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Adjuvant transarterial chemoembolization improves survival outcomes in hepatocellular carcinoma with microvascular invasion: A systematic review and meta-analysis

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ABSTRACT

Background: The benefits of adjuvant transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) patients with microvascular invasion (MVI) remain controversial. We compared the efficacy and safety of adjuvant TACE and hepatic resection (HR) alone for HCC patients with MVI.
Methods: The PubMed, EMBASE, Cochrane Library, VIP, Wan Fang, and Sino Med databases were systematically searched to compare adjuvant TACE and HR alone for the treatment of HCC with MVI from inception to January 1, 2019. The study outcomes, including overall survival (OS) and disease-free survival (DFS), were extracted independently by two authors.
Results: 12 trials involving 2190 patients were evaluated. A meta-analysis of 11 studies suggested that the 1-, 3-, and 5-year overall survival (OS) rates ($OR = 0.33$, $P < 0.001$; $OR = 0.49$, $P < 0.001$; and $OR = 0.59$, $P < 0.01$; respectively), favored adjuvant TACE over HR alone. 11 studies were included in the meta-analysis of DFS, and adjuvant TACE showed better 1-, 3-, and 5-DFS ($OR = 0.45$, $P < 0.001$; $OR = 0.50$, $P < 0.001$; and $OR = 0.58$, $P < 0.001$; respectively) compared to HR alone. Subgroup analysis demonstrated that adjuvant TACE could benefit HCC patients with MVI with tumor diameter >5 cm or multinodular tumors.
Conclusion: Adjuvant TACE may improve OS and DFS for HCC patients with MVI compared to HR alone and should be recommended for selected HCC patients with MVI. However, these results need to be validated through further high-quality clinical studies.
Lay summary: The benefits of adjuvant TACE in HCC patients with microvascular invasion remain controversial. Twelve studies involving 2190 patients were include in our meta-analysis. Adjuvant TACE may improve OS and DFS for HCC patients with MVI compared to HR alone and should be recommended for selected HCC patients with MVI.

Authors contributions

Conception and design: Shu-Qun Cheng, Zhen-Hua Chen.

Financial support: Shu-Qun Cheng.

Provision of study materials or patients: Kang Wang, Wang Hang, Collection and assembly of data: Zhen-Hua Chen, Xiu-Ping Zhang, Teng-Fei Zhou, Zong-Tao Chai, Wei-Xing Guo.

Data analysis and interpretation: Zhen-Hua Chen, Xiu-Ping Zhang, Teng-Fei Zhou, Jie Shi.

Manuscript writing: Zhen-Hua Chen.

Final approval of the manuscript: All authors.

Background

Hepatocellular carcinoma (HCC) is the fifth most common cancer and third leading cause of cancer death worldwide with dismal

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outcomes [1]. Currently, hepatic resection and liver transplantation remain the potential curative treatment modalities for HCC with preserved liver function [2]. However, the postoperative 5-year recurrence rate is as high as 70%–80%, leading to unsatisfactory long-term overall survival outcomes [3, 4]. Among all the various risk factors related to the recurrence of HCC, MVI is the most important risk factor that is significantly associated with the early postoperative recurrence of HCC and is further confirmed as an independent predictor of both overall and disease-free survival after liver resection [5–7]. According to "A Guideline of Standardized Pathological Diagnosis of Primary Liver Cancer (2015 edition)"[8], MVI was described as "a cancer cell nest with >50 cells in the endothelial vascular lumen under microscopy".

The incidence of MVI was reported to be between 15% and 57.1% in surgical specimens obtained after liver resection and transplantation [5]. Pawlik et al. [9] demonstrated a significant risk of the presence of MVI even in patients with small-sized HCC based on multicentric research of 1073 patients, with MVI rates of 25%, 40%, 55%, and 63% in patients with HCC < 3 cm, 3–5 cm, 5–6.5 cm, and >6.5 cm, respectively. Nevertheless, there is still no recommended postoperative treatment strategy for HCC patients with MVI, rendering the postoperative management of these patients a major challenge.

Currently, our group(10) has demonstrated the effectiveness of adjuvant TACE in a research of 322 HCC patients with MVI. In addition, some studies [11–13] have suggested that adjuvant TACE might benefit HCC patients with MVI as a promising postoperative therapy modality. Nevertheless Wang et al. [12] concluded that the DFS and OS rates between the adjuvant TACE and HR alone group were not significantly different. Therefore, it still remains unclear whether the evidence is scientifically adequate to recommend adjuvant TACE as an initial treatment for HCC patients with MVI. Unfortunately, there is no reported systematic review or meta-analysis resolving the disagreement.

Here, we present the first systematic review and meta-analysis exploring the efficacy and safety of adjuvant TACE for HCC patients with MVI.

Methods

Study protocol

This meta-analysis was performed according to the Cochrane Collaboration recommendations [14]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. A systematic search of PubMed, Cochrane Library, EMBASE, Web of Science, Chinese National Knowledge Infrastructure (CNKI), VIP, Wan Fang, and Sino Med databases was performed. Meanwhile, we comprehensively searched ClinicalTrials.gov to obtain the available outcomes of ongoing studies exploring the effectiveness of adjuvant TACE for HCC with MVI. There were no limitations on language, and the search was updated on January 1, 2019. The following search terms were used: "postoperative" or "after surgery" or "after hepatic resection" or "after surgical resection" or "after liver resection" or "adjuvant" AND "transcatheter arterial chemoembolization" or "TA(C)E" or "transarterial chemoembolization" or "chemoemboli*" or "emboli*" AND "(liver or hepatic or hepatocellular or hepatocellular) and (carcinom* OR cancer OR neoplasm* OR malign* OR tumor* OR tumour*)" or "HCC" or "hepatoma*" AND "microvascular invasion" or "mVI" or "MVI". All abstracts were independently screened by Chen ZH and Zhang XP, and full-text reports of the included papers were obtained for another screen.

Selection criteria

This meta-analysis focused on exploring the efficacy and safety of adjuvant TACE in the treatment of HCC patients with MVI. Therefore, only comparative analyses concerning the clinical value of adjuvant TACE versus HR alone for HCC patients with MVI were included in the study.

The inclusion criteria were as follows [1]: clinical trials comparing the therapeutic effect of adjuvant TACE with HR alone for HCC patients with MVI [2]; relevant degree papers, conference summaries, cohort studies, and some ongoing randomized controlled trials (RCTs) [3]; sufficient data available such as the baseline characteristics and 1-, 3-, and 5-year overall survival (OS) and disease-free survival (DFS).

The exclusion criteria were as follows [1]: macrovascular invasion, such as macroscopic portal vein tumor thrombus (m-PVTT), macroscopic hepatic vein tumor thrombus (m-HVTT), or bile duct tumor thrombus (BDTT) [2]; patients receiving treatments other than adjuvant TACE or HR alone [3]; case reports, narrative reviews, letters, comments, or studies unrelated to the topic of interest [4]; studies based on overlapping cohorts derived from the same center.

Data extraction

All the data were extracted and assessed by 2 independent authors (Chen ZH and Zhang XP). In the case of disagreement, a third author (Zhou TF) was invited to participate in resolving disagreements through discussion and consensus.

Data extraction was performed using a standardized form:

1. Basic data included the author names, year of publication, study design, sex, number of patients and baseline characteristics
2. Basic data from the patients with HCC, including therapy outcomes for HCC with MVI, and the outcomes of patients undergoing HR or adjuvant TACE for MVI

Some data such as study methods and OS and DFS outcomes in different years were calculated.

Quality assessment

The risk of bias in RCTs was assessed following Cochrane recommendations [14], considering random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. We used the modified Newcastle-Ottawa Scale (NOS) to assess the methodological quality of nonrandomized controlled trials (NRCTs) [16]. This score assesses studies according to selection of patients in the exposed and in the non-exposed group, comparability of the two groups and outcome of the single studies. A study can be rated 0–9 stars based on these criteria, while six stars or above was considered high quality in previous studies and was included in this review.

Statistical analysis

All the included data were presented as OR estimates with 95% CIs for the outcomes such as the OS and DFS rates. Some OS and DFS data were obtained from survival curves. According to the suggestions of the Cochrane collaboration, we quantified the degree of heterogeneity using the I2 statistic, which represents the percentage of the total variability across studies that is due to heterogeneity, with significant heterogeneity indicated at $P < 0.1$ and an I2-index >50% [17]. The estimates were pooled with a fixed-effects model if no significant heterogeneity was identified; otherwise, a random-effects model was used for estimates with heterogeneity. Subgroup analyses of outcomes were performed to reveal the potential factors which might be most beneficial from the adjuvant TACE therapy. Sensitivity analyses were performed to determine the stability of the overall treatment effects. Cumulative meta-analyses were performed to assess the stabilizing of the effect sizes. Statistical significance was taken as 2-sided ($P < 0.05$). Publication bias was assessed using funnel plots, Begg's test and Egger's test [18], with the effect of bias assessed using the fail-safe number method. For all analyses, statistical analyses were performed with the software programs Review Manager (Version 5.3, Cochrane Collaboration, Copenhagen, Denmark), and Stata (Version 12.0, Stata Corp LP, College Station, TX).

Results

Study selection and quality assessment

Based on our search strategy, 426 relevant studies were identified, among which 277 duplicates were excluded. A total of 127 articles were excluded because they were animal studies, laboratory projects, abstracts, or case reports. 10 studies were excluded for not meeting the requirements, such as combining with additional therapies and a lack of basic data (Fig. 1). After careful selection, 12 retrospectively, prospectively, or Randomized controlled studies [10–13, 19–26] meeting the inclusion standards and involving 2190 patients were eligible for inclusion in the systematic review and meta-analysis. The risk of bias in one RCT study was shown in Fig. S1. Then, the quality of the retrospectively and prospectively controlled studies was assessed. All studies achieved 6 to 8 stars in study quality assessment on a scale of 0–9 (Table 1).

Patient characteristics

The baseline characteristics of the patients in the included studies are presented in Table 1. The percentage of studies that described the mean age of their patients was 100% (12 of 12), that for the sex of patients was 91.7% (11 of 12), that for the tumor size was 100% (12 of 12), that for the tumor number was 83.3% (10 of 12), that for the Child-Pugh score was 66.7% (8 of 12), and that for the virology status, such as HBV, was 75% (9 of 12). In total, 2190 HCC patients with MVI were included, among whom 1226 received HR alone and 968 received adjuvant TACE as an initial treatment. The 12 studies were published from 2010 to 2018. In our study, we found that there were more men than women, more single tumors, and mostly Child-Pugh A liver function. Additional details of the patients' characteristics are listed in Table 1. The definition of MVI in all the included studies was similar as tumor cells in a portal vein, hepatic vein, or large capsular vessel of the surrounding hepatic tissue lined by endothelium that was visible only on microscopy (Table S1).

Treatment regimens

HR alone and adjuvant TACE were performed on patients in the two groups. The description of the operative procedure for HCC with MVI was similar in all the involved studies and included en bloc resection and partial hepatectomy. All surgical procedures were performed in accordance with our previous study [27]. R0 resection was reported in 10 studies.

The technique of TACE procedure was similar in all the included studies. TACE was conducted using the Seldinger technique. The arterial catheter was inserted into an appropriate hepatic artery through femoral artery, and a mixed emulsion of chemoembolization drugs and was infused into the remnant liver by the catheter without any selectivity intent. The courses of adjuvant TACE was reported in 9 studies and varied from 1 to 3 courses. The majority of TACE was performed 1–3 months after the hepatic resection. The most commonly used chemoembolization drugs were adriamycin (8 of 12), 5-fluorouracil (4 of 12), cisplatin (2 of 12), and oxaliplatin (3 of 12). Most studies used lipiodol alone for embolization (11 of 12), while only one study used lipiodol and gelatin sponge. The dosage of lipiodol ranged from 2 to 10 ml. Additional details are recorded in Table 2.

Overall survival

The median OS was reported in seven of the eleven included studies for the meta-analysis of OS (Table S2). For all 2190 HCC patients with MVI included, the median OS ranged from 22 to 48.4 months in the HR group and from 25 to 83 months in the adjuvant TACE group. Based on the preliminary data described in Table S1, the adjuvant TACE group showed better 1-, 2-, 3-, and 5-year OS rates than the HR-alone group.

Ten studies with contrasting results were included in the meta-analysis of the 1-, 3-, and 5-year OS rates and the corresponding ORs for OS. As shown in Fig. 2, the 1-year OS rates favored postoperative TACE rather than HR alone ($OR = 0.33$, 95% $CI = 0.26–0.43$, $I2 = 0\%$, $P < 0.001$; Fig. 2A) in all the included studies, with 929 patients undergoing postoperative TACE and 1187 patients undergoing HR, with a similar trend in the 3-year OS rates ($OR = 0.49$, 95% $CI = 0.41–0.59$, $I2 = 0\%$, $P < 0.001$; Fig. 2B). Additionally, the 5-year OS rates favored postoperative TACE rather than HR alone ($OR = 0.59$, 95% $CI = 0.48–0.73$, $I2 = 0\%$, $P < 0.001$; Fig. 2C) in 9 of the included studies, with 838 patients undergoing postoperative TACE and 1078 patients undergoing HR. A cumulative meta-analysis of 1-, 3-, and 5-year OS rates showed that the significant difference in favor of adjuvant TACE was first observed in the second study in 2012, and as more studies were added, the CI narrowed and the effect size became stable (Fig. 2D–F). As shown in Fig. 2, the meta-analysis showed that the HCC patients with MVI who underwent adjuvant TACE had significantly longer survival than those who underwent HR alone.

Disease-free survival

For all the included 2190 HCC patients with MVI, the median DFS ranged from 9 to 43 months in the HR group and from 7 to 37 months in the adjuvant TACE group as reported in 10 studies [10–12, 19, 21–26]. Based on the preliminary data described in Table S3, the 1-, 2-, 3-, and 5-year DFS rates were better for the patients receiving adjuvant TACE than for those receiving HR alone.

Eleven studies were included in the meta-analysis of the 1-, 3-, and 5-year DFS rates and corresponding ORs. As shown in Fig. 3, the 1-year DFS rates favored postoperative TACE rather than HR alone ($OR = 0.45$, 95% $CI = 0.38–0.54$, $I2 = 0\%$, $P < 0.001$; Fig. 3A) in all the included studies, with 956 patients undergoing adjuvant TACE and 1209 patients undergoing HR. The 3-year DFS rates ($OR = 0.50$, 95% $CI = 0.41–0.60$, $I2 = 0\%$, $P < 0.001$; Fig. 3B) were reported in 10 of the included studies [10–12,19,21–26] with 916 patients undergoing adjuvant TACE and 1170 patients undergoing HR alone, with a similar trend in the 5-year DFS rates ($OR = 0.58$, 95% $CI = 0.46–0.73$, $I2 = 8.9\%$, $P < 0.001$; Fig. 3C). A cumulative meta-analysis of 1-, 3-, and 5-year DFS rates showed that the significant difference in favor of adjuvant TACE was first observed in the second study in 2012, and as more studies were added, the CI narrowed and the effect size became stable (Fig. 3D–F). As shown in Fig. 3, the meta-analysis of ORs for DFS indicated that DFS was significantly greater in the adjuvant TACE group than in the HR-alone group.

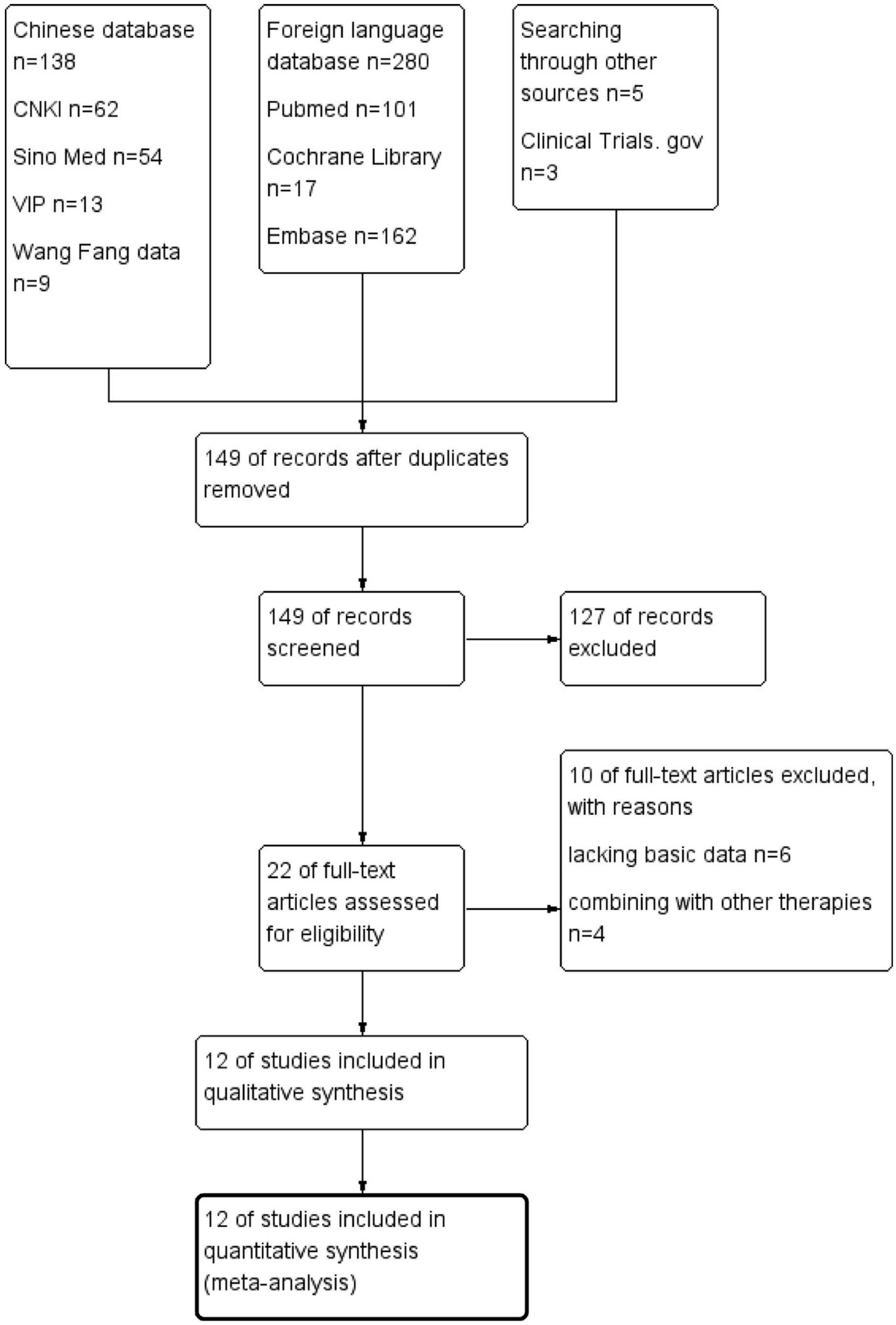

Fig. 1. PRISMA flow diagram of the process for the identification of eligible studies. CNKI: Chinese National Knowledge Infrastructure; Sino Med: Chinese Biological Medical Literature Database; VIP: Chongqing VIP database for Chinese Technical Periodicals; Wan Fang: Wan Fang Database.

Subgroup analysis

In the subgroup analysis for HCC with tumor diameter >5 cm or multinodular tumors, 4 studies with contrasting results were included in the meta-analysis of the 1-, 3-, and 5-year OS and DFS rates. As shown in Fig. 4, the 1-, 3-, and 5-year OS rates were significantly better in the adjuvant TACE group than the HR group ($OR = 0.29$, $P < 0.001$; Fig. 4A; $OR = 0.45$, $P < 0.001$; Fig. 4B; $OR = 0.38$, $P = 0.001$; Fig. 4C, respectively). Similarly, the adjuvant TACE group had better 1-, 3-, and 5-year DFS rates than the HR group ($OR = 0.42$, $P < 0.001$; Fig. 4D; $OR = 0.47$, $P < 0.001$; Fig. 4E; $OR = 0.42$, $P = 0.013$; Fig. 4F, respectively).

In the subgroup analysis in 4 high-quality studies (prospective, PSM, or RCT), the 1- and 3-year OS rates were significantly better in the adjuvant TACE group than the HR group ($OR = 0.37$, $P < 0.001$; Fig. S2A; $OR = 0.49$, $P < 0.001$; Fig. S2B; respectively). There was no significant difference in two groups regarding 5-year OS ($OR = 0.70$, $P = 0.124$; Fig. S2C). In addition, the adjuvant TACE group had better 1-, 3-, and 5-year DFS rates than the HR group ($OR = 0.48$, $P < 0.001$; Fig. S2D; $OR = 0.53$, $P < 0.001$; Fig. S2E; $OR = 0.36$, $P < 0.001$; Fig. S2F, respectively).

Table 1
Basic characteristics of patients.

Study (year)	**Study type (NOS score)[a]**	**Treatment (patients number)**	AGE	Sex(M/F)	**Tumor size(cm) (< 5/ ≥ 5)**	Tumor **Number (S/M)**	Child-Pugh (A/B/C)	Virology HBV/Other	Cirrhosis (Yes/No)	Total bilirubin level (μmol/L)	**Serum albumin level (g/L)**	AFP (mg/L) (<400/≥400)
Sun 2015	R (2004–2013) ********	HR (185)	49.91 ± 0.7240	167/18	6.993 ± 0.2898	NA	182/3/0	163/22	109/76	130/55(≤18.8/>18.8)	180/5(>34/≤34)	94/91
		HR + TACE (137)	48.88 ± 0.8695	120/17	6.511 ± 0.2682	NA	135/2/0	121/16	88/49	98/39(≤18.8/>18.8)	132/5(>34/≤34)	79/58
Ye 2017	R (2012–2015) *******	HR (174)	140/34 (≤60/>60)	150/24	76/98	137/37	172/2/0	156/18	143/31	11.2 (2.8–30.9)	NA	89/85
		HR + TACE (86)	73/13 (≤60/>60)	75/11	41/45	73/13	84/2/0	72/14	72/14	11.75 (5.1–33.1)	NA	49/37
Wang 2017	R (2008–2015) *******	HR (50)	57.22 ± 11.14	45/5	5.71 ± 2.60	46/4	50/0/0	NA	2/48	12.50 ± 5.97	NA	32/18
		HR + TACE (42)	51.38 ± 10.89	34/8	6.15 ± 3.65	38/4	42/0/0	NA	4/38	12.55 ± 5.23	NA	25/17
Li 2012	R (2005–2010) *******	HR (41)	50.3 ± 8.3	36/5	22/19	32/9	NA	35/6	NA	21/20(≤18.8/>18.8)	NA	23/18
		HR + TACE (35)	49.4 ± 9.3	29/6	19/16	28/7	NA	29/6	NA	20/15(≤18.8/>18.8)	NA	17/18
Liu 2017	R (2000–2013) *******	HR (45)	51 ± 7.23	NA	6.5 ± 2.41	NA	41/4/0	41/4	14/31	NA	NA	16/29
		HR + TACE (62)	49 ± 7.87	NA	6.3 ± 2.27	NA	53/9/0	51/11	23/39	43/19(≤20/>20)	NA	23/39
Qi 2016	R (2012–2013) ******	HR (39)	51.3 ± 10.8	34/5	8.2 ± 4.4	27/12	NA	NA	NA	13.2 ± 5.6	42.5 ± 4.8	429.3 ± 526.3
		HR + TACE (39)	50.2 ± 9.5	33/6	8.3 ± 4.2	28/11	NA	NA	NA	13.2 ± 6.1	42.8 ± 4.2	526.8 ± 563.6
Liu X 2012	R (1998–2005) ********	HR (215)	113/102 (≤50/>50)	191/24	90/125	160/50	NA	27/188	78/137	NA	NA	124/91
		HR + TACE (153)	88/65 (≤50/>50)	138/15	76/77	129/24	NA	21/132	43/110	NA	NA	91/62
Liu X 2012	P (2006–2008) ********	HR (92)	43/49 (≤50/>50)	86/6	50/42	68/24	NA	12/78	32/60	NA	NA	60/32
		HR + TACE (94)	47/47 (≤50/>50)	82/12	67/27	69/25	NA	10/83	36/58	NA	NA	58/36
Yang 2016	R (2011–2016) ******	HR (17)	7/10 (≤50/>50)	15/2	11/6	15/2	16/1/0	12/5	NA	NA	NA	12/5
		HR + TACE (12)	5/7 (≤50/>50)	12/0	4/8	8/4	11/1/0	9/3	NA	NA	NA	4/8
Qi 2018	P (2012–2014) ********	HR (109)	67/42 (≤50/>50)	93/16	34/75	84/25	NA	96/13	89/20	90/19 (≤17.1/>17.1)	100/9(>35/≤35)	59/50
		HR + TACE (91)	52/39 (≤50/>50)	78/13	20/71	68/23	NA	77/14	79/12	74/17 (≤17.1/>17.1)	88/3(>35/≤35)	47/44
Wang 2018	PSM (2004–2015) ********	HR (57)	56 ± 10	51/6	6 (2–18)	46/11	54/3/0	47/10	46/11	15 (6–33)	43 ± 3	23/34(<200/≥200)
		HR + TACE (57)	55 ± 11	47/10	6 (2–14)	46/11	54/3/0	47/10	49/8	15 (6–37)	43 ± 5	25/32(<200/≥200)
Wei 2018	RCT (2016–2018)	HR (118)	48.5 (18–74)	106/12	97/21 (≤10/>10)	118/0	116/2/0	101/17	42/76	17.3 ± 24.6	41.6 ± 3.4	36/82(<250/≥250)
		HR + TACE (116)	44.0 (18–75)	106/10	82/34 (≤10/>10)	116/0	116/0/0	94/22	50/66	14.4 ± 5.8	41.4 ± 5.7	37/79(<250/≥250)
Wang H 2018	R (2010–2014) *******	HR (84)	54.49 ± 10.18	76/8	3.83 ± 1.09	0/84	82/2/0	NA	60/24	15.16 ± 6.21	42.19 ± 3.48	367.45 ± 474.58
		HR + TACE (44)	52.07 ± 7.24	42/2	3.84 ± 1.27	0/42	43/1/0	NA	21/23	13.53 ± 4.74	42.73 ± 3.85	357.00 ± 444.12

Note: [a]The retrospective studies were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS).
R (1996–1998): Retrospective study and the time of patients included in case-control cohort, P (2012–2014): Prospective study and the time of patients included in case-control cohort, NA: Not applicable, TACE: Transarterial chemoembolization, HR: Hepatic resection.

Table 2
Procedures of postoperative adjuvant TACE and HR alone therapy.

Study	TACE			HR	
	Courses	Chemotherapeutic agents	Embolic agents	Methods and procedure	R0 resection
Sun 2015	1 course 4 weeks postoperation	Adriamycin 10 mg pirarubicin or pharmorubicin 20–40 mg	Lipiodol 2–10 ml	En-bloc resection, partial hepatectomy or hemihepatectomy	Yes
Ye 2017	3 courses 1,3,6 months postoperation	Lobaplatin 50 mg and Raltitrexed 4 mg	Lipiodol 3–5 ml	En-bloc resection, partial hepatectomy or hemihepatectomy	Yes
Wang 2017	1 course 2months postoperation	Adriamycin 20–30 mg	Lipiodol 5–10 ml Gelfoam (2–3-mm strips)	En-bloc resection, partial hepatectomy or hemihepatectomy	Yes
Li 2012	NA	Oxaliplatin 50 mg and Adriamycin 30 mg	Lipiodol 5–10 ml	En-bloc resection, partial hepatectomy or hemihepatectomy	NA
Liu 2017	NA	5-fluorouracil 0.5–1 g Adriamycin 20–40 mg Carboplatin 100–200 mg	Lipiodol 4–10 ml	En-bloc resection, partial hepatectomy	Yes
Qi 2016	1 course 2 months postoperation	Oxaliplatin 50 mg and Adriamycin 30 mg	Lipiodol 3–5 mL	En-bloc resection, partial hepatectomy	Yes
Liu X 2012	2 coursed 1,3 months postoperation	5-fluorouracil(250–1000 mg/m^2) Cisplatin(40 mg/m^2) Mitomycin(10 mg/m^2) Hydroxycamptothecin 10–15 mg Pirarubicin 20 mg	Lipiodol 2–8 ml	En-bloc resection, partial hepatectomy or hemihepatectomy	Yes
Yang 2016	1 course 2 months postoperation	5-fluorouracil(250–1000 mg/m^2) Cisplatin(40 mg/m^2) Mitomycin C(10 mg/m^2) Pirarubicin (20 mg/m^2)	Lipiodol 2–8 ml	En-bloc resection, partial hepatectomy or hemihepatectomy	Yes
Qi 2018	1course 1 month postoperation	oxaliplatin or lobaplatin (25–100 mg) pirarubicin or pharmorubicin (10–50 mg)	Lipiodol 2–10 ml	En-bloc resection, partial hepatectomy	Yes
Wang 2018	1-2 courses 1 or 2 months postoperation	fluorouracil (750 mg) epirubicin (40 mg) pharmorubici (40 mg)	Lipiodol 5–10 ml	En-bloc resection, partial hepatectomy	NA
Wei 2018	1-2 courses 4–6 weeks postoperation	carboplatin (200 mg/m^2) mitomycin (6 mg/m^2) epirubicin (40 mg/m^2)	Lipiodol 4–5 ml	En-bloc resection, partial hepatectomy or hemihepatectomy	Yes
Wang H 2018	1–3 months postoperation	Doxorubicin hydrochloride (10 mg) pirarubicin (THP), or pharmorubicin (20–40 mg)	Lipiodol 5–10 ml	Curative hepatic resection	Yes

Adverse effects

Most studies reported no serious side effects. The most common adverse effects were those associated with adjuvant TACE: fever, mild nausea and mild abdominal pain, and were usually self-limited. Two studies reported the grade 3-4 adverse effects(10, 24). The grade 3-4 adverse effects were not statistically different between the two treatment modalities (OR = 1.57, 95% CI = 0.41–6.10, I2 = 74.8%, P = 0.512; Fig. S3).

Risk factors of adjuvant TACE and HR alone in HCC patients with MVI.

It remains unknown whether potential correlations exist between OS and included variables. Thus, risk factors such as gender, age, and tumor characteristics were analyzed regarding the long-term OS rates for MVI patients in 8 studies [10–12, 21–23, 25, 26]. In the univariate analysis, cirrhosis, tumor size >5 cm, Child-Pugh B status, multinodular tumor status, HR alone, AFP level ≥400 ng/mL, and MVI classification were found to predict poor OS across the 8 articles. Multivariate Cox proportional hazards regression analysis of all 8 studies indicated that the adjuvant TACE may be a positive prognostic factor for OS.

Regarding the risk factors between DFS and selected variables, 8 studies [10–12, 20, 21, 23, 25, 26] performed univariate and multivariate analyses. Blood loss, tumor size, envelope invasion, initial modality of treatment, AST level, AFP level, and MVI classification were reported to be associated with the DFS among the 8 studies. Similarly, the multivariate Cox proportional hazards regression analysis revealed the adjuvant TACE as a positive prognostic factor for DFS.

Publication bias and sensitivity analysis

The funnel plots of 1-, 3-, and 5-year OS and DFS for HR and adjuvant TACE are shown in Fig. S4 and visual inspection of funnel plots suggested a symmetric distribution of main studies. Begg and Egger tests confirmed there was no significant publication bias (Fig S5). A sensitivity analysis was performed by excluding each study to determine the stability of the overall treatment effects. This did not influence the results (Fig. S6).

Discussion

To date, our study is the first systematic review and meta-analysis to compare OS and DFS in HCC patients with MVI who received adjuvant TACE and HR alone that offers an objective suggestion to select appropriate clinical treatment, which may be of great significance to resolve the disagreement to choose adjuvant TACE. Additionally, this study is the first comprehensive research to focus on exploring the efficacy and safety of adjuvant TACE for HCC patients only with MVI. Furthermore, we firstly reviewed 12 high-quality researches with 2190 patients with MVI included, which was the largest sample size to explore the efficacy and safety of adjuvant TACE for these patients. Despite all the 12 studies are conducted in China, we have confirmed the high quality of the studies by methodological quality and publication bias test. In addition, China has great advantage in conducting the research in HCC patients with MVI due to the high incidence rate of HCC.

Regarding HCC patients with MVI in our included studies, the research results of Ye et al. [11] and Li et al. [13] favored adjuvant TACE compared with HR alone in accordance with the long-term OS

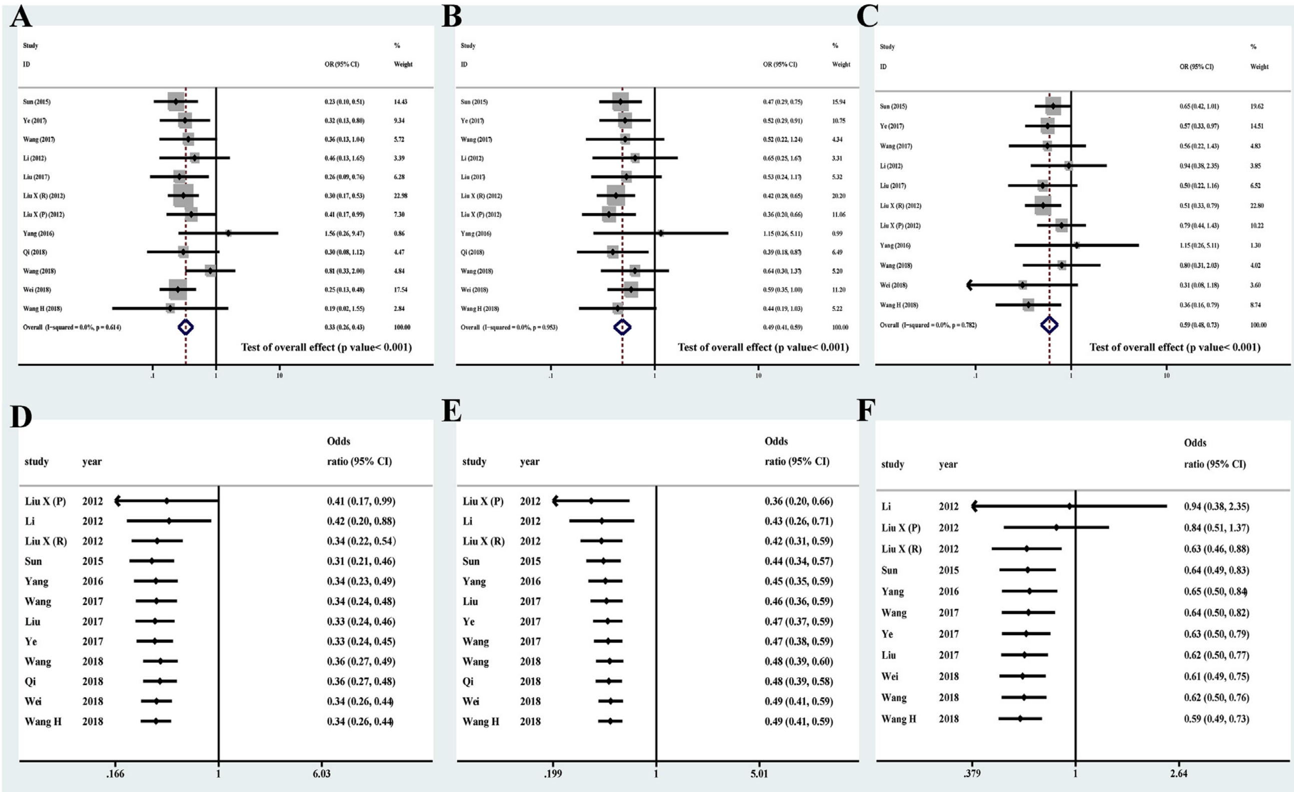

Fig. 2. Forest plots of meta-analysis and cumulative meta-analysis for overall survival. Outcomes: A. Forest of OR of 1-year overall survival; B. Forest of OR of 3-year overall survival; C. Forest of OR of 5-year overall survival; D. Cumulative meta-analysis of 1-year overall survival; E. Cumulative meta-analysis of 3-year overall survival; F. Cumulative meta-analysis of 5-year overall survival.

and DFS. As reported in Sun et al. [10], the 1-, 2-, 3-, and 5-year overall survival rates were 94.2%, 78.8%, 71.5%, and 54.0%, respectively, for the adjuvant TACE group, higher than the 78.9%, 62.2%, 54.1%, and 43.2%, respectively, for the HR group ($P = 0.012$), with a similar trend in the DFS rates($P = 0.006$). Similarly, Liu X et al. [21] and Liu et al. [19] demonstrated that adjuvant TACE is a safe intervention and can efficiently prevent tumor recurrence and improve the overall survival of HCC patients with MVI. However, Wang et al. [12] concluded that the DFS and OS rates between the adjuvant TACE and HR-alone groups were not significant. Then, after comprehensive analysis of this systematic review and meta-analysis, 2190 HCC patients with MVI were included in this analysis, with results showing that adjuvant TACE was more effective and led to better improvements in the 1-, 3-, and 5-year OS and DFS rates for all included patients compared with HR alone.

Our study further indicates that adjuvant TACE could benefit HCC patients with MVI with tumor diameter >5 cm or multinodular tumors. Currently, Wei et al. conducted the first RCT to explore the efficacy and safety of adjuvant TACE for HCC patients with a solitary tumor≥ 5 cm and MVI, which concluded that hepatectomy followed by adjuvant TACE is an appropriate option after radical resection in HCC patients with solitary tumor≥ 5 cm and MVI, with acceptable toxicity. In our subgroup analysis, 4 studies reporting the OS and DFS rates were included in the meta-analysis, and we confirmed the benefits of adjuvant TACE for HCC patients with MVI with tumor diameter >5 cm or multinodular tumors. It may be that adjuvant TACE significantly improves OS in HCC patients with MVI by decreasing early recurrence. This may explain why the survival benefit of adjuvant TACE was greater among HCC patients with tumor diameter >5 cm or multinodular tumors, since these two factors are thought to facilitate the formation of micro-metastases that give rise to early recurrence [28, 29].

Currently, MVI can only be accurately diagnosed by histologic assessment of whole-liver specimens because of the obstacle to predict MVI preoperatively [30]. Thus, adjuvant treatment such as TACE after HR is of great importance. Previous studies have documented the effectiveness of TACE as an adjuvant therapy for HCC patients [31–35].adjuvant TACE aims to eradicate the invisible intrahepatic metastases that may lead to postoperative recurrence. For HCC patients with portal vein tumor thrombi, previous RCT and non-RCT studies [36,37] showed that adjuvant TACE prolongs survival of these patients. Zhong et al. [38] conducted an RCT recruiting 115 Stage III A HCC patients, demonstrating that the 1-, 3-, and 5-year overall survival rates and median overall survival for hepatectomy with adjuvant TACE were 80.7%, 33.3%, 22.8% and 23.0 months, respectively, significantly higher than the 56.5%, 19.4%, 17.5% and 14.0 months, respectively, for those who underwent hepatectomy alone.

Most adverse effects associated with adjuvant TACE were mild and transient, including fever, nausea, vomiting, fatigue and upper abdominal pain. In most cases, these symptoms were alleviated within 1 week without specific treatment. Although all the included studies stated that there was no patient mortality and the incidence of infection, bleeding and acute liver failure was very rare, the safety of the adjuvant TACE is still one of the most concerning aspects that require further evaluation.

Several limitations persist in this analysis that should be considered. First, this meta-analysis contained only one RCT and numerous NRCT studies; therefore, selection bias was possible. Second, all the included studies were conducted in China, yet all the studies had high quality to present the conclusion. Our findings need further validation from international centers with different

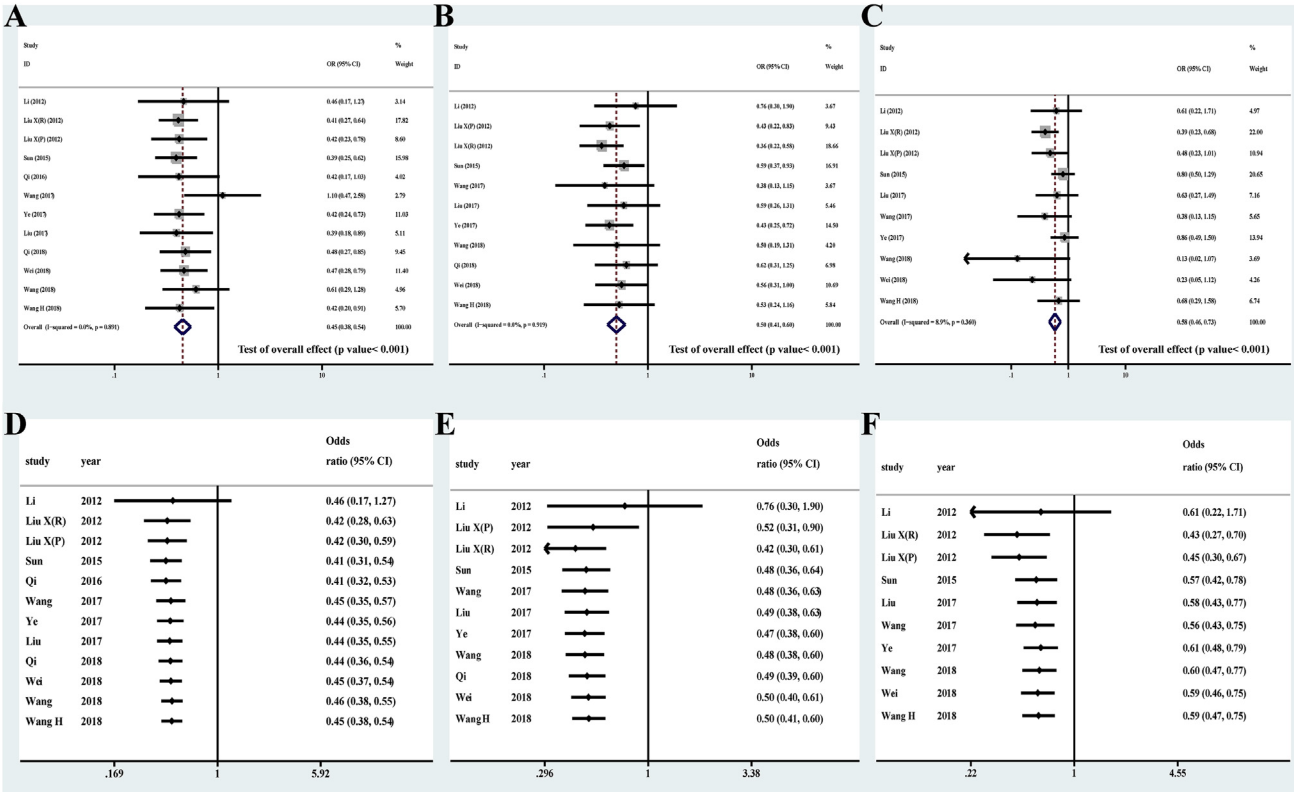

Fig. 3. Forest plots of meta-analysis and cumulative meta-analysis for disease-free survival. Outcomes: A. Forest of OR of 1-year disease-free survival; B. Forest of OR of 3-year disease-free survival; C. Forest of OR of 5-year disease-free survival; D. Cumulative meta-analysis of 1-year disease-free survival; E. Cumulative meta-analysis of 3-year disease-free survival; F. Cumulative meta-analysis of 5-year disease-free survival.

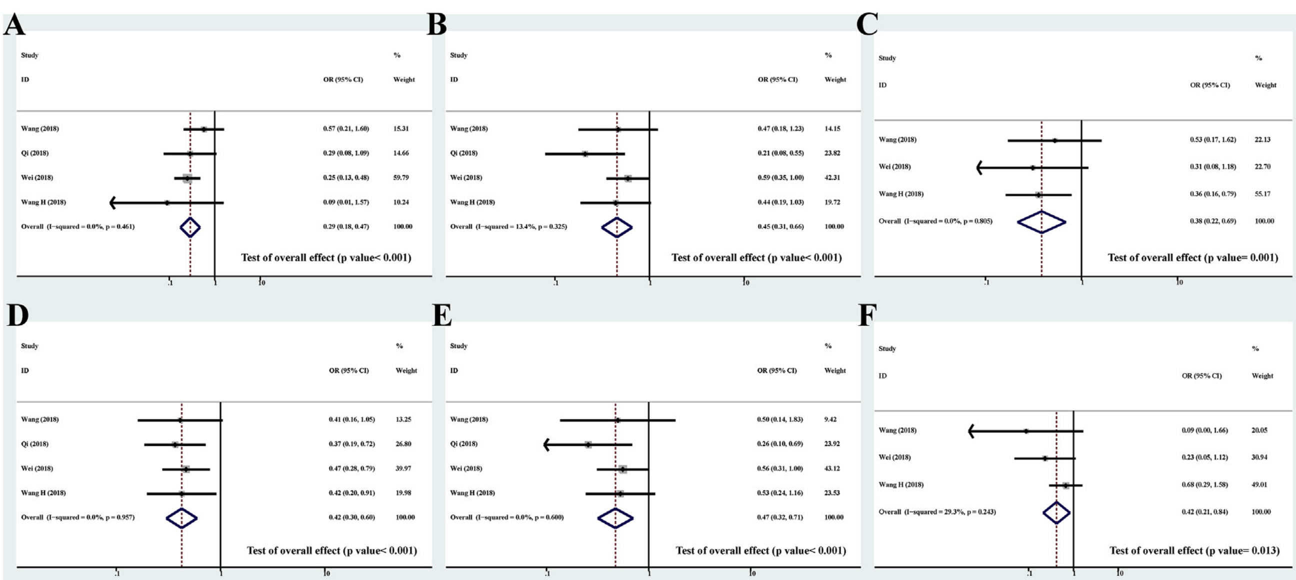

Fig. 4. Forest plots of meta-analysis for overall survival and disease-free survival in the subgroup of HCC patients with tumor diameter >5 cm or multinodular tumors. Outcomes: A. Forest of OR of 1-year overall survival; B. Forest of OR of 3-year overall survival; C. Forest of OR of 5-year overall survival; D. Forest of OR of 1-year disease-free survival; E. Forest of OR of 3-year disease-free survival; F. Forest of OR of 5-year disease-free survival.

etiologies. We have systematically searched databases based on our search strategy, and all relevant studies were included in our analysis. The above limitations could have affected the results of this meta-analysis.

Conclusion

In conclusion, this systematic review and meta-analysis suggests that adjuvant TACE may produce a survival benefit for HCC patients with MVI over hepatic resection alone. Importantly, these results need to be validated in further high-quality clinical trials from international centers.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.031.

Declarations of interest

None.

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