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REVIEW ARTICLE

Transarterial embolization with hepatectomy for ruptured hepatocellular carcinoma: a meta-analysis

Feng-Qin Zhang[a], Lin Li[b], Ping-Chao Huang[c], Yu-Fei Fu[d] and Qing-Song Xu[d]

[a]Department of Ultrasound, Binzhou Medical University Hospital, Binzhou, China; [b]Department of Gynaecology, Binzhou People's Hospital, Binzhou, China; [c]Department of Interventional Vascular Surgery, Binzhou People's Hospital, Binzhou, China; [d]Department of Radiology, Xuzhou Central Hospital, Xuzhou, China

ABSTRACT

Purpose: To compare the clinical effectiveness between transarterial embolization (TAE) with staged hepatectomy (SH) and emergency hepatectomy (EH) for ruptured hepatocellular carcinoma (HCC).

Material and methods: Pubmed, Embase, and Cochrane Library databases were screened for eligible publications from the inception of the databases till February 2021.

Results: This meta-analysis included seven studies comprising 162 patients who underwent TAE with SH and 266 patients who underwent EH. The pooled intraoperative blood loss was less in the TAE with SH cohort, as compared to the EH cohort without significant difference ($p = .20$). The pooled blood transfer rate ($p < .00001$), blood transfer volume ($p = .002$), and 30-day patient death ($p = .04$) were all markedly reduced in the TAE with SH cohort versus the EH cohort. No significant differences in surgery duration ($p = .27$), hospital stay period ($p = .81$), complication rate ($p = 0.92$), disease-free survival (DFS) ($p = .79$), and overall survival (OS) ($p = 0.28$) were found between the two groups.

Conclusions: Compared with EH for ruptured HCC, TAE with SH could effectively decrease intraoperative blood loss and 30-day mortality. However, the long-term DFS and OS might not be beneficial to preoperative TAE.

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Hepatectomy; hepatocellular carcinoma; rupture; transarterial embolization

Introduction

Hepatocellular carcinoma (HCC) ranks sixth among global tumors and second among cancer-associated mortality [1]. Apart from the cancer progression – related deaths, spontaneous rupture is another cause of death in patients with HCC. HCC rupture is seen in 2.3%–26% of HCC patients in Asia and in <3% in the West [2].

At present, the commonly used treatment methods for ruptured HCC include hepatectomy, transarterial embolization (TAE), and conservative treatment [3–7]. Compared with conservative treatment, both hepatectomy and TAE could effectively decrease 30-day mortality [3]. A previous meta-analysis showed that TAE, like hepatectomy, was effective in managing hemostasis and improving one-year patient survival [7]. However, hepatectomy is superior to TAE in terms of long-term survival [3].

Emergency hepatectomy (EH) has been suggested for ruptured HCC because EH could not only achieve the purpose of hemostasis and tumor resection but also block the spreading of tumor cells into the abdominal cavity, thereby reducing the probability of postoperative recurrence and metastasis [8,9]. However, emergency surgery is correlated with an enhanced morbidity and mortality risk, relative to staged surgery [10]. Preoperative TAE is usually performed in patients with ruptured HCC to convert EH into staged hepatectomy (SH) [11–17]. Although several prior studies analyzed the clinical effectiveness of TAE compared with that of SH and EH in managing ruptured HCC, these studies were all retrospective in nature [11–17]. Conclusions from a single retrospective study can be affected by multiple factors. Hence, it is necessary to conduct a meta-analysis to reduce unintentional bias and enhance the statistical power of the study.

Therefore, we performed the present meta-analysis to delineate the clinical effectiveness of TAE with SH and EH in patients with ruptured HCC.

CONTACT Qing-Song Xu xuqingsong79@163.com Department of Radiology, Xuzhou Central Hospital, Xuzhou, China

Material and methods

Publication eligibility

Pubmed, Embase, and Cochrane Library databases were screened for eligible publications from their establishment dates till February 2021 using the following [Title/Abstract] search strategy: ((((Hepatocellular Carcinoma) or (HCC)) and (rupture)) AND (((Transcatheter Arterial Embolization) or (TACE)) OR (TAE))) and (((hepatectomy) or (resection)) or (surgery)).

The inclusion criteria were as follows:

- Type of study: comparative studies
- Disease: ruptured HCC
- Types of intervention: TAE with SH versus EH
- Language: no limitation

Alternately, the following studies were excluded:

- Single-arm investigations
- Case reports
- Non-human studies

Data extraction

Two researchers worked separately to extract data from all eligible studies, and a third author helped resolve any discrepancies in the extracted information. The extracted items included the following: study and patient baseline data and treatment-associated data.

Quality and bias assessment

The quality and bias were assessed with the nine-point Newcastle–Ottawa scale [18], carrying scores of $\geq$7, 4–6, and $<$4 corresponding to low-, moderate-, and high-bias risk, respectively.

Endpoints

The primary endpoint for this meta-analysis was 30-day mortality. The secondary endpoints included intraoperative blood loss, blood transfer rate, blood transfer volume, operative time, hospital stay time, rate of complication, disease-free survival (DFS), and overall survival (OS).

Statistical analyses

RevMan v5.3 was employed for all meta-analyses. The Mantel–Haenszel method was employed to measure pooled odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables, while continuous variables were analyzed according to the mean difference (MD) and 95% CIs. The hazard ratio (HR) with a 95% CI was used to measure pooled DFS and OS. Study heterogeneity was assessed *via* X^2 and I^2 tests, with I^2>50% indicating significant heterogeneity. The fixed-effects model was employed for analyses when significant heterogeneity was not observed, whereas the random-effects model was employed in presence of significant heterogeneity. Causes of heterogeneity were evaluated *via* sensitivity analysis, while funnel plots were employed to assess publication bias risk.

Results

Included studies

A total of 189 studies were initially selected, seven of which were finally included in the meta-analysis. The details of the study selection are shown in Figure 1. All studies were retrospective in nature, and the Newcastle–Ottawa scales of the seven studies ranged from 6 to 8. These seven studies included 162 patients who underwent TAE with SH and 266 patients who underwent EH. The baseline data of the studies and patients are shown in Table 1. The raw data of the treatment details are shown in Table 2.

Surgical blood loss

The data of surgical blood loss were extracted from two publications [12,15]. The pooled intraoperative blood loss was lower in the TAE with SH cohort verses the EH cohort, with no significant difference (MD: −194.97, 95% CI: −492.56 to 102.63, $p = .20$; Figure 2(a)). Marked heterogeneity was detected among these studies ($I^2 = 87\%$).

Blood transfer rate

The data of blood transfer rate were extracted from two publications [12,15]. The pooled blood transfer rate was markedly reduced in the TAE with SH cohort versus the EH cohort (25.4% vs 67.6%, OR: 0.17, 95% CI: 0.08–0.34, $p < .00001$; Figure 2(b)). No marked heterogeneity was detected among the included studies ($I^2 = 12\%$).

Blood transfer volume

The data of blood transfer volume were extracted from two studies [12,17]. The pooled blood transfer volume was significantly smaller in the TAE with SH

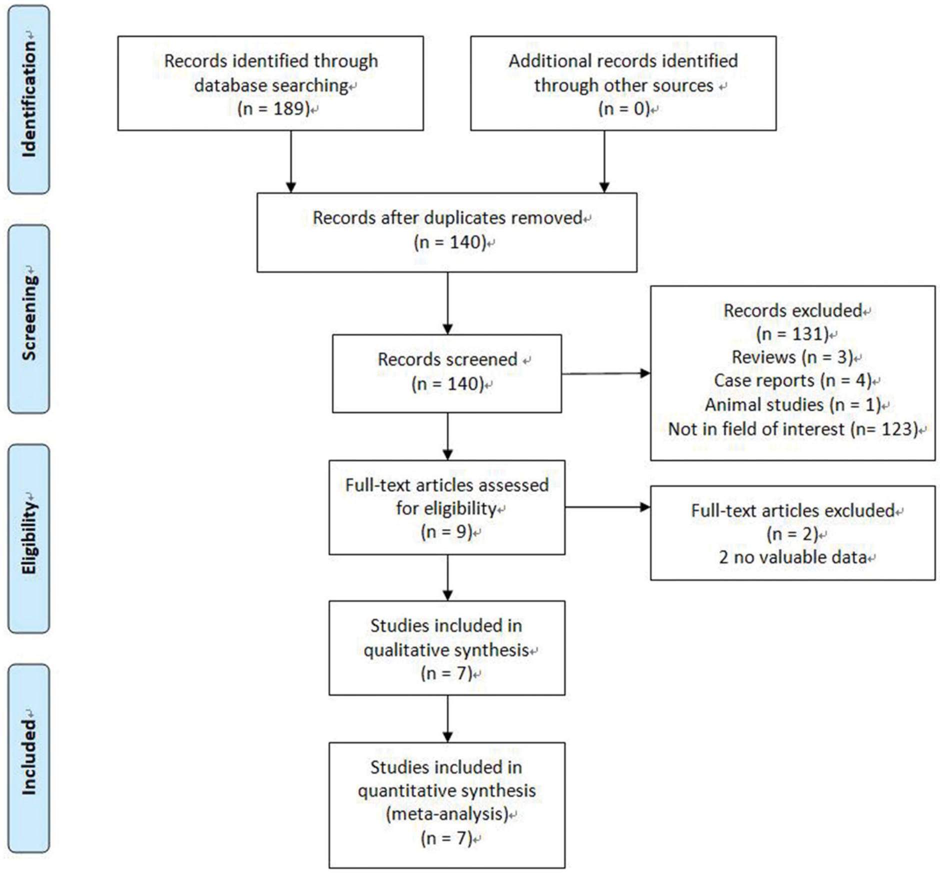

Figure 1. The flowchart of this study.

Table 1. Characteristics of the included studies.

Study/year/country	Groups	Sample size	Male/ Female	Age (y)	BCLC Stage	Child-Pugh	Tumor size (mm)	NOS
Hsueh/2012/China (Taiwan) [11]	TAE + SH	18	NG	NG	NG	NG	NG	6
	EH	19	NG	NG	NG	NG	NG	
Ou/2016/China [12]	TAE + SH	58	45/13	57	NG	A: 47; B + C: 10	110	8
	EH	73	59/14	52	NG	A: 61; B + C: 12	100	
Yang/2002/China [13]	TAE + SH	15	12/3	46.5	NG	A: 13; B: 2	89	8
	EH	6	6/0	51.1	NG	A: 5; B: 1	87	
Yang/2014/China [14]	TAE + SH	11	NG	NG	NG	A: 8; B: 3; C: 0	NG	6
	EH	17	NG	NG	NG	A: 10; B: 7; C: 0	NG	
Zhang/2019/China [15]	TAE + SH	13	11/2	45.5	A + B: 10; C + D: 3	A + B: 12; C: 1	NG	8
	EH	32	28/4	43.4	A + B: 29; C + D: 3	A + B: 30; C: 2	NG	
Zhong/2016/China [16]	TAE + SH	27	24/3	58.3	NG	A: 15; B: 9; C: 3	90	8
	EH	79	68/11	58.8	NG	A: 53; B: 17; C: 9	88	
Zhou/2020/China [17]	TAE + SH	20	18/2	NG	A: 17; B: 3; C: 0	A: 11; B: 9	73	8
	EH	40	37/3	NG	A: 33; B: 6; C: 1	A: 31; B: 9	71	

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; EH: emergency hepatectomy; NG: not given; NOS: Newcastle-Ottawa scale; TAE: transcatheter embolization; SH: staged hepatectomy.

cohort versus the EH cohort (MD: −569.43, 95% CI: −935.60 to −203.27, $p = .002$; Figure 2©). Marked heterogeneity was observed in the eligible publications ($I^2 = 72\%$).

Operative time

The data of operative time were extracted from three studies [12,15,17]. The pooled operative time was comparable between the two cohorts (MD: 3.71, 95% CI: −2.90 to 10.32, $p = .27$; Figure 2(d)). No marked heterogeneity was observed among the included publications ($I^2 = 48\%$).

Hospital stay time

The data of hospital stay time were extracted from two studies [12,17]. The pooled hospital stay time was

Table 2. Characteristics of the treatments.

Study	Groups	Blood loss (ml)	Blood transform rate	Blood transform volume (ml)	Operation time (min)	Hospital stay (d)	Complication rate	30-d mortality
Hsueh [11]	TAE + SH	NG	NG	NG	NG	NG	NG	0%
	EH	NG	NG	NG	NG	NG	NG	0%
Ou [12]	TAE + SH	496	19.0%	140	129	22	6.9%	0%
	EH	890	63.0%	560	125	17	12.3%	11.0%
Yang [13]	TAE + SH	NG	NG	NG	NG	NG	NG	0%
	EH	NG	NG	NG	NG	NG	NG	16.7%
Yang [14]	TAE + SH	NG	NG	NG	NG	NG	NG	0%
	EH	NG	NG	NG	NG	NG	NG	0%
Zhang [15]	TAE + SH	400	53.8%	NG	230	NG	69.2%	0%
	EH	450	78.1%	NG	222	NG	37.5%	6.3%
Zhong [16]	TAE + SH	NG	NG	NG	NG	NG	NG	7.4%
	EH	NG	NG	NG	NG	NG	NG	7.6%
Zhou [17]	TAE + SH	NG	NG	420	138	11	10%	0%
	EH	NG	NG	1223	153	14	22.5%	2.5%

NG: not given.

comparable between the two cohorts (MD: 0.98, 95% CI: −6.86 to 8.82, $p = 0.81$; Figure 2(e)). Marked heterogeneity was observed among the included publications ($I^2 = 95\%$).

Complication rate

The data of complication rate were extracted from three studies [12,15,17]. The pooled complication rates were similar between the two cohorts (16.5% vs 20.7%, OR: 0.93, 95% CI: 0.23–3.75, $p = 0.92$; Figure 2(f)). Marked heterogeneity was observed among the included publications ($I^2 = 66\%$). Significant heterogeneity disappeared when the Zhang *et al.* [15] study was removed ($I^2 = 0\%$). Under this condition, the pooled complication rates were still similar between the two cohorts ($p = 0.13$).

Thirty-day mortality

The data of 30-day mortality were extracted from 6 studies [12–17]. The pooled 30-day mortality was markedly reduced in the TAE with SH cohort verses the EH cohort (1.4% vs 7.3%, OR: 0.32, 95% CI: 0.11–0.95, $p = .04$; Figure 2(g)). No significant heterogeneity was detected among the included publications ($I^2 = 0\%$).

Disease-free survival

The data of DFS were extracted from three studies [12,15,17]. The pooled HR for DFS was similar between the two cohorts (HR: 1.06, 95% CI: 0.70–1.61, $p = .79$; Figure 2(h)). Marked heterogeneity was observed in all eligible publications ($I^2 = 82\%$). The significant heterogeneity still existed after removing any of the included studies.

Overall survival

The data of OS were extracted from six studies [11,12,14–17]. The pooled HR for OS was similar between the two cohorts (HR: 1.05, 95% CI: 0.96–1.15, $p = .28$; Figure 2(i)). Marked heterogeneity was observed in all eligible publications ($I^2 = 94\%$). Significant heterogeneity still existed after removing any of the included studies.

Publication bias

No publication bias pertaining to selected study endpoints was observed in funnel plot analyses.

Discussion

Spontaneous rupture hemorrhage is one of the main causes of death in HCC [19,20]. Among the treatments of ruptured HCC, conservative treatment alone and TAE alone were performed for approximately 22.6% and 32.4% of patients, respectively [19]. However, the one-year OS rate after conservative treatment alone and TAE alone was only 1% and 37.3%, respectively [19]. Compared with conservative treatment alone and TAE alone, the one-year OS rate after EH and TAE with SH was 78.7% and 75.7%, respectively [19]. Although TAE with SH and EH were both effective alternative treatment options for ruptured HCC, no consensus was reached about which was the better treatment option.

First, although no significant difference was observed in pooled surgical blood loss between the two groups, the forest plot showed a pronounced tendency that surgical blood loss was lower in the TAE with SH cohort. These results indicated that preoperative TAE could effectively reduce the intraoperative blood loss for patients with ruptured HCC.

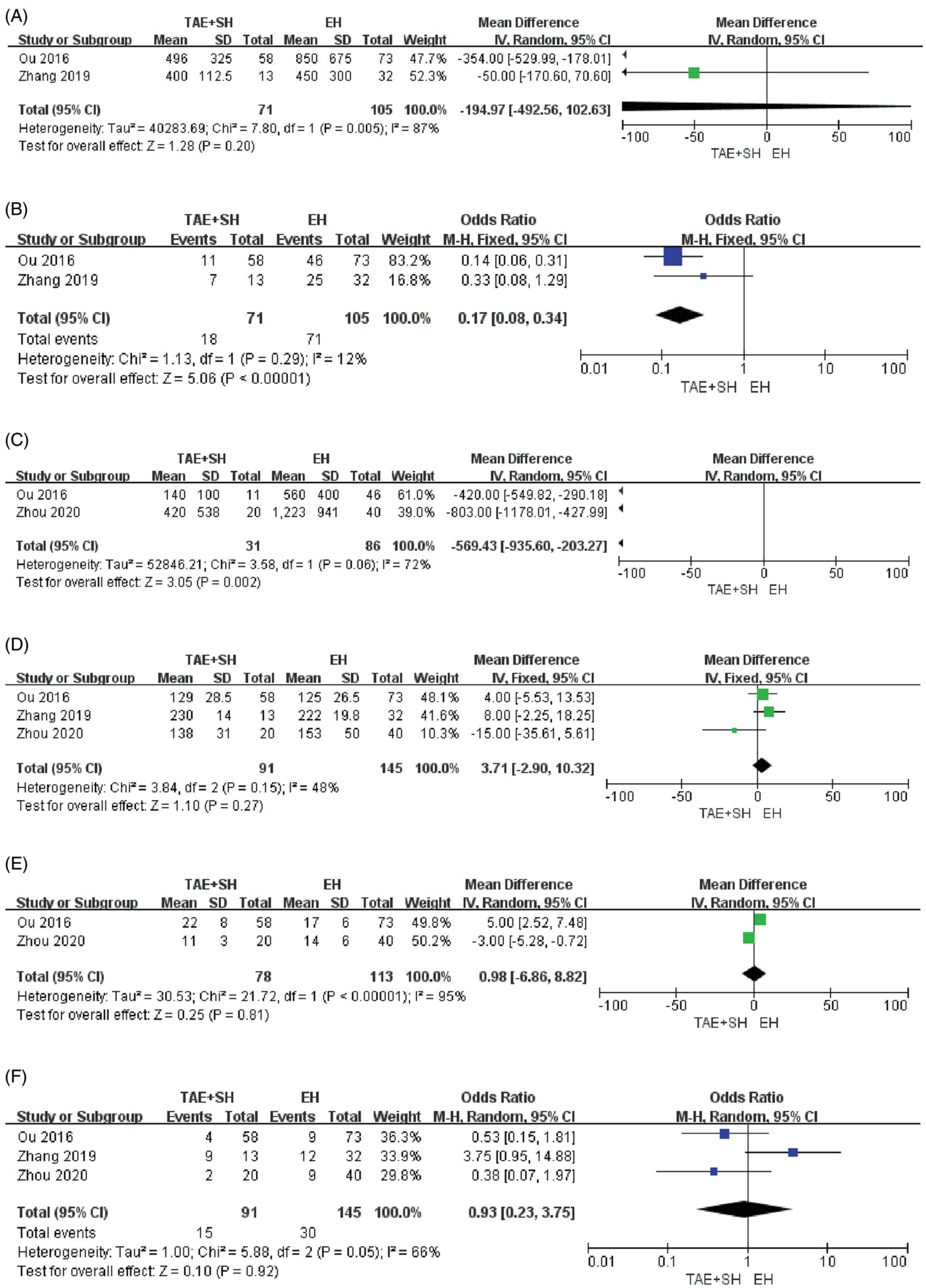

Figure 2. The forest plots show the comparative results of (a) intra-operative blood loss, (b) blood transfer rate, (c) blood transfer volume, (d) operative time, (e) hospital stay time, (f) complication rate, (g) 30-d mortality, (h) DFS, and (i) OS.

Furthermore, the blood transfer rate and volume were both significantly lower in the TAE with SH group. EH under the condition of active bleeding often required exploratory laparotomy to confirm the diagnosis [2]. Continuous hemorrhage might lead to exacerbation of the patient's condition and increase the death rate [4–6]. Therefore, rapid hemostasis and blood transfusion were required during the surgery.

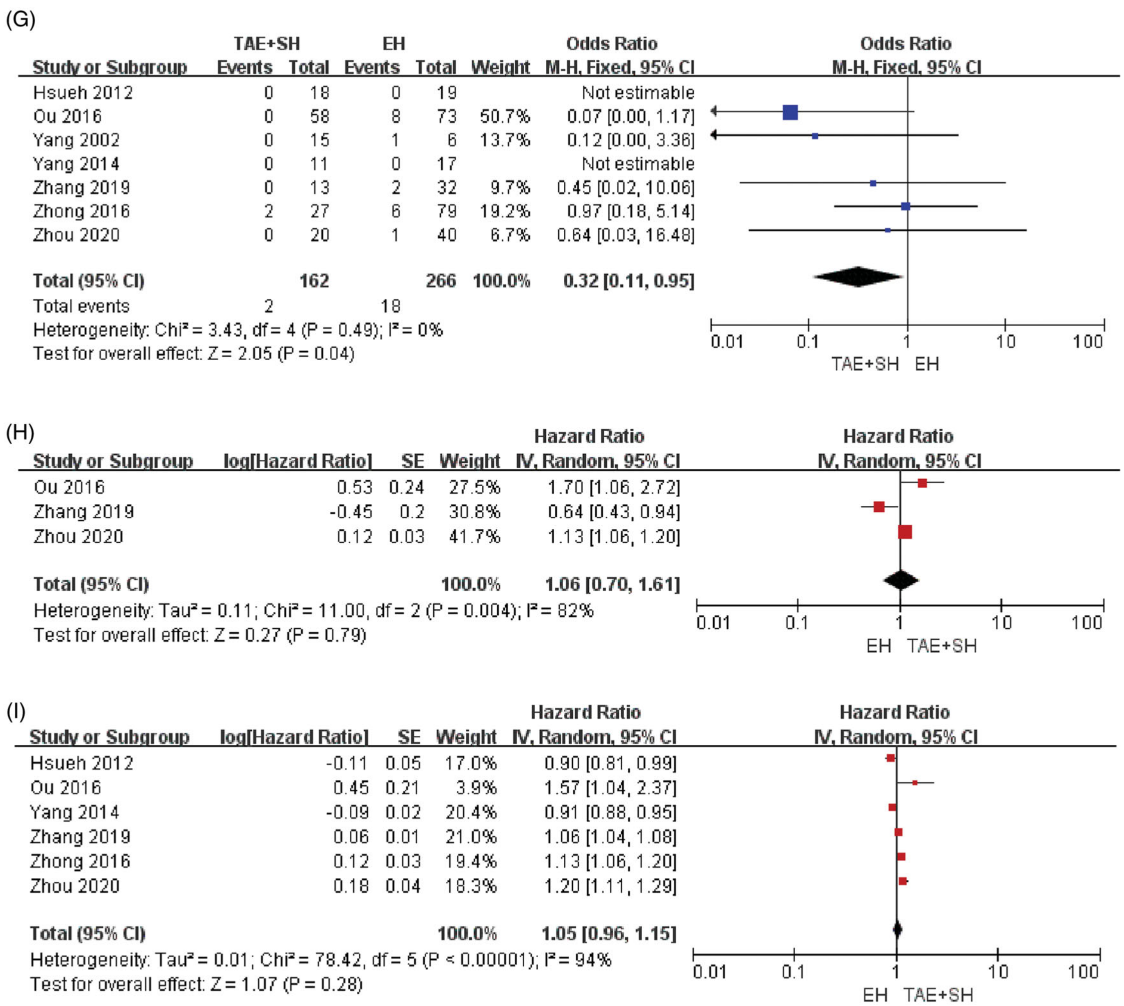

Figure 2. (Continued).

Many unstable factors, such as liver parenchymal edema, coagulation disorder after massive hemorrhage, or bleeding from liver wound surface, were observed, which might increase the difficulty and risk of EH [4–6]. SH was performed under the condition of stable vital signs of patients after TAE. If both doctors and patients had made proper preparations before the surgery, the patients would have had a relatively good tolerance.

The pooled surgical duration and hospital stay time were comparable between the two cohorts. These results indicated that preoperative TAE could not simplify the procedure of surgery or accelerate the postoperative recovery. However, the data of operative time and hospital stay time could only be extracted from three and two studies. Therefore, more data are still required.

The pooled postoperative complication rates were comparable between the two cohorts. The postoperative hospital stay was closely related to postoperative complications. The major postoperative complications reported in this study were liver insufficiency, pleural effusion, infection, abdominal metastasis, and biliary fistula [12,15,17]. The incidence rates in different studies were different, which might be associated with the different surgical procedures and the experience level of the surgeons.

The results showed that TAE with SH could significantly reduce the 30-day mortality compared with EH. The main causes of 30-day death were hepatic and kidney failure or multiorgan failure, postoperative re-bleeding, and septic shock [12–17]. EH was an independent risk factor for the 30-day mortality for patients with Child-Pugh B grade ruptured HCC [21]. Patients with ruptured HCC often had poor tolerance to surgery due to preexisting coagulopathy, poor hepatic functional reserve, hemodynamic instability, and cirrhosis. Therefore, the resection of ruptured HCC might reduce the residual hepatic function and elevate liver failure risk and operative mortality [12–17]. TAE could provide rapid hemostasis and promote ischemic necrosis of the tumor [17]. EH could be effectively converted into SH by TAE. SH was usually performed one to two months after TAE [12–17]. At this time, patients had better surgery tolerance because of recovery of hepatic function and coagulation function, which could facilitate the safety of the second-stage surgery.

Our meta-analysis showed similar pooled DFS and OS between TAE with SH and EH groups. These results indicated that preoperative TAE did not influence the long-term survival after hepatectomy. However, marked heterogeneity was also observed among these endpoints. Among the eligible publications, only Ou *et al.* [12] reported a longer DFS ($p = .019$) and OS ($p = .034$) with TAE and SH than with EH. Furthermore, all included studies were retrospective studies, which had a high risk of bias. Therefore, the long-term progression should be evaluated by randomized controlled trials.

Liver transplantation for advanced HCC with perioperative adjuvant treatment appears to have resulted in improved DFS [22,23]. However, liver transplantation with TAE for ruptured HCC has only been reported in some case reports and these cases suggested that extended RFS might be possible after liver transplantation with TAE for ruptured HCC [24–26]. Definitely, further studies with larger sample size are needed.

This meta-analysis had some limitations. First, randomized controlled trials offer the highest level of evidence in evidence-based research. However, currently, ruptured HCC requires urgent treatment. The treatment options of ruptured HCC are mainly based on the clinician's experience. Strict randomization was difficult to conduct in this study. Therefore, selection bias could not be eliminated, and prospective randomized controlled trials were difficult to perform. As a result, a majority of the eligible publications in the current study were nonrandomized trials that were limited by their retrospective nature. Second, the basic information report of patients was not comprehensive, thereby reducing the strength of evidence. Third, all included studies were conducted in China. A more general, worldwide study should be performed in the future, following increase in stent usage in other countries.

In conclusion, TAE with SH was effective in decreasing the intraoperative blood loss and the 30-day mortality compared with EH for ruptured HCC. However, the long-term DFS and OS may not be beneficial to preoperative TAE.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Yu-Fei Fu http://orcid.org/0000-0002-6772-6557

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