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ORIGINAL ARTICLE

Comparison of TACE combined with and without iodine-125 seeds implantation therapy for advanced stage hepatocellular carcinoma: a systematic review and meta-analysis

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Summary

Purpose: *Hepatocellular carcinoma (HCC) has the second-highest cancer-related mortality in patients worldwide. Recently, TACE plus Iodine-125 (^{125}I) seed strand endovascular implantation (ISEI) was shown to be feasible in advanced HCC patients. The aim of this study was to evaluate the efficacy and safety of this combined therapy for the treatment of advanced stage HCC by meta-analysis.*

Methods: *A systematic search in PubMed, EMBASE and Cochrane Library Databases was conducted until April 1st 2018. Outcomes included overall survival (OS), objective response rate (ORR) of primary liver tumor, and procedure-related complications. All statistical analyses were performed using Review Manager 5.3 and Stata 12.0.*

Results: *Nine eligible studies on 1059 advanced HCC patients were included. The results showed that TACE plus ISEI had significantly improved the 6-month OS (OR, 5.01: 95%CI, 3.19~7.86: P<0. 01) and 1-year OS (OR, 4.97: 95%CI, 3.12~7.92: P<0.01) compared to TACE alone.*

Conclusion: *The safety and efficacy of TACE plus ISEI is superior to TACE alone for advanced HCC.*

Key words: *hepatocellular carcinoma, transarterial chemoembolization, ^{125}I implantation, meta-analysis*

Introduction

Hepatocellular carcinoma (HCC), with an increasing morbidity year by year, has the second-highest cancer-related mortality in patients worldwide [1]. It also has a high recurrence rate, the 5-year recurrence rate being up to 80% [2]. Current therapies for HCC include liver resection, liver transplantation, transcatheter arterial chemoembolization (TACE), ablation therapy, systemic therapy (e.g. sorafenib), etc [3]. However, most patients are diagnosed in advanced stages. Consequently, few of them can benefit from surgical treatment [2], while most of the patients have to receive regional treatment (e.g. TACE) or systemic therapy.

TACE is effective both in terms of tumor response and overall survival (OS). However, it causes hypoxia leading to increased levels of vascular endothelial growth factor receptor and insulin-like growth factor receptor 2, which is associated to metastasis [3]. In order to decrease this flaw, numerous studies have explored combination therapies for advanced HCC patients. Among these procedures, TACE combined Iodine-125 (^{125}I) seed strand

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endovascular implantation (ISEI) could be a feasible therapeutic option, but the results are disputable [4-12]. Therefore, we performed a meta-analysis to compare the efficacy and safety of TACE with or without ISEI as an add-on treatment in advanced-stage of HCC.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PPISMA) guidelines [13].

Search strategy

We systematically searched the relevant studies in PubMed, Embase, Science Citation Index Expanded (Web of Science) and Cochrane Library Databases up to April 1st 2018. The following terms were included: "iodine-125" and "liver cancer" or "hepatocellular carcinoma" or "HCC" or "hepatic cancer" and "chemoembolization" or "TACE". In addition, the references' lists of the retrieved studies were also screened. The language was restricted to English.

Selection criteria

Two reviewers independently conducted the search process, quality assessment and eligibility evaluation. The disagreements were discussed to reach a consensus, and if not possible, the dispute was settled by arbitration by a third reviewer. Studies published in English were eligible according to the following criteria: 1) the participants were advanced HCC patients; 2) treatment modalities included TACE with or without ISEI; 3) sufficiently detailed data on methods, patient characteristics and survival. Case reports, abstracts, letters, reviews, proceedings, studies without controls or without necessary data were excluded. The detailed search strategy is shown in Figure 1.

Data extraction and risk of bias assessment

Basic publication information (first author name, publication year, study population, interventions, sample size, population characteristics, baseline characteristics and outcomes) was extracted. The outcomes included: 1) overall survival (OS), defined as the time from the commencement of treatment until death or last follow-up; 2) HCC baseline response according to the modified Response Evaluation Criteria in Solid Tumors mRECIST) guidelines for HCC [14]; 3) procedure-related adverse events based on the National Cancer Institute common terminology criteria for adverse events, version 3.0 [15].

The risk of bias of each potentially included study was assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions* and the Cochrane Hepato-Biliary Group web site instructions for authors. The detailed risk of bias assessment is shown in Figure 2.

Statistics

Statistical analyses were performed using Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and Stata 12.0 (Statacorp, college station, Tex). Statistical heterogeneity was assessed by the I^2 test, the Cochran Q statistic (heterogeneity could be accepted if $P>0.1$ and $I^2<50\%$) and Galbraith plot for heterogeneity. According to the heterogeneity between studies, the random-effects model was used when there was significant heterogeneity ($I^2>50\%$); otherwise, the fixed-effects model was used. P values were calculated by x^2 test. Publication bias was assessed using the funnel plot with the bias indicator test from Egger [16].

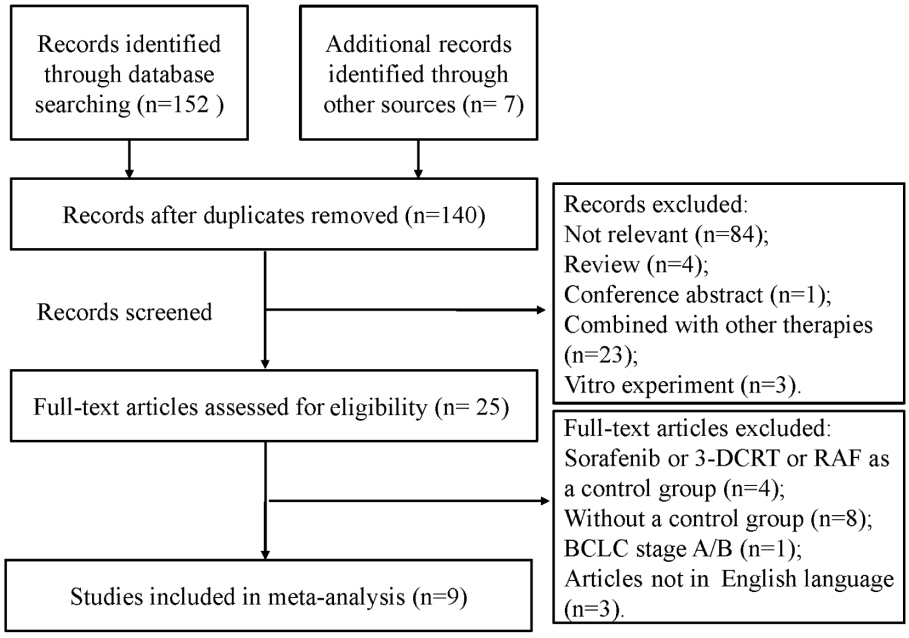

Figure 1. Study flow diagram. 3-DCRT: 3-dimensional conformal radiation therapy; RAF: Radiofrequency ablation; BCLC: Barcelona Clinic Liver Cancer.

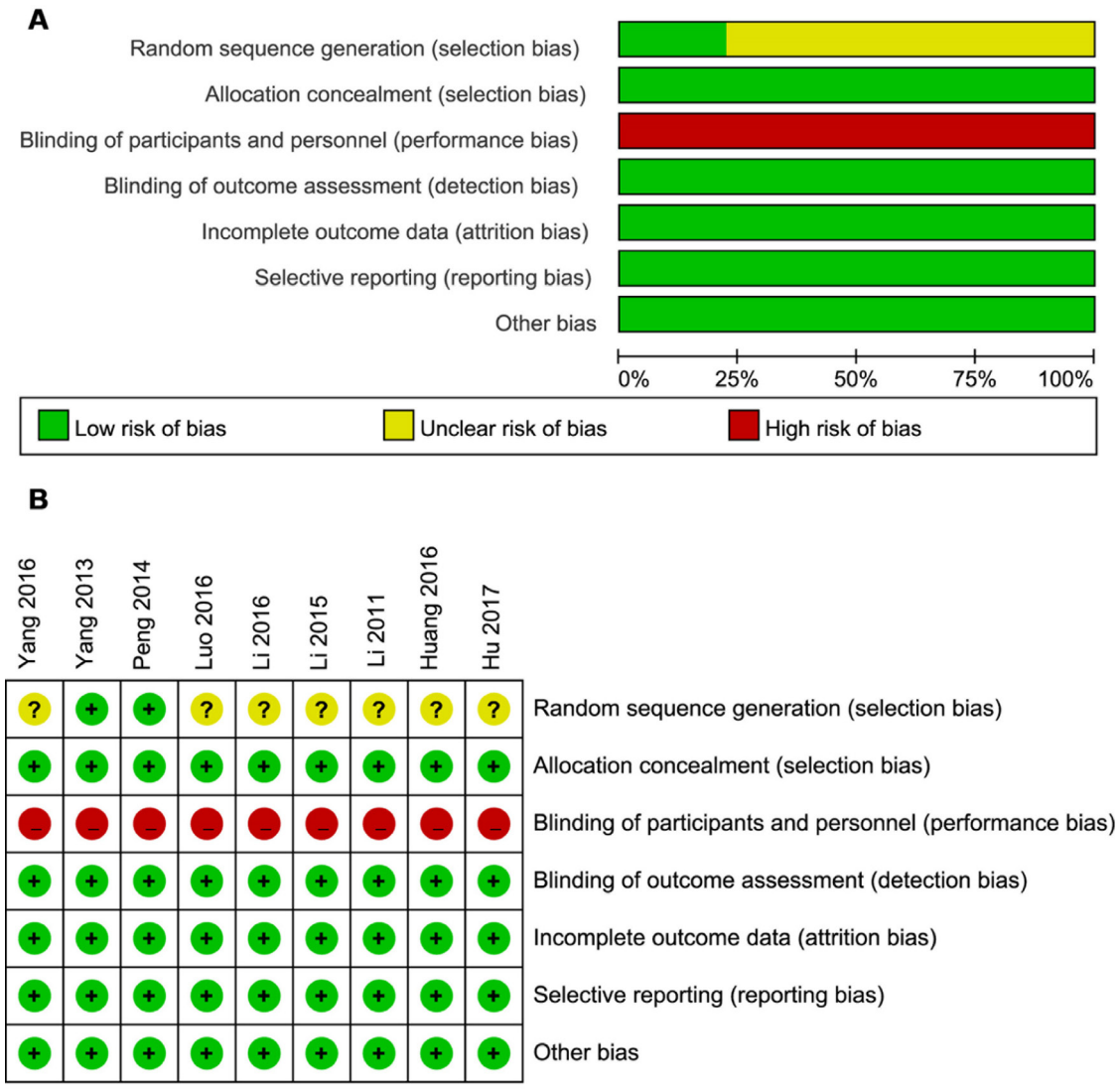

Figure 2. Risk of bias graph: review. **A:** Authors' judgments about each risk of bias item presented as percentages across all included studies; **B:** Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Results

Characteristics of the studies

The initial search resulted in a total of 159 relevant studies, but 150 studies were excluded based on the selection criteria (Figure 1). We finally included 9 studies [4-12]. Detailed baseline characteristics of the studies are shown in Table 1. The total sample size was 1059, out of which 520 patients were in the treatment group (TACE plus ISEI or TACE plus ISEI and PVS) and 539 patients were in the control group (TACE alone, or TACE plus PVS).

Overall survival

Compared to TACE alone, or TACE plus PVS, advanced HCC patients treated with TACE plus ISEI or TACE plus ISEI and PVS showed a significant increase in 6-month overall survival (4 studies [5,6,8,10]) (OR, 5.01; 95% CI, 3.19-7.86: p<0.01) and 1-year (5 studies [5-8,10]) (OR, 4.97; 95% CI, 3.12-7.92: p<0.01). There was no statistical heterogeneity, as indicated by an I^2 value of 0% and 37%, respectively. Thus, the fixed-effects models were used (Figure 3).

Objective response of primary liver tumor

The objective response rate (ORR) of primary liver tumor in advanced HCC patients was reported in seven studies [4-6, 9-12] which included 830 patients. Out of 411 patients in the treatment group, 188 (45.74%) achieved complete response (CR) or partial response (PR), compared to 169 (40.33%) out of 419 patients in the control group. Heterogeneity seemed to exist (I^2=60%, p=0.02) and the random-effects model was used. Further subgroup

Table 1. Characteristics of clinical trials included in the meta-analysis

Study and treatment	*Trial*	*Male (%)*	*Mean age (y)*	*Etiology HBV/HCV/others*	*Child-pugh A/B*	*Morphology Massive/ Multi-nodular/Diffuse*	*Maximum diameter >5cm / ≤5cm*	*AFP (ng/mL) >400 / ≤400*	*ECOG (0/1-2)*	*Extrahepatic spread*
Hu (2017)[4]										
TACE+ISEI (n=50)	R	84	47.6±6.3	42/7/1	42/8	26/24/0	30/20	26/24	27/23	19
TACE (n=50)		80	45.4±5.2	40/8/2	44/6	27/23/0	31/19	28/22	25/25	18
Huang (2016)[5]										
TACE+ISEI (n=70)	R	90	51.1±11.1	NA	31/39	NA	31/39	39/31	41/29	NA
TACE(n=140)		91	51.6±10.8		68/72		61/79	81/59	79/61	
Peng (2014)[6]										
TACE+ISEI (n=32)	P	97	NA	23/0/9	38/5	NA	NA	NA	NA	3
TACE (n=43)		91		31/1/11	27/5					2
Li (2016)[7]										
TACE+ISEI (n=66)	R	85	48.8±10.7	NA	58/8	NA	NA	33/33	25/41	12
TACE (n=78)		86	48.1±10.0		63/15			32/46	37/41	13
Yang(2013)[8]										
TACE+ISEI (n=43)	P	91	NA	40/2/1	24/19	9/15/19	28/15	25/18	8/35	NA
TACE (n=42)		93		40/1/1	23/19	7/18/17	29/13	29/13	7/35	
Li(2015)[9]										
TACE+PVS+ISEI(n=18)	R	100	61.0±10.0	NA	15/3	NA	NA	18/0	NA	NA
TACE+PVS (n=34)		79	62.0±10.0		28/6			34/0		
Luo(2016)[10]										
TACE+PVS+ISEI(n=182)	R	92	53.6±10.2	154/16/12	160/22	0/145/37	123/59	112/70	21/161	NA
TACE+PVS (n=94)		87	55.1±11.1	74/10/10	86/8	0/79/15	61/33	52/42	9/85	
Yang(2016)[11]										
TACE+PVS+ISEI (n=33)	R	82	53.3±8.6	22/2/9	22/11	0/4/29	NA	20/13	10/23	15
TACE+PVS (n=28)		89	50.9±12.1	21/2/5	20/8	0/4/24		20/8	6/22	20
Li(2011)[12]										
TACE+PVS+ISE(n=30)	R	77	51.0±2.3	21/0/9	17/13	NA	NA	26/4	NA	NA
TACE+PVS (n=26)		65	48.0±1.6	23/0/3	13/11			20/6		

PVS, portal vein stent ; ISEI, Iodine-125 seed implantation; TACE, transarterial chemoembolization; AFP, alpha fetoprotein; ECOG, Eastern cooperative oncology group. HBV, hepatitis B virus, HCV, hepatitis C virus; NA, not available, R, retrospectively; P, prospective

analysis results showed that there were significant differences with regard to ORR of primary liver tumor between the two procedures (OR, 2.21; 95% CI, 1.21-4.05: p=0.01). The pooled OR was found to be 2.01 in the TACE plus ISEI group (95% CI, 1.26-3.20: p<0.01) and 2.96 in the TACE plus ISEI and PVS group (95% CI, 0.81-10.86: p=0.10). Namely, TACE plus ISEI significantly improved the ORR of primary liver cancer while TACE plus ISEI and PVS did not (Figure 4).

Adverse events

Four studies [5,7,11,12] reported fever, nausea and/or vomiting, but no significant differences were noted between the treatment group and the control group. The odds ratio was 1.14 (95% CI, 0.71-1.83: p=0.58) and 1.16 (95% CI, 0.74-1.83: p=0.53), respectively. Two studies [5,11] revealed upper abdominal pain, however, we found no difference between the treatment group and the control

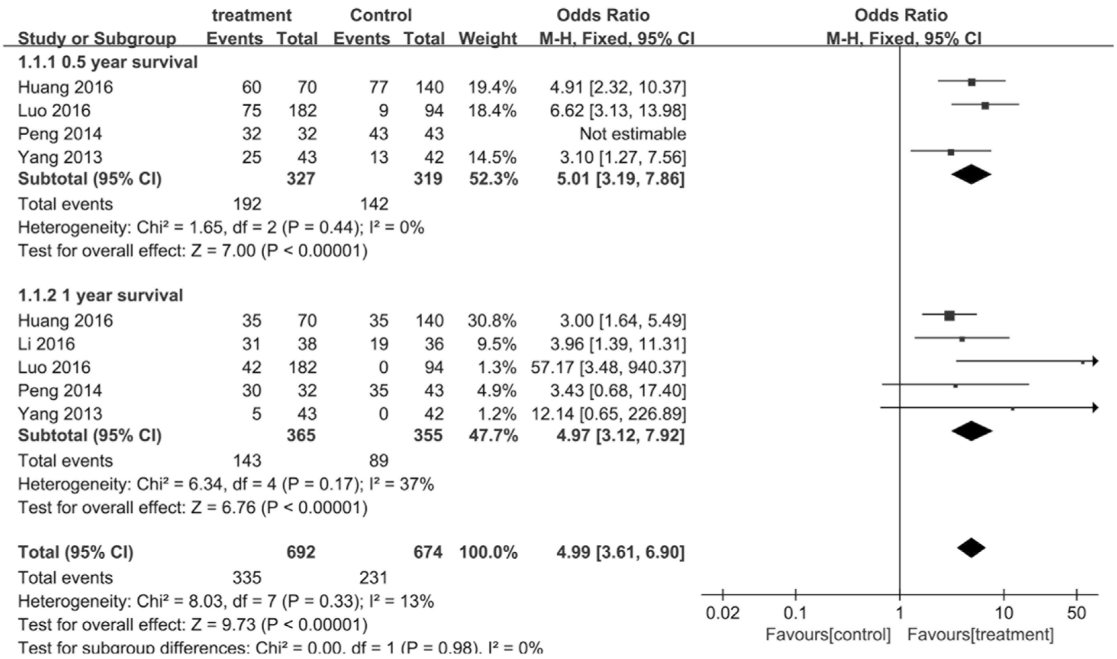

Figure 3. Survival rates in advanced HCC patients after treatment. CI: confidence interval; OR: odds ratio; HCC: hepatocellular carcinoma.

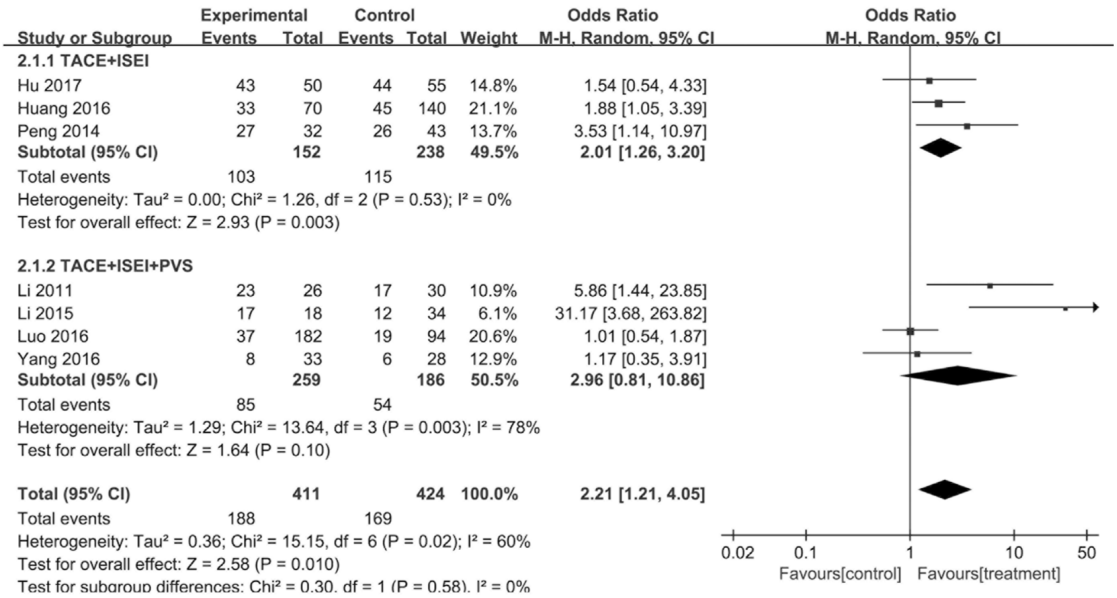

Figure 4. Odds ratios and 95% confidence intervals for objective response rate of primary liver tumor. CI: confidence interval; OR: odds ratio. TACE: transarterial chemoembolization; ISEI: Iodine-125 (^{125}I) seed strand endovascular implantation; PVS: portal vein stenting.

group (OR, 2.34; 95% CI, 0.81-6.74: p=0.12). There was no significant transaminase elevation observed in the two groups from an analysis of three trials [5,6,12] (OR, 0.36; 95% CI, 0.05-2.50: p=0.30). There was no evidence of an increased risk of biloma [5,6] (OR, 0.89; 95% CI, 0.34-2.32: p=0.81) and granulocytopenia [7,12] (OR, 1.02; 95% CI, 0.26-4.06: p=0.97) in the two groups either. Finally, the total risk rate of these adverse events between the two groups was 1.15 (95% CI, 0.83-1.58: p=0.41) (Figure 5).

Discussion

Although sorafenib is the standard of care for advanced HCC, its use is unfortunately limited in developing countries due to high costs [17]. The observed survival benefits for patients are also modest [18]. Especially in advanced HCC patients with portal vein tumor thrombosis (PVTT), the overall survival time when treated with TACE alone [19], sorafenib monotherapy [19] and TACE combined with sorafenib [20,21] was 4.1, 3.0 and 3.0~5.8

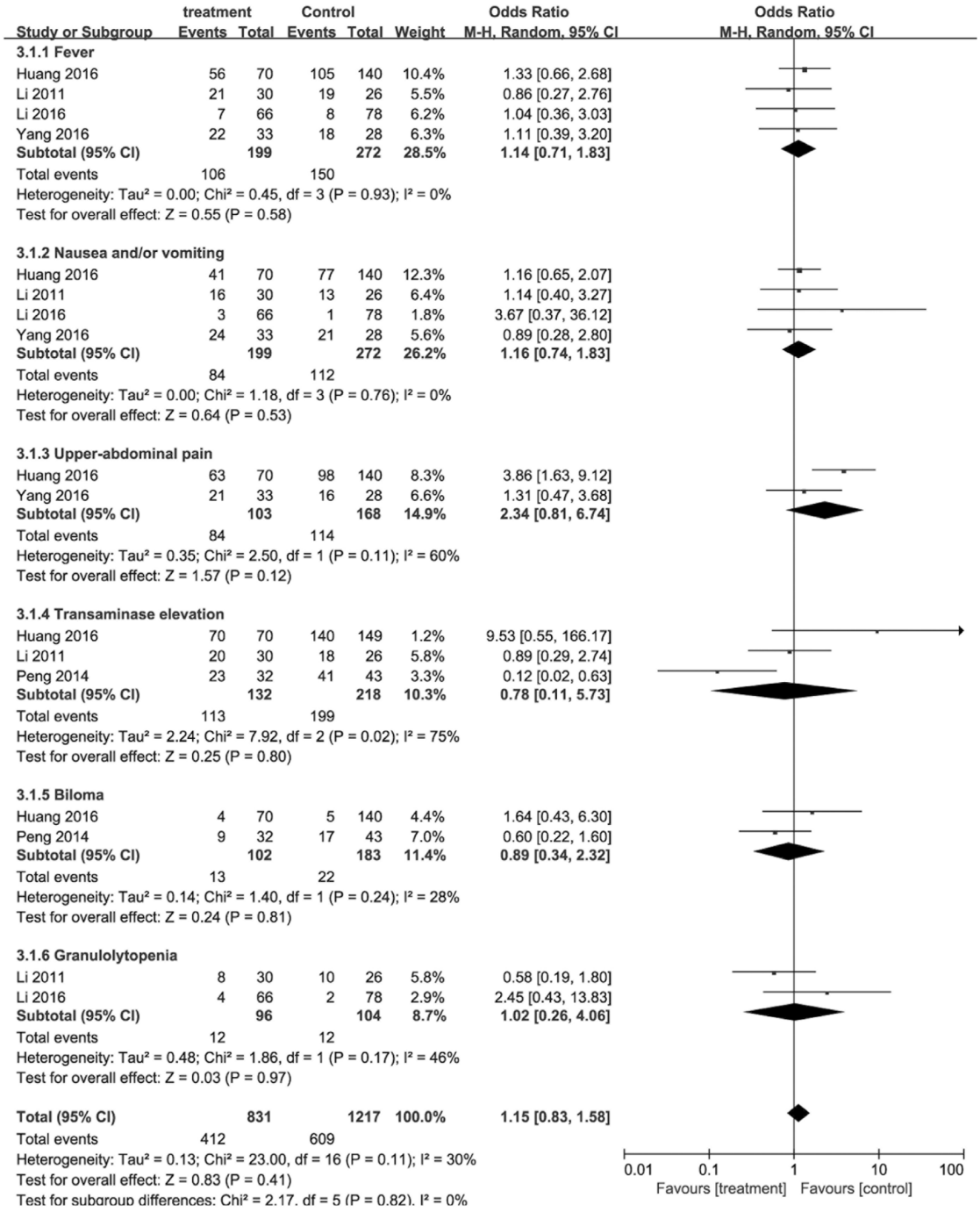

Figure 5. Adverse events in advanced HCC patients after treatment. CI: confidence interval; OR: odds ratio; HCC: hepatocellular carcinoma.

months, respectively. Therefore, new procedures have to be explored in order to further investigate the survival benefit in these patients.

^{125}Iodine (I) seeds have been used to treat solid tumors and their use in combination with TACE in advanced HCC patients was reported as safe and feasible [22]. In addition, ^{125}I could inhibit tumor cell proliferation and induce apoptosis [23,24]. In particular, a continuous low dose of radiotherapy had an anti-neointimal hyperplasia effect that could prevent clinical stent restenosis in advanced HCC patients with portal vein tumor thrombus [25]. In our meta-analysis, both TACE plus ISEI and TACE plus ISEI and PVS appeared to have a better OS and ORR than TACE alone or TACE plus PVS in advanced HCC patients. Furthermore, the combination therapy also seems to have no increased risks of procedure-related complications (such as acute hepatic failure, intraperitoneal bleeding, radiation hepatitis or enteritis) when compared to controls.

This study focused on all the articles reporting the combination therapy of TACE plus ISEI up to April 2018. Nine articles included according to the selection criteria, out of which 5 reported TACE plus ISEI and 4 reported TACE plus ISEI and PVS. The overall quality of the evidence was modest. All the trials were at high risk of bias due to lack of blinding. We did not include trials in languages other than English as the data in those trials were repeated or came from the same research center. We performed Egger's test to examine publication bias as our analyses included fewer than 10 trials, but no publication bias was detected in any of the measured outcomes ($p>0.05$).

Several limitations of the review should also be taken into consideration when interpreting the results. 1) This review included only patients with advanced stage HCC (i.e. BCLC C stage). One trial [7] reported HCC patients with BCLC A to C. However, we only extracted the data for BCLC C patients in this analysis. Therefore, this review is applicable only to people with advanced stage HCC. 2) It included a mixture of viral and non-viral etiologies, which indicates that the review is applicable to viral or non-viral etiologies. 3) All the studies included in this review were conducted on Chinese populations. Thus, the global applicability of the evidence is limited. 4) We only included RCTs which are known to focus mostly on benefits rather than harmful events. Accordingly, this review is biased towards benefits and ignores harmful events.

Conclusion

This review provides evidence that TACE plus ISEI may lower mortality and increase complete and overall response rates in advanced HCC patients, despite increased adverse events such as fever, nausea and/or vomiting, elevated alanine aminotransferase, abdominal pain, biloma and granulocytopenia, in comparison with TACE alone. However, the data for all comparisons were of median quality, thus, we could not reach definitive conclusions. We await the results of further well-designed controlled trials to provide additional data regarding the role of TACE plus Iodine-125 seeds implantation therapy in advanced HCC patients.

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Conflict of interests

The authors declare no conflict of interests.

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