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Efficacy and Safety of Transcatheter Arterial Chemoembolization and Transcatheter Arterial Chemotherapy Infusion in Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Hepatocellular carcinoma (HCC) is a worldwide health threat with increasing incidence and a high mortality rate. Most HCC patients are diagnosed at an advanced stage and are unable to undergo potential curative surgery. Transcatheter arterial chemoembolization (TACE) and transcatheter arterial chemotherapy infusion (TACI) are two of the main palliative treatments for advanced HCC patients. The clinical efficacy and safety of TACE and TACI are controversial. For this reason, we conducted a systematic review and meta-analysis to summarize the current evidence. We searched for randomized controlled trials (RCTs) and cohort studies that compared the clinical outcomes and adverse effects in HCC patients who received TACE or TACI treatments. The database search was performed and last updated on November 1, 2016. Overall survival and clinical response were compared using a hazard ratio (HR) with a 95% confidence interval (CI). A total of 11 clinical studies that included 13,090 patients were included based on the inclusion/exclusion criteria, of which 9 were cohort studies and 2 were RCTs. TACE was associated with a 23% lower hazard of death compared to TACI (pooled HR = 0.77, 95% CI = 0.67–0.88, $p = 0.0002$). Patients receiving TACE had a 28% higher disease control rate (DCR) and 162% higher objective response rate (ORR). Only the increase in ORR associated with TACE was statistically significant [DCR: odds ratio (OR) = 1.28, 95% CI = 0.35–4.64, $p = 0.71$; ORR: OR = 2.62, 95% CI = 1.33–5.15, $p = 0.002$]. TACE is associated with more favorable survival and response rate than TACI in patients with intermediate or advanced HCC.

Key words: Hepatocellular carcinoma (HCC); Transcatheter arterial chemoembolization (TACE); Transcatheter arterial chemotherapy infusion (TACI); Efficacy; Safety; Randomized clinical trials; Cohort studies; Meta-analysis

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major threat to global healthcare[1]. It is the fifth most common type of cancer and the third most common cause of cancer-related mortality worldwide, resulting in more than 600,000 deaths per year. Of note, more than half of the cases diagnosed each year and the cancer-related mortality occurred in China[2]. The high incidence in China has been largely associated with hepatitis B infection[3]. However, an increasing incidence of HCC is also observed in Western countries due to chronic liver disease and liver cirrhosis caused by hepatitis C and alcohol and drug abuse[4]. Surgical resection, liver transplantation, and radiofrequency ablation are the only curative treatments for early stage HCC patients[5]. Despite the development of diagnostic methods, early detection of HCC is still difficult, and most HCC patients present with locally advanced or metastatic disease[6].

For the large majority of patients with HCC, palliative treatments are the only choice at the time of initial diagnosis[7]. HCC is highly vascular and angiogenic, and it largely depends on the hepatic artery for its blood

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supply, while the rest of the normal liver parenchyma is predominantly supplied by the portal vein. Thus, arterial obstruction has been considered to be an effective treatment for HCC, which can induce regional ischemic tumor necrosis[8]. Based on this assumption, transcatheter arterial embolization (TAE) was first developed and conducted in Japan in 1974[9]. Transcatheter arterial chemoembolization (TACE) was subsequently developed by adding chemotherapeutic agents mixed with or without lipiodol into the hepatic artery prior to embolization[10].

The survival benefit of TACE in treating advanced HCC is now well established by multiple randomized clinical trials[11]. This approach is widely used as a palliative treatment and is included in the NCCN and ESMO HCC treatment guidelines as the standard locoregional treatment for unresectable HCC[12]. It is also used for HCC patients awaiting liver transplantation to prevent tumor progression[13]. However, overall prognosis is complicated by the underlying liver function status, which, in turn, affects the potential applicability of these treatments[14]. Therefore, TACE is not always indicated, especially for patients with poor liver function and large tumor size, because the risk of hepatic failure and treatment-related death is relatively high[8]. In addition, embolization of the hepatic artery may lead to a hypoxic and ischemic tumor microenvironment surrounding the HCC. There is evidence showing that ischemia may stimulate expression of multiple growth factors, including vascular endothelial growth factor (VEGF) and epithelial growth factor (EGF), leading to neovascularization, invasion and metastasis, and tumor growth and progression[15].

With this in mind, an alternative procedure—transcatheter arterial chemotherapy infusion (TACI)—was developed to achieve comparable clinical efficacy and reduce treatment-related adverse effects[16]. TACI includes the injection of mixed iodized oil and therapeutic antitumor agents into the tumor-feeding artery without any embolic substances. Although lipiodol has a potential embolic function, it acts more as a carrier of chemotherapeutic agents[17]. Therefore, in the present study, TACE should have more effective embolic agents, such as gelatin sponges, polyvinyl alcohol particles, and microspheres. This classification of TACE and TACI is also consistent with all of the studies included in the present meta-analysis.

Various anticancer drugs can be used in TACE and TACI for HCC treatment, and these agents include doxorubicin hydrochloride (ADM), epirubicin hydrochloride, mitomycin C (MMC), zinostatin stimalamer (SMANCS), and cisplatin[16]. Multiple anticancer agents are usually mixed together in TACE and TACI procedures, and these combinations have proven to be more effective than single agents. Unfortunately, to date, there is no evidence to indicate which combination is the most effective.

The main clinical concern relates to whether embolization should be included, especially when multiple anticancer agents are used. Controversial results were published with regard to comparing the efficacy and safety of TACE and TACI. In order to make a comprehensive comparison of efficacy and safety between the two techniques, we have performed the first meta-analysis comparing TACE and TACI.

MATERIALS AND METHODS

Literature Search Strategy

This analysis was in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement[18] (PRISMA 2009 checklist). We searched the online databases MEDLINE (PubMed), Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) through November 1, 2016, without language limitations. Reference lists of identified studies and reviews were also manually searched.

Study Selection

Study eligibility was determined independently by two reviewers (Z.W. and X.L.). Disagreements were solved by consensus. Full papers and abstracts were included that (i) compared TACE (using gelatin sponge) versus TACI in treating HCC, (ii) reported data necessary to calculate the hazard ratio (HR) on survival outcome and/or objective response rate (ORR), and disease control rate (DCR). Studies were excluded if they were (i) reviews, case-only studies, or familial studies; (ii) missing sufficient data for the calculation of HR with 95% confidence interval (CI); and (iii) duplication of previous publications or replicated samples.

Data Extraction and Quality Assessment

Data extraction was carried out independently by two reviewers (Z.W. and XYL.) using a predefined form. Disagreements were resolved by discussion with a local mentor (Q.G.). From each study, the following information was extracted: first author's name, year of publication, study design, characteristics of study population (including mean/median age, percentage of males, background of liver cancer, whether patients with multiple tumors were included, percentage of patients with portal vein thrombosis, and percentage of patients with extrahepatic metastasis), definition of intervention and control, number and kind of antitumor agents, HR for overall survival with corresponding 95% CI, DCR, ORR, and adverse events. If the HR and CI were not reported, the total observed death events and the numbers of patients in each group were extracted to determine the HR and its variance indirectly[19]. In studies where only Kaplan–Meier plots were available, data were extracted from the graphical survival plots[20].

Study quality was assessed independently by Z.W. and X.L. using the following items: (i) clear definition of the intervention and control; (ii) intervention and control groups are comparable in terms of anticancer agents used; (iii) sample size larger than 100; and (iv) clear definition of the outcome assessment. Quality assessment for the cohort study was evaluated using the Newcastle–Ottawa quality scale.

Statistical Analysis

For survival analysis, HRs with 95% CIs were combined using the inverse variance method. For efficacy analysis, DCR and ORR were combined. Heterogeneity was assessed by a Q-test. A fixed-effect model was used when there was no heterogeneity ($p \geq 0.10$)[21], otherwise a random-effect model was used[22]. For exploration of heterogeneity, subgroup analysis was performed based on study design, number of antitumor agents, background of liver cancer, mean/median age of the population, and whether patients with multiple tumors were included. Sensitivity analysis was performed to assess the stability of the results by excluding studies in which the intervention and control groups were not totally comparable besides gelatin sponge (in two studies, lipiodol was not used in the control group). Begg's funnel plots and Egger's tests[23] were used to assess the publication bias. All p values were two sided, with $p < 0.05$ being considered statistically significant. Statistical analysis was conducted using Review Manager 5 and STATA 11.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics of Included Studies

The process of literature search and study selection is summarized in the flow diagram in Figure 1. Our database search initially revealed 417 potentially relevant publications, and eventually only 11 studies were eligible

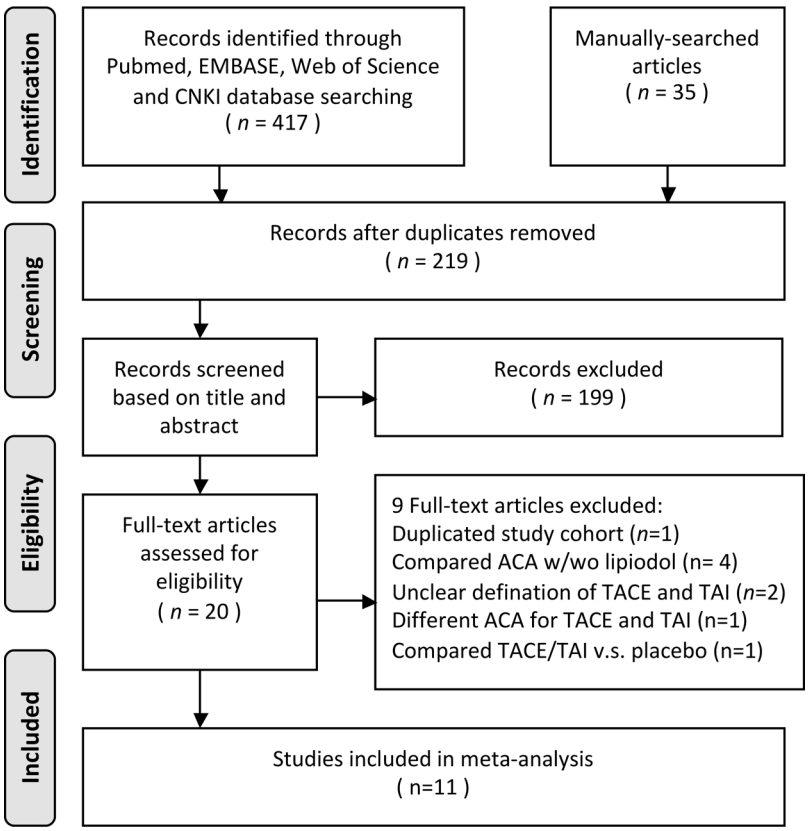

Figure 1. Flowchart for selection of included studies.

based on the defined inclusion/exclusion criteria[24–34]. One study lacked data on HR[34], and 4 studies[25–27,32] lacked data on DCR and ORR, so the meta-analysis consisted of 10 studies for HR and 7 studies for DCR and ORR. The main characteristics of the included studies are presented in Table 1. In brief, of the 11 studies, 9 were cohort studies[16,24–27,30,32–34], and only 2 were randomized controlled trials (RCTs)[28,29]. Viral infection was the dominant cause of HCC in all studies included in this analysis. The percentage of cases with multiple tumors, portal vein thrombosis, extrahepatic metastasis, and adverse effects of the procedures were not regularly reported.

Effect of TACE Versus TACI on Overall Survival and Efficacy

A total of 13,090 subjects from 10 studies were included in the pooled analysis of overall survival. TACE was associated with a 23% lower hazard of death compared to TACI (pooled HR = 0.77, 95% CI = 0.67–0.88, $p = 0.0002$) (Fig. 2). The random-effect model was adopted because of significant heterogeneity ($I^2 = 82\%$, value of $p < 0.00001$ for heterogeneity). A total of 1,468 subjects from seven studies were included in the analysis of clinical efficacy. Patients who received TACE had a 28% higher DCR and 162% higher ORR. However, only the increase in ORR was statistically significant [DCR: odds ratio (OR) = 1.28, 95% CI = 0.35–4.64, $p = 0.71$; ORR: OR = 2.62, 95% CI = 1.33–5.15, $p = 0.002$] (Fig. 3A and B). In the one study without sufficient data on HR[34], TACE versus TACI was a significant predictor for ORR in both univariate (OR = 2.79, 95% CI = 1.31–5.93, $p = 0.007$) and multivariate (OR = 2.97, 95% CI = 1.17–7.49, $p = 0.021$) analyses.

Subgroup and Sensitivity Analysis

Because of the limited number of studies that reported data on ORR and DCR, only data on HR were used for subgroup and sensitivity analyses (Table 2). Patients who received TACE had longer overall survival both in HBV-dominant (HR = 0.71, 95% CI = 0.60–0.84, $p = 0.0001$) and HCV-dominant (HR = 0.82, 95% CI = 0.70–0.96, $p = 0.01$) populations, when multiple tumors were included as part of the review criteria (HR = 0.75, 95% CI = 0.61–0.91, $p = 0.004$). This association was significant in an older population with mean/median age >60 years (HR = 0.80, 95% CI = 0.66–0.97, $p = 0.02$) but was not significant in a younger patient population (HR = 0.74, 95% CI = 0.52–1.05, $p = 0.09$). In 12,654 patients from seven studies where multiple anticancer agents were used in the procedures, TACE was associated with a 25% reduction in hazard of death (HR = 0.75, 95% CI = 0.64–0.88, $p = 0.0004$), while in 436 patients from three studies that only used one anticancer agent, the reduction associated with TACE was smaller and of only borderline significance (HR = 0.83, 97% CI = 0.68–1.01, $p = 0.06$) but showed higher homogeneity ($I^2 = 0$, p for heterogeneity = 0.66). Interestingly, the effect was only significant in cohort studies (HR = 0.70, 95% CI = 0.62–0.79, $p < 0.00001$) but not in RCTs (HR = 1.08, 95% CI = 0.86–1.35, $p = 0.5$).

In all of the 11 included studies, the TACE and TACI groups were comparable in terms of anticancer agents used. However, in two studies[30,33], lipiodol was only used in the TACE but not the TACI group, while in other studies it was used in both groups. A sensitivity analysis was conducted by excluding these two studies in which gelatin sponge was not the only difference between TACE and TACI. The HR decreased to 0.85 (95% CI = 0.68–1.05, $p = 0.13$) and was no longer significant.

Publication Bias and Quality Assessment

In the analysis of HR, inconsistent results from the Egger's test ($p = 0.001$) and the Begg's test ($p = 0.243$) suggested the existence of potential publication bias. The funnel plot was visually asymmetrical, further confirming the publication bias (Fig. 4). Since most of the included studies are cohort studies, the quality was assessed using the Newcastle–Ottawa quality scale[35].

Adverse Events

Not all of the studies included in this analysis reported on the adverse events associated with TACE and TACI (Table 1). The difference in reporting adverse effects makes it hard to summarize the adverse effects using meta-analysis. However, it should be noted that similar results were reported in these various studies. In the TACE and TACI treatment groups, the most common adverse events were fever, loss of appetite, abdominal pain, and nausea[31]. The symptoms were transient and mostly resolved within 2 weeks after initial treatment using conventional symptom control management. A higher number of adverse events associated with TACE therapy was reported in several studies[25,26,31], whereas similar rates in both groups were reported in other studies[24,28,29]. Of note, the development of hepatic abscess was observed to be significantly higher in the TACI group when compared to the TACE group[34]. No significant differences were detected in terms of procedure-related liver failure, acute respiratory failure, or mortality.

DISCUSSION

Despite the wide use of TACE in HCC treatment for many years, its clinical efficacy was not well established and recognized until clinical trials and meta-analysis concluded that TACE could significantly improve survival compared to supportive care[14,36]. TACE is usually not recommended for patients with poor liver function and advanced stage of disease, and TACI was initially developed using anticancer agents without gelatin sponge particles or other embolic agents. Several studies have been

Table 1. Characteristics of Included Studies

Study ID	Design	No. of Subjects	No. of TACE	No. of TAI	Age	Male (%)	HBV (%)	HCV (%)	Multiple (%)	PVTT (%)	Cirrhosis	Extrahepatic (%)	Anticancer Agents	Adverse Events
Ikeda et al.[24]	Cohort	168	74	94	Median 63/64	73	15	80	60	Excluded if in the trunk	A 55/48% B+C, 45/52%	0	Cisplatin	Reported
Kawaoka et al.[25]	Cohort	107	62	45	73	70	7	77	60	0	A 75 B 29 C 3	–	Cisplatin	Reported
Hatanaka et al.[26]	Cohort	237	78	159	62/61	68	15	–	0	–	A 6/9 B 50/71 C 2/21	3	Cisplatin, adriamycin, FUdR	Reported
Maeda et al.[27]	Cohort	356	189	167	Mean 63	73	11	77	56	–	A 41/27 B 102/76, C 46/64	0	Zinostatin stimalamer, cisplatin	Not reported
Okusaka et al.[28]	RCT	161	79	82	Median 65/67	81	11	73	85	0		0	Zinostatin stimalamer	Reported
Shi et al.[29]	RCT	243	122	121	Median <50	94	76	–	–	33	A 70/63, B 0 C 0	–	Lobaplatin, epirubicin, mitomycin C	Reported
Imai et al.[34]	Cohort	162	122	40	Median 72/74	67	–	–	–	–	–	–	Miriplatin	Reported
Liu et al.[30]	Cohort	455	387	69	Mean 56.2	78	87	4	–	57	A 252/14 B 197/73 C 20/32	–	5-FU, mitomycin, epirubicin	Not reported
Nishikawa et al.[31]	Cohort	226	145	81	72.5/70.3	67	8	66	–	–	A 100/46 B 45/35	–	Epirubicin, mitomycin	Reported
Takayasu et al.[32]	Cohort	11,030	8,507	2,523	Median >60	72	14	77	57	–	A 51/45% B 39/41% C 10/14%	0	Doxorubicin, epirubicin, mitomycin, cisplatin, zinostatin stimalamer	Not reported
Li et al.[33]	Cohort	107	100	7	Median 52	–	78	–	–	38	A B C included	–	3 ACA	Not reported

RCT, randomized controlled trial; HBV, hepatitis B virus; HCV, hepatic C virus; TACE, transcatheter arterial chemoembolization; TACI, transcatheter arterial chemotherapy infusion; ACA, anticancer agents.

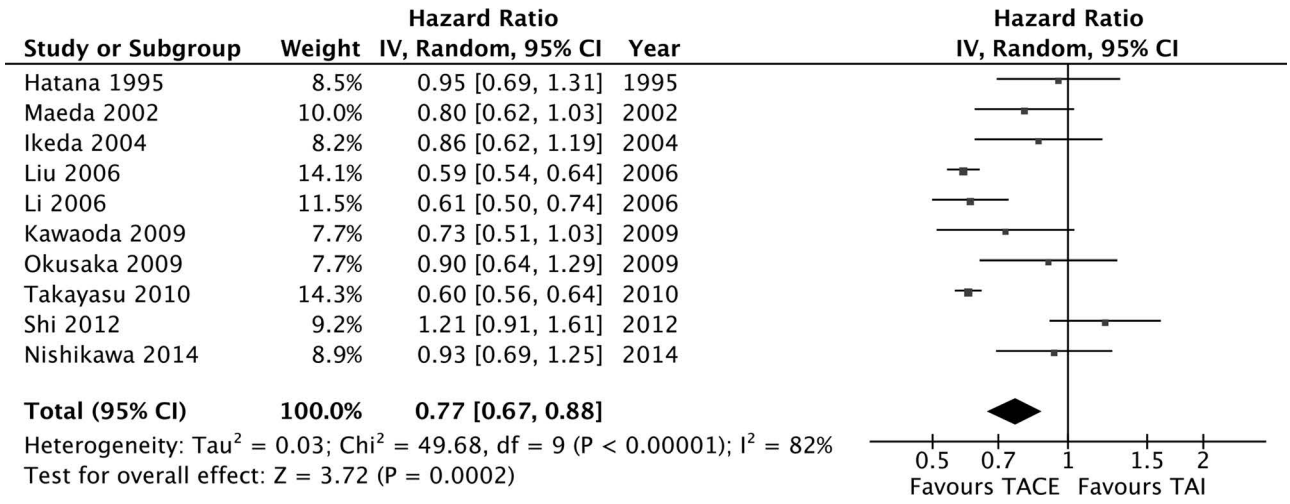

Figure 2. Forest plot of pooled meta-analysis of overall survival of included studies.

conducted to evaluate the clinical outcomes between TACE and TACI in HCC patients. However, inconsistent results have been reported in the literature. Therefore, in this systematic review and meta-analysis, we evaluated all published randomized clinical trials and cohort studies to provide a comprehensive comparison of TACE and TACI in all available data.

Our analysis showed that TACE therapy is associated with significant improvement in overall survival and ORR of HCC patients compared to TACI. Because of the relatively large number of total patients in this pooled analysis, we believe that our results are solid and statistically significant. Subgroup analysis further revealed that TACE had favorable findings regardless

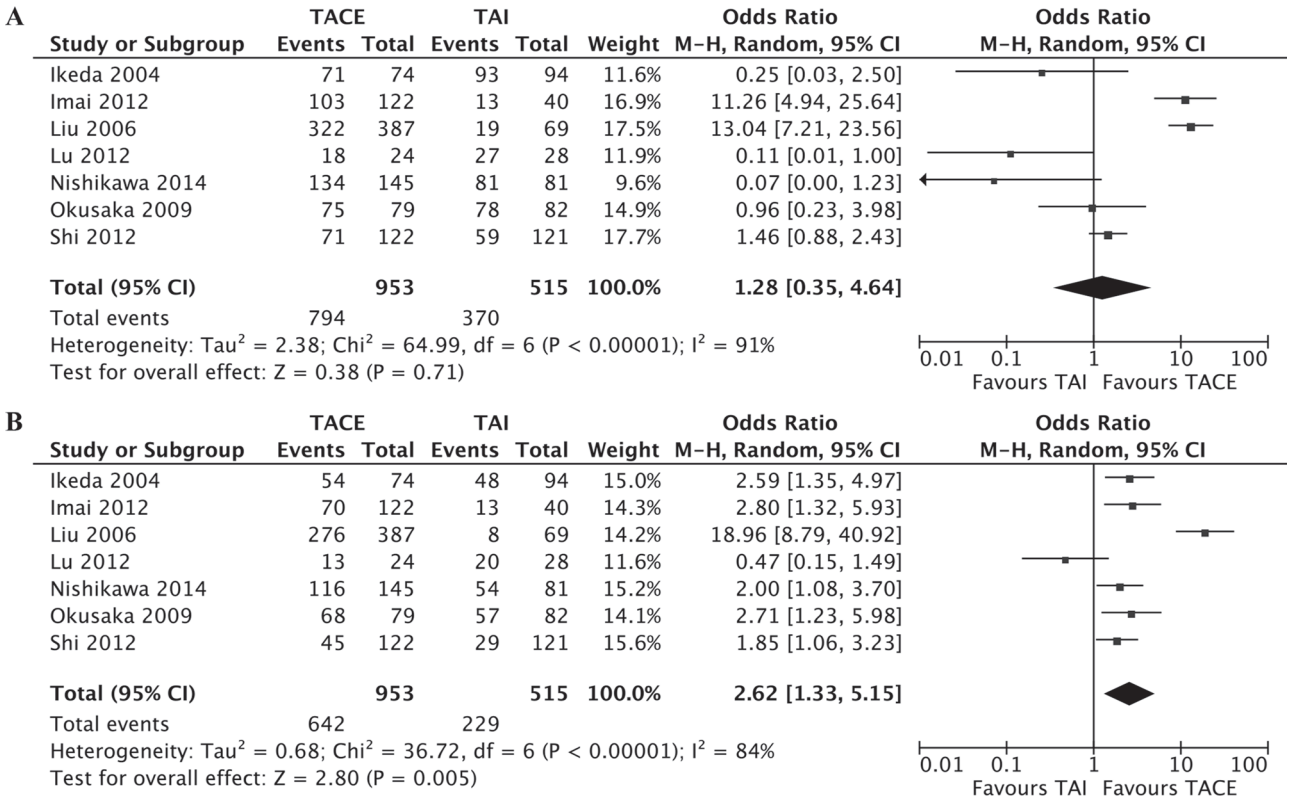

Figure 3. Forest plot of pooled meta-analysis of disease-control rate (A) and objective response rate (B) of included studies.

Table 2. Subgroup Analyses and Sensitivity Analyses of Hazard Ratio Comparing TACE Versus TAI

Subgroup	No. of Studies	No. of Subjects	HR	95% CI	*p* Value	I^2	*p* for Heterogeneity	Model
No. of drugs								
Multiple drugs	7	12,654	0.75	0.64–0.88	0.0004	86	<0.00001	Random
Single drug	3	436	0.83	0.68–1.01	0.06	0	0.66	Fixed
Background of liver cancer								
HBV dominate	5	12,061	0.71	0.60–0.84	0.0001	87	<0.00001	Random
HCV dominate	4	792	0.82	0.70–0.96	0.01	0	0.83	Fixed
No. of tumors								
Multiple tumors included	5	11,822	0.75	0.61–0.91	0.004	70	0.009	Random
Only single tumor or unknown	5	1,268	0.81	0.61–1.07	0.13	89	<0.00001	Random
Age of population								
Mean/median age <60	7	805	0.74	0.52–1.05	0.09	91	<0.00001	Random
Mean/median age >60	3	12,285	0.80	0.66–0.97	0.02	76	0.0003	Random
Study design								
Cohort studies	8	12,684	0.70	0.62–0.79	<0.00001	73	0.0006	Random
RCTs	1	404	1.08	0.86–1.35	0.5	37	0.21	Fixed
Sensitivity analysis								
Excluding control group without lipiodol	8	12,528	0.85	0.68–1.05	0.13	84	<0.00001	Random

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; RCT, randomized controlled trial.

of the underlying hepatitis background. In the elderly patient population and with the use of multiple anticancer agents, TACE appears to have a significant clinical benefit for HCC patients compared to TACI.

Potential publication bias was detected by statistical analysis. Therefore, the conclusions made from our analysis must be viewed with some caution. In addition, the subgroup analysis revealed that the association was only significant in cohort studies but not in RCTs. Although there were only two RCTs, they had a high level of homogeneity. We were unable to perform a stratified analysis according to potential confounders or combine adjusted HRs due to limited data, which is one major limitation of our analysis. Additional high-quality RCTs are still needed to further determine the potential differences in clinical efficacy between TACE and TACI.

Different definitions of TACE and TACI currently exist in the literature. Whether lipiodol should be considered as an embolization is an unclear question. Although lipiodol has potential embolic functions, it generally

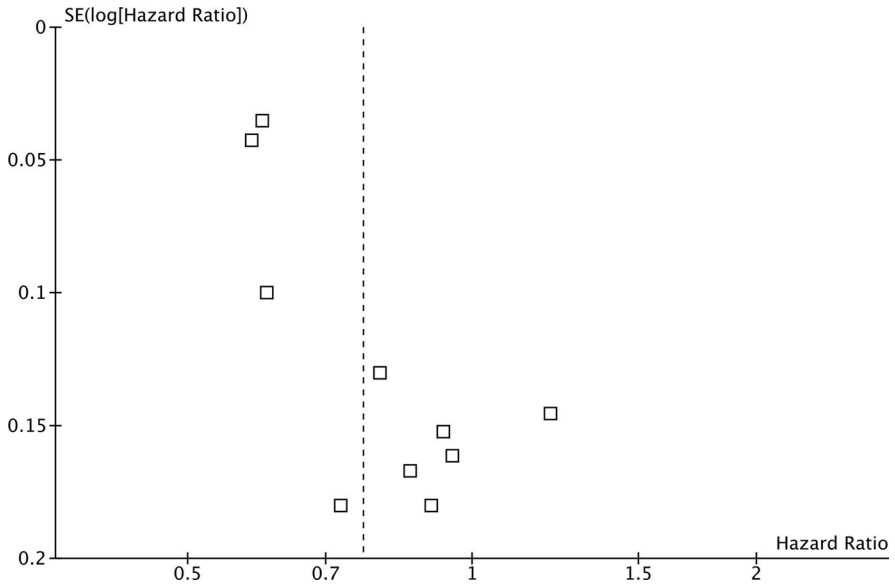

Figure 4. Funnel plot of publication bias.

serves as a carrier of chemotherapeutic agents. Therefore, in the literature the infusion of anticancer agents together with lipiodol was considered to be TACI and, as such, our study also used this definition.

Various anticancer agents used in the included studies may also introduce potential bias in the meta-analysis. However, our sensitivity analysis revealed that different anticancer agents would not change the overall results as they relate to clinical efficacy. Because of the limited number of studies, we were unable to conduct subgroup analysis based on the various chemotherapy regimens. Further studies are needed before we are able to identify the optimal regimen of anticancer agents for TACE and TACI therapies. With our growing understanding of the underlying molecular mechanisms of HCC initiation and progression, additional treatments for advanced HCC will certainly be developed in the future.

The results of our meta-analysis are subject to several limitations. First, the differences in baseline severity in patients may lead to treatment group assignment bias, especially for cohort studies. Selection criteria used to identify candidates for TACE and TACI may also differ among clinical centers. Therefore, clearer guidelines are needed to determine the selection criteria for different treatments. Second, our study was unable to address the subgroup analysis based on pathological parameters, including severity of underlying liver cirrhosis and the number and size of tumors due to insufficient data. Third, the adverse effects reported from each study cannot be easily combined in one integrated analysis as a standardized format was not used to report toxicity.

In conclusion, our analysis demonstrated that TACE was associated with longer overall survival and higher ORR, but there are several confounding biases that may also contribute to this association. The actual causal relationship between TACE and clinical efficacy needs further exploration, and well-conducted randomized clinical trials to compare the clinical efficacy and toxicity of TACE versus TACI are warranted.

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