3.86)
Yang 2017	25	54	9	41	17.0	3.07 (1.23, 3.63)
Total (95% CI)		**353**		**275**	**100**	**1.84 (0.78, 4.36)**
Total events	218		126			

Heterogeneity: τ^2=0.91; χ^2=26.21, *df*=5 (*P*<0.0001); I^2=81%
Test for overall effect: *Z*=1.39 (*P*=0.16)

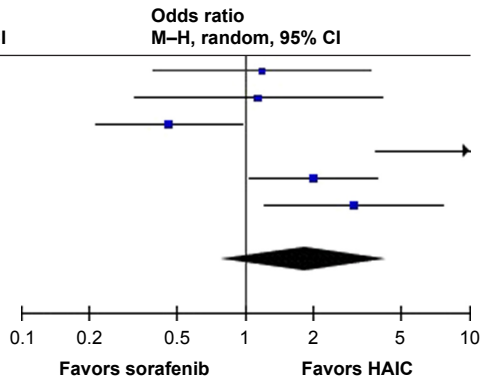


Figure 4 HAIC vs sorafenib for BCLC stage C HCCs in terms of DCR.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; DCR, disease control rate; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma.

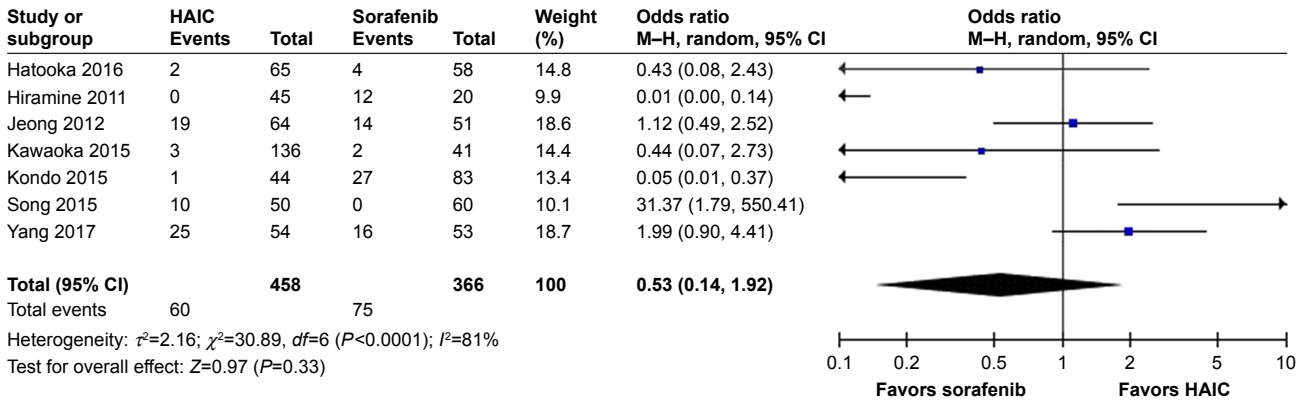


Figure 5 HAIC vs sorafenib for BCLC stage C HCCs in terms of SAE.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; SAE, serious adverse event.

(OR 1.84, 95% CI_{DCR}: [0.78–4.36], P_{DCR} =0.16) (Figure 4 and Table 3).

Serious adverse events

In this meta-analysis, the incidence of serious adverse events (SAEs) of HAIC and sorafenib in the treatment of patients with BCLC stage C HCC was analyzed and compared. Here, the SAEs were defined as Common Terminology Criteria for Adverse Events grade 3/4 adverse events or adverse events that lead to discontinuation of treatment with HAIC or sorafenib. Seven studies reported the comparative data on SAEs of HAIC and sorafenib for patients with BCLC stage C HCC. From the results of tests for heterogeneity between trials (χ^2_{SAE} =30.89, P_{SAE} ≤0.0001, I^2_{SAE} =81%), the random-effects model was used to pool the results in the analysis of the effects of SAEs. The data and forest plot of our study showed no statistically significant difference in SAEs between HAIC and sorafenib (OR 0.53, 95% CI_{SAE}: [0.14–1.92], P_{SAE} =0.33) (Figure 5 and Table 3).

Assessment of publication bias

In this study, the risk of publication bias was assessed by visual inspection of the symmetry level of funnel plot. The fixed-effects model was used to pool the results in the analysis of the effects of CR, PR, OR, and 1-, 2-, and 3-year OSRs. The results of our meta-analysis revealed that the symmetry level of the funnel plots was high. This suggested that there was no serious publication bias in the trials included in this study (Figure 6).

Discussion

The BCLC staging classification is one of the most widely used guidelines for the clinical treatment of HCC in many countries. According to the BCLC staging classification, BCLC stage C HCC is suggested as the advanced-stage HCC, and sorafenib is considered as the primary treatment option for HCCs of that stage. However, because of the adverse effects, moderate efficacy, and high cost of sorafenib, its application is limited. Thus, the clinical benefits of sorafenib are still not satisfactory. To improve the prognosis of patients with advanced HCC, alternative treatment strategies are being investigated. In the recent years, HAIC was proved as an effective and safe therapy for advanced HCC. Previous studies had reported that HAIC was associated with better efficacy than sorafenib for patients with advanced HCCs.[8,12–14] However, some other studies had reported conflicting results.[10,11,15] Meta-analysis is a method that combines data from all eligible studies, and has the advantages of reducing random error, obtaining more precise estimates, and defining the effect of clinical interventions more precisely.[18,19] Hence, meta-analysis is an eligible method to resolve such conflicts. In this study, the OSR, tumor response rate, and the incidence of SAEs were analyzed and compared. The results of this study showed that HAIC was associated with significantly better OSR and tumor response rate in comparison with sorafenib. This indicated that HAIC was superior to sorafenib in the treatment of patients with advanced HCCs.

In this meta-analysis, epirubicin-, cisplatin-, or 5-fluorouracil-based HAIC was performed by the transcatheter method, and the chemotherapeutic agent was delivered through the hepatic arterial infusion chemoport. From previous studies and our clinical practice, we found that the mechanisms by which HAIC affects HCCs might include the inhibition of angiogenesis, stimulation of immunity, and direct inhibition of tumor cell proliferation.[8,14,20–22] Inhibition of angiogenesis is the most important mechanism. During HAIC treatment, the angiogenesis of tumor cells can be inhibited by direct destruction and inhibition of proliferation of endothelial cells. Further, the expression

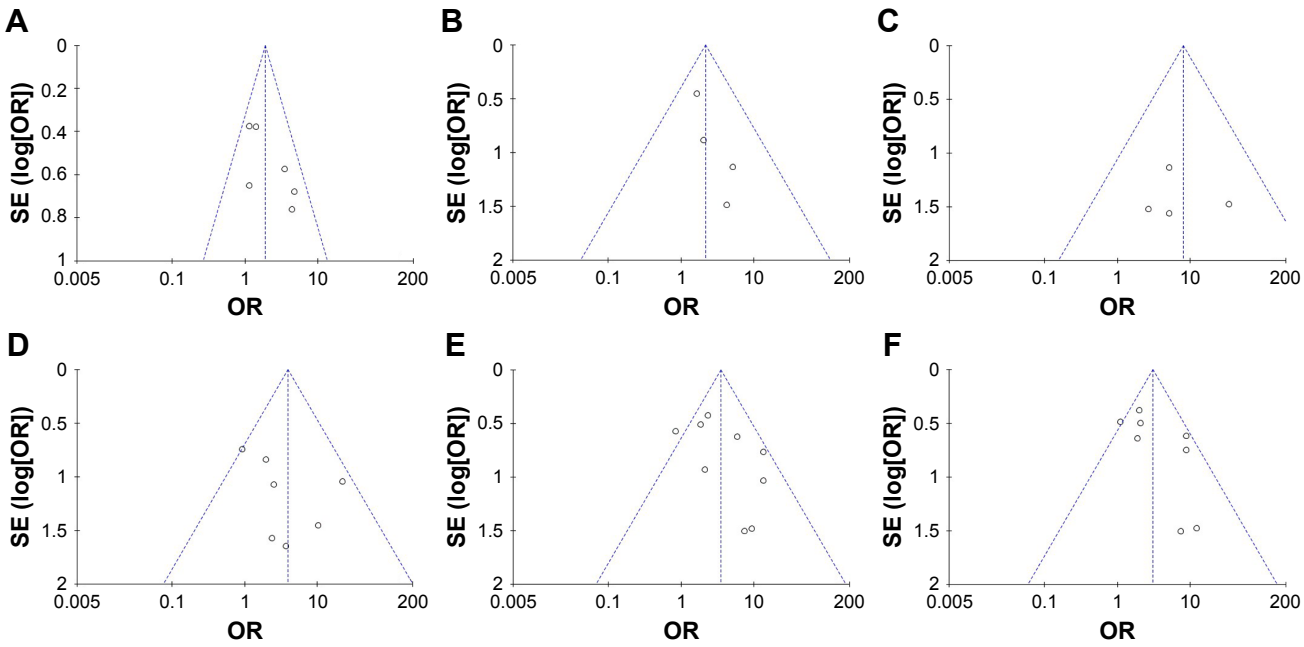


Figure 6 Funnel plots in the analysis of the effects of OSR and tumor response rate.
Notes: (**A**) Funnel plot of 1-year OSR. (**B**) Funnel plot of 2-year OSR. (**C**) Funnel plot of 3-year OSR. (**D**) Funnel plot of CR rate. (**E**) Funnel plot of PR rate. (**F**) Funnel plot of ORR.
Abbreviations: CR, complete response; OSR, overall survival rate; ORR, objective response rate; PR, partial response.

levels of endogenous antiangiogenic factors and endogenous angiogenic factors were reported to be upregulated and downregulated, respectively.[23,24] Recently, the reduction in endothelial progenitor cell mobilization and stimulation of immunity were also investigated as mechanisms of HAIC for HCC.[23,24]

PVTT is an important cause of tumor spread, portal hypertension, and deterioration of liver function, leading to variceal rupture, intractable ascites, and hepatic encephalopathy. Patients with advanced HCC and PVTT were associated with poor prognosis, with a median survival time ranging from 2.7 to 4 months. As the first-line treatment option suggested by the BCLC staging system, sorafenib can prolong the survival of patients with PVTT from 6.5 to 8 months.[25,26] However, the survival benefits and treatment responses of sorafenib in patients with advanced HCCs with PVTT were modest. Thus, the availability of sorafenib is limited. In recent years, surgical resection or transarterial chemoembolization in selected patients, HAIC, external radiation, I^{125} seed implantation, radioembolization, and combination therapies have been performed as alternative treatment options for patients with advanced HCCs with PVTT.[25–27] Compared to sorafenib, HAIC was proved to be associated with more favorable clinical efficacy in terms of overall survival and tumor response in the treatment of patients with PVTT. In previous studies in which HAIC was performed for HCC with PVTT, the ORR and DCR ranged from 33% to 52.6% and 47.1% to 77%, respectively.[27–30] Two randomized controlled trials (RCTs) showed that ORR was 2%–3%, and the DCR was 57.3%–73%.[6,7] Hence, from the data of previous studies and our study, we found that the ORR of HAIC was significantly higher than that of sorafenib, whereas the DCR of the two treatments appeared to be identical. In this study, the meta-analysis data showed that HAIC was associated with significantly better 1-, 2-, and 3-year OS rates and CR, PR, and ORR in comparison with sorafenib. This indicated that the results of our meta-analysis study were reliable.

This study is the first meta-analysis designed to comprehensively compare the clinical efficacy and safety of HAIC with those of sorafenib in the treatment of patients with HCCs of BCLC stage C. In this study, the OSR, tumor response rate, DCR, and the incidence of SAEs were compared and analyzed. The risk of publication bias in the included studies was assessed by the visual inspection of the symmetry level of the funnel plot.[31,32] The results of our study showed that the level of symmetry of the funnel plot was high. This suggested that there was no serious publication bias in the trials included in this meta-analysis. Thus, we can see that the studies included in the meta-analysis are strong evidence to support our results.

Finally, the potential limitations of this study must be mentioned. First, there were limited available and applicable

RCTs comparing the effectiveness and adverse event of HAIC and sorafenib for the treatment of advanced HCCs in the last several years. However, although a meta-analysis has traditionally been applied and is best confined to RCTs, meta-analytical techniques using non-RCTs might be a valid method in clinical settings in which either the number or the sample size of the RCTs is insufficient.[33] In the future, more RCTs should be conducted to provide further evidence. Second, because all included studies in this meta-analysis were from Asian countries, data bias caused by the source of patients might be present. More high-quality RCTs from other continents and countries are needed to provide more data for future research.

Conclusion

Our meta-analysis showed that HAIC was associated with better clinical efficacy and reliable safety in comparison with sorafenib for patients with BCLC stage C HCCs. Therefore, HAIC can be considered as an alternative treatment option for advanced HCCs.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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