**INTRODUCTION**

**Review question / Objective:** To compare the efficacy, safety, and survival outcomes of hepatic arterial infusion chemotherapy (HAIC) versus transarterial chemoembolization (TACE) for treatment of advanced hepatocellular carcinoma (HCC).

**Condition being studied:** Hepatocellular carcinoma (HCC) is the seventh most common malignancy and the third most common cause of cancer death in the world, posing a serious threat to the health of world’s people. The occurrence of HCC is usually insidious. Most of patients were diagnosed with intermediate-advanced HCC at initial diagnosis, and less than 30% of them could receive radical resection.

**Information sources:** MEDLINE, PubMed, Web of Science, Embase and the Cochrane Central Register of Controlled Trials from the beginning to February 20, 2022 were retrieved.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 April 2022 and was last updated on 12 April 2022 (registration number INPLASY202240070).
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METHODS

Participant or population: The primary inclusion criteria were as follows: (1) Diagnosed advanced HCC of clinical and histopathological evidence; (2) Randomized controlled trials or observational studies; (3) all patients aged 18 years or older; (4) patients with Eastern Cooperative Oncology Group (ECOG) performance status<2; (5) patients had not been previously treated with surgical resection. The major exclusion criteria were as follows: (1) Patients combined with other malignant tumors; (2) risk estimates and associated 95% CI were not provided. (3) the publication was in the format of an abstract, comment, or review.

Intervention: Hepatic arterial infusion chemotherapy (HAIC).

Comparator: Transarterial chemoembolization (TACE).

Study designs to be included: Randomized controlled trials or observational studies.

Eligibility criteria: (1) Diagnosed advanced HCC of clinical and histopathological evidence; (2) Randomized controlled trials or observational studies; (3) all patients aged 18 years or older; (4) patients with Eastern Cooperative Oncology Group (ECOG) performance status<2; (5) patients had not been previously treated with surgical resection.

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Main outcome(s): Primary endpoints were objective response rate (ORR) and overall survival (OS).

Quality assessment / Risk of bias analysis: The quality of observational studies was determined according to the Newcastle-Ottawa Scale (NOS). Any study that scored over 7 stars was regarded as a high-quality study, and those with a score between four and six stars were regarded as moderate-quality studies. Jadad scale was used to evaluate the quality of the included RCTs.

Strategy of data synthesis: Pooled odds ratio (OR) with the corresponding 95% confidence interval (CI) was calculated to assess the efficacy of HAIC versus TACE on tumor response as well as on the incidence of grade 3-4 adverse events. Hazard ratio (HR) and the 95% CI were used to evaluate the survival advantage of HAIC compared with TACE. Homogeneity of effect size across studies was tested by Q statistics at the P<0.10 level of significance. The I² statistic, which is a quantitative measure of inconsistency across studies, was also calculated. A fixed-effect model was used for P>0.10 and I²<50%; otherwise, a random-effect model was used.

Subgroup analysis: We performed subgroup analyses (according to grade 3-4 adverse events) to reduce the degree of heterogeneity.

Sensitivity analysis: We further conducted a sensitivity analysis to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall risk estimate.

Country(ies) involved: China.

Keywords: hepatocellular carcinoma; hepatic arterial infusion chemotherapy; transarterial chemoembolization; meta-analysis.

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