The Role of Hepatic Arterial Infusion Chemotherapy in the Treatment of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Keywords

Hepatocellular carcinoma · Hepatic arterial infusion chemotherapy · Meta-analysis

Abstract

Background: The main aim of this study was to investigate comprehensively the clinical effect of hepatic arterial infusion chemotherapy (HAIC) on patients suffering from hepatocellular carcinoma (HCC). **Methods:** The following electronic databases were searched for eligible articles published from inception to July 2020: PubMed, Web of Science, Embase, and Cochrane Library. The main final indicators were overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS). **Results:** A total of 26 studies entailing 4,506 cases were included for a meta-analysis. The results showed that HAIC could improve advanced HCC patients' OS (HR, 0.49; 95% CI: 0.37–0.61) and PFS (HR, 0.52; 95% CI: 0.36–0.68). Remarkably, compared with Japan (HR, 0.58) and Korea (HR, 0.54), for the unresectable HCC patients, the HAIC group achieved higher efficacy on OS than the control group in China (HR, 0.24). The resectable HCC patients, who received HAIC adjuvant chemotherapy, exhibited favorable prognosis for OS (HR, 0.58; 95% CI: 0.27–0.88) and DFS (HR,

0.49; 95% CI: 0.31–0.68). **Conclusion:** HAIC improved long-term survival for both resectable and unresectable HCC patients in comparison with other therapies. However, the clinical effect of HAIC needs to be ascertained by large-scale well-designed studies.

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Introduction

Hepatocellular carcinoma (HCC) ranks sixth among the most common neoplasms worldwide, and it is attributed to >700,000 deaths yearly [1, 2]. In Eastern Asia (mainly in China, Korea, and Japan), HCC is associated with high incidence rates, malignancy, and rapid development [3]. Hepatic resection, liver transplantation, and local ablation are regarded as the common curative treatment approaches for the patients. However, for most patients, the tumor stage had already advanced by the time of their first diagnosis. Besides, they exhibit liver dysfunction, extrahepatic metastasis, or macro/microscopic vascular invasion [4]. The treatment for advanced HCC pa-

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tients is focused on transcatheter arterial chemoembolization (TACE), yttrium-90 radioembolization, sorafenib, and immunotherapy. Nevertheless, the overall therapeutic effect is limited [5–8]. The overall prognosis of the patients undergoing liver resections is normally poor as a result of the high postoperative recurrence rate [9].

A novel regimen exhibiting great safety as well as efficacy is urgently necessary to prolong the survival rate of the HCC patients. Recently, hepatic arterial infusion chemotherapy (HAIC) has been carried out as a new palliative chemotherapy for treating the advanced HCC patients [10–12]. Besides, it is an appropriate adjuvant chemotherapy for the resectable HCC patients following hepatic resection [13–15]. The HAIC procedure made chemotherapeutic agents to be delivered directly into the feeding arteries of the liver tumors, at high local drug concentrations using an implantable port system. As such, it ensured antitumor efficacy and minimized systemic toxicity, due to the stronger first-pass effect in comparison with the systemic chemotherapy [16]. Previous literature had assessed the effect of HAIC in treatment of the unresectable/resectable HCC patients in the palliative chemotherapy as well as adjuvant chemotherapy. However, HAIC efficacy and safety findings differed exceptionally and have been controversial [17]. As such, the main objective of this meta-analysis was to evaluate the outcomes of the long-term prognosis of HCC patients exhaustively using HAIC in the palliative chemotherapy and adjuvant chemotherapy.

Materials and Methods

Literature Search Strategy

Meta-analysis was carried out with respect to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines [18]. Published studies in the English language from the inception to July 2020 were searched in the following electronic databases: PubMed, Web of Science, Embase, and Cochrane Library. The article search strategies that were used included (“HAIC” OR “Hepatic Arterial Infusion Chemotherapy”) AND (“Hepatocellular Carcinoma” OR “Liver Cell Carcinomas” OR “Hepatoma” OR “Adult Liver Cancer” OR “HCC”). The reference lists of the retrieved studies were reviewed manually to obtain eligible articles.

Inclusion Criteria

The inclusion criteria in the meta-analysis entailed (1) HCC patients subjected to palliative HAIC or adjuvant HAIC after hepatic resection in the intervention group, (2) the included literature should be the original study, including observational studies (OBSs) or randomized controlled trials (RCTs), and (3) at least OS, DFS, and PFS related to prognostic information should be reported.

Exclusion Criteria

The exclusion criteria in the meta-analysis included the following: (1) in case of duplicate publications, the latest or high-quality study was included, (2) HAIC as a regimen instead of the only variable, such as HAIC + TACE versus sorafenib, (3) relevant data were unavailable, and (4) the studies included secondary liver carcinoma.

Data Extraction and Quality Evaluation

Under both the inclusion and exclusion criteria, two authors independently reviewed the included studies and extracted the related information. Disagreements between the two investigators regarding data extraction were solved via discussion or third-party intervention. The extracted appropriate information included author, year of publication, country, and patients’ demographic and clinicopathological characteristics such as etiology and extra-hepatic metastasis as well as the long-term prognosis for OS, PFS, or DFS.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the incorporated OBSs under three aspects: patient selection, comparability of the groups, and outcome evaluation. The literature scores >6 were considered to be of high quality [19]. The Cochrane Collaboration’s tool was used to evaluate the potential risks of bias on the retrieved RCTs.

Statistical Analysis

The hazard ratio (HR) and 95% confidence interval (CI) of each literature were used to establish the relationship between the therapies and prognosis. I^2 statistic was used to carry out the heterogeneity test. Since many regimens were included, the random-effect models were used to ensure greater reliability. Stata 12.0 software was used to conduct publication bias assessment and sensitivity analysis, when the number of the included literature is ≥ 10 . Publication bias was quantitatively assessed using the Begg’s and Egger’s test. Sensitivity analysis was used to determine the stability of the conclusions. The p value <0.05 was considered statistically significant.

Results

Data Collection and Characteristics

With regard to the search strategy, a total of 4,512 records were initially produced from the electronic databases. After the extraction of the duplicates, 2,003 records remained altogether. Twenty-six studies [5, 8, 10–15, 20–37] totaling 4,506 cases were eventually included following a strict layered screening. The comprehensive study review and selection process is as shown in Figure 1.

Twenty-six studies comprising 6 RCTs and 20 OBSs originated from China, Japan, and Korea. Among them, 21 and 5 studies presented the role of HAIC in palliative and adjuvant chemotherapies, respectively. Concerning the unresectable HCC patients, either HAIC alone or HAIC + sorafenib was the common interventional meth-

Fig. 1. A schematic flow for the selection of the articles included in this meta-analysis. HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy.

od. However, for the resectable HCC patients, HAIC was the adjuvant chemotherapy following surgery (Table 1). Besides, other information such as the status of extrahepatic metastasis, previous treatment, and hepatitis B virus (HBV) and hepatitis C virus infections was also recorded (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000518257).

The outcomes of OBS assessment indicated that the incorporated studies were of high quality. However, in the RCTs, personnel and patients were not blinded, and other biases were not mentioned (online suppl. Table 2).

Efficacy of HAIC on Palliative Treatment of Unresectable HCC

The random-effects model showed that the meta-analysis of the 21 studies of palliative chemotherapy had potential OS advantage for the unresectable HCC patients in the HAIC group unlike the control group (HR, 0.49; 95% CI: 0.37–0.61) (Fig. 2). Besides, the heterogeneity was high. It was also noted that for the unresectable HCC patients, the HAIC group achieved higher efficacy on OS than the control group in China (HR, 0.24) in comparison with Japan (HR, 0.58) and Korea (HR, 0.54). In various regimens of

Table 1. Characteristics of all the studies included in the meta-analysis

Author	Year	Country	Patients, <i>n</i>		Regimen		HAIC regimen	Role of HAIC	Study
			intervention	control	intervention	control			
Choi et al. [10]	2018	Korea	29	29	HAIC	Sorafenib	Cisplatin, 5-FU	Palliative	RCT
Kondo et al. [11]	2019	Japan	35	33	HAIC + sorafenib	Sorafenib	Cisplatin	Palliative	RCT
Kudo et al. [12]	2018	Japan	102	103	HAIC + sorafenib	Sorafenib	Cisplatin, 5-FU	Palliative	RCT
He et al. [20]	2019	China	125	122	HAIC + sorafenib	Sorafenib	Oxaliplatin, 5-FU, leucovorin	Palliative	RCT
Ikeda et al. [21]	2016	Japan	65	41	HAIC + sorafenib	Sorafenib	Cisplatin	Palliative	RCT
Hu et al. [22]	2020	China	22	24	HAIC	TACE/TAE	Oxaliplatin, 5-FU, leucovorin	Palliative	OBS
Ikuta et al. [23]	2018	Japan	26	72	HAIC + sorafenib	Sorafenib	Cisplatin, 5-FU	Palliative	OBS
Guo et al. [24]	2020	China	35	35	HAIC + TAE	TACE	Oxaliplatin, 5-FU, leucovorin	Palliative	OBS
Yang et al. [5]	2017	Korea	54	53	HAIC	Sorafenib	Cisplatin, 5-FU, epirubicin	Palliative	OBS
Hiramane et al. [25]	2011	Japan	45	20	HAIC	Sorafenib	Cisplatin, 5-FU, mitomycin-C, epirubicin	Palliative	OBS
Tsai et al. [26]	2014	Japan	58	44	HAIC	Systemic treatment	Cisplatin, 5-FU, mitomycin-C, leucovorin	Palliative	OBS
Song et al. [27]	2015	Korea	50	60	HAIC	Sorafenib	Cisplatin, 5-FU, epirubicin	Palliative	OBS
Nouso et al. [28]	2013	Japan	476	1,466	HAIC	Systemic treatment	Cisplatin, 5-FU	Palliative	OBS
Sumie et al. [8]	2003	Japan	16	21	HAIC	TACE	Cisplatin, 5-FU	Palliative	OBS
Moriya et al. [29]	2018	Japan	21	45	HAIC	Sorafenib	Cisplatin, 5-FU	Palliative	OBS
Moriguchi et al. [30]	2017	Japan	32	14	HAIC	Sorafenib	Cisplatin, 5-FU	Palliative	OBS
Lyu et al. [31]	2018	China	147	147	HAIC	Sorafenib	Oxaliplatin, 5-FU, leucovorin	Palliative	OBS
Kim et al. [32]	2014	Korea	50	49	HAIC	TACE	Cisplatin, 5-FU, carboplatin, adriamycin	Palliative	OBS
Kang et al. [33]	2018	Korea	95	44	HAIC	Sorafenib	Cisplatin, 5-FU	Palliative	OBS
Ikeda et al. [34]	2013	Japan	66	48	HAIC	Sorafenib	Cisplatin	Palliative	OBS
Akiyama et al. [35]	2008	Japan	10	13	HAIC	Systemic treatment	Cisplatin, 5-FU	Palliative	OBS
Huang et al. [36]	2015	China	42	43	Surgery + HAIC	Surgery	Oxaliplatin, 5-FU, gemcitabine	Adjuvant	RCT
Hsiao et al. [13]	2017	China	61	160	Surgery + HAIC	Surgery	Cisplatin, 5-FU, leucovorin, epirubicin	Adjuvant	OBS
Nitta et al. [14]	2013	Japan	38	35	Surgery + HAIC	Surgery	Cisplatin, 5-FU, mitomycin-C	Adjuvant	OBS
Kojima et al. [15]	2015	Japan	27	25	Surgery + HAIC	Surgery	Cisplatin, 5-FU, epirubicin	Adjuvant	OBS
Niguma et al. [37]	2005	Japan	6	6	Surgery + HAIC	Surgery	Cisplatin, 5-FU	Adjuvant	OBS

HAIC, hepatic artery infusion chemotherapy; RCT, randomized controlled trial; OBS, observational study; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization; 5-FU, 5-fluorouracil.

intergroup (HAIC vs. sorafenib, HAIC vs. TACE, HAIC vs. others, and HAIC + sorafenib vs. SORAFENIB), the patients receiving HAIC showed improved OS, and the results were statistically significant (Table 2).

Analysis on the 11 included studies referred to as PFS implied that HAIC could improve PFS of unresectable patients (HR, 0.52; 95% CI: 0.36–0.68) (Fig. 3). Besides, subgroup analyses showed that in comparison with the

control group, the HAIC group achieved the most benefit on PFS in China (HR, 0.29), followed by Korea (HR, 0.50). However, in Japan (HR, 0.98), the HAIC did not improve the patients' PFS. The HAIC group evidently increased the PFS (HR, 0.32) compared with the TACE regimen. However, HAIC efficacy was not statistically significant in comparison with sorafenib (HR, 0.64; 95% CI: 0.26–1.03) (Table 2).

Fig. 2. Forest plot of the overall survival of the patients with unresectable hepatocellular carcinoma on palliative hepatic arterial infusion chemotherapy ($p < 0.001$).

Table 2. Subgroup analysis of the prognosis of HCC patients receiving HAIC

	Studies, <i>n</i>	HR	95% CI	Heterogeneity (I^2), %
Palliative chemotherapy				
OS				
Japan	12	0.58	0.42–0.74	67.3
China	4	0.24	0.10–0.38	82.4
Korea	5	0.54	0.40–0.68	13.3
HAIC versus sorafenib	10	0.45	0.25–0.65	80.5
HAIC versus TACE	3	0.52	0.12–0.92	81.8
HAIC versus others	3	0.38	0.22–0.54	63.1
HAIC + sorafenib versus sorafenib	5	0.67	0.39–0.96	81.2
HAIC versus sorafenib/TACE/others	16	0.43	0.30–0.57	86.5
PFS				
Japan	4	0.98	0.63–1.32	63.0
China	4	0.29	0.14–0.43	82.2
Korea	3	0.50	0.23–0.78	51.8
HAIC versus sorafenib	4	0.64	0.26–1.03	82.3
HAIC versus TACE	2	0.32	0.17–0.81	89.6
HAIC + sorafenib versus sorafenib	4	0.68	0.34–1.01	86.4
HAIC versus sorafenib/TACE/others	6	0.49	0.24–0.75	87.6
HAIC + (sorafenib/TACE) versus sorafenib/TACE	5	0.58	0.34–0.83	82.3
Adjuvant chemotherapy				
OS				
Japan	3	0.43	0.08–0.78	49.6
China	2	0.78	0.25–1.31	74.4
DFS				
Japan	2	0.51	0.28–0.74	0.0

HAIC, hepatic artery infusion chemotherapy; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival.

Fig. 3. Forest plot of the progression-free survival of the patients with unresectable hepatocellular carcinoma on palliative hepatic arterial infusion chemotherapy ($p < 0.001$).

Fig. 4. Forest plot for the long-term survival of the patients with resectable hepatocellular carcinoma on adjuvant hepatic arterial infusion chemotherapy after hepatectomy (**a** OS, $p < 0.001$; **b** DFS, $p < 0.001$).

Efficacy of HAIC on Adjuvant Chemotherapy of Resectable HCC

HAIC was vital in adjuvant and palliative chemotherapies. Five and 3 studies entailed the OS and DFS, respectively, for the resectable HCC patients in the adjuvant chemotherapy. The HAIC group had a favorable prognosis on OS in comparison with the control group (HR, 0.58; 95% CI: 0.27–0.88) and DFS (HR, 0.49; 95% CI: 0.31–0.68) (Fig. 4). HAIC improved the Japanese patients' OS (HR, 0.43) and DFS (HR, 0.51). However, in China, the HAIC did not improve DFS (HR, 0.78; 95% CI: 0.25–1.31) (Table 2).

Sensitivity Analysis and Publication Bias

Due to the limitation of the included literature of adjuvant chemotherapy, the sensitivity and publication bias tests were carried out for the included literature of

palliative chemotherapy. The sensitivity analysis demonstrated a terrific stability of the HR for OS after sequentially omitting each included literature on palliative chemotherapy (online suppl. Fig. 1). The quantificational Egger's and Begg's tests were used to evaluate publication bias, and the result of Egger's and Begg's tests was not significantly different ($p > 0.05$). This suggested that there were no publication biases among the included literature on HAIC and OS (online suppl. Fig. 2).

Besides, the sensitivity analysis indicated that individual study had little impact on the final PFS results, and as such, the results remained stable (online suppl. Fig. 3). Similarly, no publication biases were realized in the included studies on HAIC and PFS ($p > 0.05$) (online suppl. Fig. 4).

Discussion

The findings of this meta-analysis suggested that HAIC improves OS and PFS of the advanced HCC patients unlike other therapies in the palliative chemotherapy. Prolonged OS and PFS was realized in the patients treated with HAIC, and this was consistent with the findings reported in previous studies [10–12]. In a randomized phase 3 trial [12], HAIC plus sorafenib combination therapy exhibited longer PFS in the advanced HCC patients in comparison with sorafenib monotherapy. This implies that combination therapy probably had additive anticancer effects on the patients. Remarkably, a comparative study [26], published in 2014, demonstrated that HAIC could achieve longer OS in patients suffering from advanced HCC than sorafenib treatment. However, the results were not statistically significant, which could have resulted from the status of most advanced HCC patients with extrahepatic spread and large tumor size (>10 cm). Besides, another OBS [35], originating from Japan, reported that HAIC improved OS significantly for the unresectable HCC patients in comparison with the systemic treatment (HR 0.17, $p = 0.021$). However, the study size of the sample was small, only incorporating 23 patients, and this made the findings unconvincing.

To comprehensively explain the mechanism of HAIC affecting HCC, from the previous literature, we found out that the mechanism probably involves inhibition of the tumor cell proliferation and induction of tumor cell apoptosis [38–42]. Through HAIC, the chemotherapeutic drugs are delivered directly into the hepatic arteries of the liver, at high local drug concentrations. This improves the efficacy of the drug on malignant cells as much as possible. Meanwhile, with a first-pass effect of the hepatic clearance, the drugs are generally metabolized in the liver, resulting in low drug concentrations in the peripheral blood besides reducing the side effects [16]. 5-Fluorouracil (5-FU), a chemotherapeutic drug used in HAIC, prevents tumor cell proliferation via antimetabolism. With high local drug concentrations, HAIC enhances the mechanism by which 5-FU inhibits enzyme thymidylate synthase, thus preventing the thymidine formation demanded for DNA synthesis [38]. Besides, cisplatin, another chemotherapeutic agent used in HAIC, can cross connect with adenine and cytosine in the DNA, hence destroying the structure and function of DNA. It also interferes with the synthesis and repair mechanisms of DNA and consequently induces the apoptosis of the cancerous cells [39]. With regard to oxaliplatin, normally, it exerts its antitumor effect via inhibiting the replication

and transcription of DNA [40, 41]. Recent studies have reported that oxaliplatin can not only bind to a variety of subcellular structures but also act on tumor microenvironment and enhance the immune response to the tumor cells [41, 42].

This meta-analysis showed that HAIC could improve OS and PFS of the advanced HCC patients unlike other therapies. Although the heterogeneity was high, we performed the subgroup analysis to make the results more convincing and scientific. Among the different countries (China, Japan, and Korea), compared with the control group, HAIC improved the advanced HCC patients' OS and PFS. In China, the HAIC group exhibited the highest benefit for the patients than the control group (HR, 0.24). For Japan (HR, 0.58) and Korea (HR, 0.54), the results were also statistically significant. We realized that the selection of chemotherapeutic agents in HAIC treatment is an important factor in the prognosis of advanced HCC patients. In the previous research, cisplatin-based HAIC treatment had been applied in the unresectable HCC patients. However, the therapeutic program effect was unsatisfactory. In comparison with cisplatin, oxaliplatin had better biochemical, immunologic, and pharmacokinetic effect [43, 44]. As such, it is better to use oxaliplatin instead of cisplatin in the HAIC scheme. In the included studies for the Chinese patients, most HAIC regimens adopted HAIC of oxaliplatin, leucovorin, and fluorouracil. On the other hand, Japan and Korea generally adopted HAIC treatment based on cisplatin for the advanced HCC patients [20, 22, 24, 26, 31]. We also realized that the average age of patients in China was lower than that in Japan and Korea. Many elderly patients were exceedingly pessimistic once they were diagnosed unlike the young patients who faced the disease with a positive mood. In addition, the elder patients' emotion and psychological status had a negative impact on the HCC development. During the clinical diagnosis and subsequent treatment, the elderly patients easily exhibited a variety of psychological problems including anxiety, tense, depression, and other aftermaths. This in turn reduced the treatment effect of the HCC greatly [45]. Also, a study found that the HBV-related HCC patients had benefited more from the treatment in comparison with non-HBV patients [23]. HBV infection is the major etiology of HCC patients in China.

With regard to the PFS subgroup analysis, we realized that the patients receiving HAIC did not improve PFS compared to the control group in Japan (HR, 0.98). A potential risk factor for the disease is chronic stress. In Japan, under a long-term chronic stress, the cortisol secre-

tion level of HCC patients increased, which probably decreased the expression of the cortisol receptor. This in turn reduces the anti-inflammatory reaction thus promoting inflammation [46]. HCC is a malignant tumor that is closely associated with inflammation, which contributes to the occurrence and metastasis of HCC [47].

As an adjuvant chemotherapy, HAIC also plays a vital role in patients subjected to liver resection. The outcome of the subgroup analysis demonstrated that the Japanese patients receiving adjuvant HAIC regimen had longer OS and PFS than those who underwent liver resection only. In China, the HAIC regimen was not effective on the patients. The main reason behind this difference is probably the small number of the included literatures.

Before we conducted this study, we realized that some researchers had already carried out relevant meta-analyses. However, due to the lack of some related data and in-depth research, the studies had certain limitations [48–50]. Zhuang et al. [48] suggested that in comparison with sorafenib treatment, HAIC enhanced advanced HCC patients' long-term survival for OS (HR, 0.60) and PFS (HR, 0.69). However, the regimens only included HAIC and sorafenib, and this was therefore not appropriate for a comprehensive and systematic evaluation of the effect of HAIC on advanced HCC patients. Another limitation was that all of the included studies in the meta-analysis were OBSs. Ouyang et al. [49] suggested that sorafenib plus HAIC regimens showed significant improvement on OS (HR, 0.59) than sorafenib monotherapy. In addition, there were no statistics on the patient's PFS data, and the number of the included studies was only 5, which notably decreased the quality of evidence. Long et al. [50] reported that HAIC improved HCC patients' OS (HR, 0.61) and DFS (HR, 0.66) in comparison with other therapies. However, an evident limitation was uncertainty in patient selection, and patients with various liver malignant tumors involving primary HCC and secondary HCC were included.

This study had several limitations as follows: first, most of the included articles in this study were OBSs, and a few articles were RCTs. This might have led to selection bias of the results and as such inevitably caused overvaluation or undervaluation of the measured effects. Second, due to the lack of relevant data on HCC patients, we could not perform more subgroup analyses in terms of age, HAIC regimen, and etiology, so as to explore the effects of HAIC in the specific research patients. Third, all of the populations evaluated in this meta-analysis were from Asian countries. For this reason, this conclusion could not be directly applied to the Western or African population.

Conclusion

Our study demonstrated that HAIC improved long-term survival in OS and PFS unlike other conventional therapies in patients suffering from advanced HCC. This was particularly observed among the patients in China. Besides, the combination of hepatic resection with adjuvant HAIC improved OS and DFS for patients suffering from resectable HCC. As such, HAIC is an alternative therapeutic choice for both resectable and unresectable HCC patients. However, large-scale prospective RCTs should be designed to ascertain the clinical effect of HAIC.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Each author contributed significantly to the concept and development of the present manuscript. D.C.Z. and S.Z.L. designed the research process. J.X.X. and J.Z.H. searched the database for corresponding articles. H.Y.Z. and Y.X.S. extracted useful information from the articles above. T.Y. used statistical software for analysis. Y.J.H. drafted the meta-analysis. D.M.N. polished this article. All authors had read and approved the manuscript and ensured that this was the case.

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