Arsenic trioxide combined with transarterial chemoembolization for unresectable primary hepatic carcinoma

A systematic review and meta-analysis

Peng Song, PhD\textsuperscript{a,c}, Yang Hai, MD\textsuperscript{b}, Wantong Ma, MD\textsuperscript{b}, Longhe Zhao, MD\textsuperscript{b}, Xin Wang, PhD\textsuperscript{b}, Qinjian Xie, PhD\textsuperscript{a}, Yang Li, PhD\textsuperscript{b}, Zhengrong Wu, PhD\textsuperscript{b}, Yingdong Li, PhD\textsuperscript{d}, Hongyu Li, PhD\textsuperscript{a,b,∗}

Abstract

**Background:** Primary hepatic carcinoma (PHC) is the third commonest leading to cancer death around the world, and transarterial chemoembolization (TACE) has been proposed as the first-line therapeutic treatment for patients with unresectable PHC. This study aims to determine whether the combination of As\textsubscript{2}O\textsubscript{3} and TACE is superior to alone TACE for achieving more clinical therapeutic efficacy, survival time, life quality and safety in patients with unresectable PHC.

**Methods:** A comprehensive literature search was conducted on the clinical controlled trials comparing therapeutic effects of As\textsubscript{2}O\textsubscript{3} & TACE versus alone TACE for unresectable PHC through English databases (including PubMed, Embase, and the Cochrane Library) and Chinese databases (including China Knowledge Resource Integrated Database, Wanfang Database, Weipu Database, and Chinese Biomedical Database). The last search was in 30 August 2017. A recursive search was performed with bibliographies of relevant studies. There were no language restrictions. Primary outcomes, defined a priori, were therapeutic responses (clinical effective rate and clinical benefit rate), survival time, life quality, and adverse events of As\textsubscript{2}O\textsubscript{3} & TACE compared with alone TACE expressed as relative risk (RR) with 95% confidence intervals (CI).

**Results:** 25 clinical controlled trials involving 1886 participants were included. We found that there were significant superiority associated with As\textsubscript{2}O\textsubscript{3} & TACE compared with alone TACE in clinical benefit rate (RR: 1.24, 95% CI: 1.12–1.37), clinical effective rate (RR: 1.35, 95% CI: 1.17–1.55), 2-year survival rate (RR: 1.45, 95% CI: 1.20–1.75), and improving of KPS (RR: 1.31, 95% CI: 1.14–1.50). These associations were also observed in subgroups by intervened methods of As\textsubscript{2}O\textsubscript{3} and pulmonary metastasis. Notably, the pooled relative risk of retention of sodium and water was obviously raised in patients with As\textsubscript{2}O\textsubscript{3} & TACE therapy (RR: 16.616, 95% CI: 8.01–34.486).

**Conclusion:** The superiority of adjuvant As\textsubscript{2}O\textsubscript{3} therapy combined with TACE in PHC individuals will outweigh alone TACE therapy, especially in PHC populations with pulmonary metastasis.

**Abbreviations:** ALP = acute promyelocytic leukemia, CBR = clinical benefit rate, CER = clinical effective rate, CI = confidence intervals, CR = complete response, KPS = Karnofsky performance scale, PD = progressive disease, PHC = primary hepatic carcinoma, PR = partial response, RCT = randomized controlled trials, RR = relative risk, SD = stable disease, TACE = transarterial chemoembolization.

**Keywords:** arsenic trioxide, meta-analysis, primary hepatic carcinoma, systematic review, transarterial chemoembolization

1. Introduction

Primary hepatic carcinoma (PHC) is the third commonest leading to cancer death around the world, and being liable for about 700,000 deaths annually, based on precious statistic with an increasing incidence.\textsuperscript{[1]} Furthermore, the GOLOBOCAN database demonstrates geographical differences in the incidence of PHC, with the severe disease spreading further commonly in China, southern Asia, and eastern Africa in which the popularity of the disease surpasses 20 cases per 100,000 people.\textsuperscript{[2]} Therefore, PHC has a substantial influence on morbidity around the world, extraordinarily common in the developing countries, which causes both medical and economic burdens to our society.

Surgical resection and liver transplantation, supported by level IIA evidence, are considered to possess positive therapeutic effect on the patients. However, the rarely available organ and the undesirable surgical effect can impose restrictions on the cure among 90% of patients.\textsuperscript{[3]} Besides, aside from the above facts, there are 80% of these patients could suffer from the tumor recurrence within 5 years after surgical resection. What’s more, the tumor recurrence of disease could happen to half of these...
patients approximately within 2 years.\textsuperscript{[14]} There are 90\% of patients, as the remaining, being not suitable for surgical candidates, while interventional oncology can supply a broad extent of treatment as alternatives.\textsuperscript{[23]} In recent years, transarterial chemoembolization (TACE) has been proposed as the first-line therapeutic treatment for patients with unresectable PHC, because it is capable of allowing the synergistic influence of greater local levels ofchemotherapeutic agents and occlusion of the artery supplying nutrients to a tumor.\textsuperscript{[5,6]} Chemotherapeutic agents commonly used in TACE include 5-fluorouracil, antibiotics (mitomycin, adriamycin, and pirarubicin), and platinum drugs (cisplatin and oxaliplatin).

Arsenic trioxide (As\textsubscript{2}O\textsubscript{3}) is one of the oldest drugs in the world but was progressively revived between the 1970s and 1990s, because of its striking efficacy on acute promyelocytic leukemia (APL), which represented the most malignant type of acute leukemia.\textsuperscript{[17]} These paradoxical effects of As\textsubscript{2}O\textsubscript{3} reflect its multiple properties, thus, it has been considered to be an effective chemotherapeutic agent for various solid tumors such as PHC.\textsuperscript{[23]} Currently, As\textsubscript{2}O\textsubscript{3} was only approved for palliative treatment for the patients with unresectable PHC by China Food and Drug Administration. However, recent studies have reported that the treatments of single-agent As\textsubscript{2}O\textsubscript{3} were not a significant benefit for patients with PHC, but the benefit of adjuvant As\textsubscript{2}O\textsubscript{3} dramatically emerged when it was combined with other therapeutic treatments such as TACE.\textsuperscript{[9,10]}

Moreover, in the last few years, As\textsubscript{2}O\textsubscript{3} combined with TACE is used to treat PHC, as seen in the increasing number of clinical research reports. Those reports explored the potential effects of adjuvant As\textsubscript{2}O\textsubscript{3} therapy in patients with PHC and revealed that As\textsubscript{2}O\textsubscript{3} could induce the apoptosis of hepatic carcinoma cells by activating mitochondrial pathway of apoptosis and inhibiting the expression of proliferating cell nuclear antigen.\textsuperscript{[11]}

Currently, only 2 meta-analysis reviews have been published to evaluate the benefits of As\textsubscript{2}O\textsubscript{3} combined with TACE in the treatment of PHC.\textsuperscript{[12,13]} However, previous reviews have been nonsystematic, have not focused on specific intervened methods or adverse events, and have not included the latest clinical trials. Additionally, there were some unknown high heterogeneity and possible publication bias in those meta-analysis reviews, which suggests the evidence on the benefits of As\textsubscript{2}O\textsubscript{3} combined with TACE should also be revisited. The objective of this systematic review and meta-analysis is to evaluate broadly the available evidence that combination of As\textsubscript{2}O\textsubscript{3} and TACE is superior to alone TACE for achieving more clinical therapeutic efficacy, survival time, life quality, and safety in patients with PHC.

2. Methods

2.1. Search strategy

A systematic literature search was conducted in English databases, including PubMed, Embase, and the Cochrane Library, and Chinese databases, including China Knowledge Resource Integrated Database (CNKI), Wanfang Database, Weipu Database (VIP), and Chinese Biomedical Database (CRBM). The literature search was performed from inception to August 1, 2017. Randomized controlled trials (RCTs) including patients with primary hepatic carcinoma, either treated with alone TACE or combination of As\textsubscript{2}O\textsubscript{3} were identified. The following search terms were used: “arsenic trioxide (or) arsenious acid (or) As\textsubscript{2}O\textsubscript{3} (or) arsenic sesquioxide (or) arsenious oxide (or) arsenious anhydride (or) white arsenic (or) arsenic (III) oxide (or) arsenite (or) trisenox (or) trienox (or) naonobin (or) arsenolate (or) arsenous,” “liver cancer (or) liver neoplasms (or) hepatic carcinoma (or) hepatocellular cancer,” and “transcatheter arterial chemoembolization (or) transarterial chemoembolization (or) TACE.” There were no language restrictions, and abstracts of the papers identified by the initial search were evaluated by the lead reviewer for appropriateness to the study question. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature.

2.2. Study selection

Articles were assessed independently by 2 investigators using pre-designed eligibility forms according to the eligibility criteria, defined prospectively. Any disagreement between investigators was resolved by consensus. The inclusion criteria were as follows: clinical controlled trials were published as peer-reviewed articles; participants were diagnosed with primary hepatic carcinoma clinically; therapeutic effects of As\textsubscript{2}O\textsubscript{3} & TACE and TACE were compared in the references; and main outcomes, such as therapeutic responses (categorized as clinical effective rate and clinical benefit rate according to the World Health Organization criteria), survival time, life quality, and adverse events were reported. Exclusion criteria for this meta-analysis were as follows: As\textsubscript{2}O\textsubscript{3} was used in a combination with other treatment options; studies including participants with secondary hepatic carcinoma; studies including participants who were duplicated in similar studies; As\textsubscript{2}O\textsubscript{3} was used by exceeding one method of administration in a study; and unsuitable publication types, such as meeting abstracts, comments, reviews, or case reports.

2.3. Data abstraction

Data extraction was completed by 2 reviewers independently, and disagreements were settled by a third reviewer. The following data were extracted from each study: the study characteristics, including first author’s name, year of publication, number of patients for each group, age distribution, sex distribution, Child-Pugh classification, presence or absence of pulmonary metastasis, and protocols for each group, and the main outcomes, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), half-year survival rate, 1-year survival rate, 2-year survival rate, 3-year survival rate, improvement rate of Karnofsky performance scale (KPS) scores, maintaining rate of KPS scores, and various adverse events. The corresponding authors were contacted for supplementary data which were not included in original articles.

2.4. Assessment of risk of bias

Risk of bias assessment was performed independently by 2 investigators, with disagreements resolved by discussion. Risk of bias was assessed as described in the Cochrane Collaboration’s tool by recording the method used to generate the randomization schedule and conceal allocation; whether blinding was implemented for participants, staff, and outcome assessment; what proportion of subjects completed follow-up; and whether there was evidence of selective reporting of outcomes.\textsuperscript{[14]}

2.5. Data synthesis and statistical analysis

The clinical benefit rate (CBR) was defined as the percentage of CR, PR, and SD patients, and the clinical effective rate (CER) was
defined as the percentage of CR and PR patients. Data of risk ratios (RR) were pooled using a random effects model to give a more conservative estimate of the effect of As$_2$O$_3$ & TACE therapy on the subsequent occurrence of CER and CBR, allowing for any heterogeneity. Heterogeneity between studies was assessed using both the $I^2$ statistic with a cut off of $\geq50\%$ and the chi-squared test with a $P$ value $<.10$ used to define a significant degree of heterogeneity. Where the degree of statistical heterogeneity was greater than this between trial results, possible explanations were investigated using subgroup analyses according to intervened methods of As$_2$O$_3$ (intravenous drip, arterial chemoembolization with other drugs in TACE group, arterial perfusion, and arterial chemoembolization without other drugs) and presence or absence of pulmonary metastasis. The survival rates for the different time, the improvement and maintaining rates of KPS scores, and various adverse events were presented as RR with 95% confidence interval (CI) by using the fixed-effects model (Mantel–Haenszel method). We compared individual relative risks between these analyses using the Cochran $Q$ statistic. Publication bias was tested with funnel plots regression, and Egger test$^{[16]}$ and Harbord modified test$^{[17]}$ were used to measure funnel plot asymmetry. However, the publication bias would not be formally assessed if a small number of studies ($<10$) were included in the analyses of outcome measures.$^{[18]}$ These were exploratory analyses only and may explain some of the observed variability, but the results should be interpreted with caution. All statistical analyses were performed using the Review Manager version 5.3.4 (RevMan for Windows WIN7, the Nordic Cochrane Centre, Copenhagen, Denmark) and StataSE version 12.0 (Stata Corporation, College Station, TX). All analyses were based on previous published studies; thus, no ethical approval and consent from patients are required.

3. Results
3.1. Search result
The search of literature initially identified 161 potentially relevant references. The references included 6 English articles and 155 Chinese articles. Sixty-two studies were excluded as duplicates in different databases. Following the examination of titles and abstracts, 40 studies were selected for further full-text evaluation. Of the remaining records, 25 RCTs fulfilled the criteria for inclusion in a quantitative synthesis (meta-analysis)$^{[10,19–42]}$ Details of study selection are presented in Fig. 1.

3.2. Description of the included studies
Of the remaining 25 articles we identified, 3 studies were written in English and 22 studies were written in Chinese. All included studies were published in China between 2003 and 2017. Descriptive data for the studies included in our analysis were summarized in Table 1. A total of 1886 patients were enrolled, comprising 940 patients from the experimental group and 946 patients from the control group. The total male/female ratio was 1476/410, and the age range was 21 to 82 years. All included trials used similar inclusion criteria for each group. The TACE therapy was implemented with a standard protocol in each study, including the following steps: the Seldinger method was adopted for the puncture of the femoral artery; a catheter was inserted, then digital subtraction arteriography-guided celiac arteriography was performed; a 3F microcatheter was used to infuse chemotherapeutic agents, and gelatin sponge particles into each target vessel. In the experimental group, the intervened methods of As$_2$O$_3$ were respectively implemented by intravenous drip, arterial chemoembolization with other drugs in TACE group, arterial perfusion, and arterial chemoembolization without other
Table 1
Baseline characteristics of the included studies.

| No | Study reference   | Year (language) | Samples (male/female) | Sex | Age | Child-Pugh classification | Pulmonary metastasis | Protocol (per course) | Number of course |
|----|------------------|-----------------|-----------------------|-----|-----|---------------------------|---------------------|---------------------|------------------|
| 1  | Wang XD (37)     | 2013 (Chinese)  | 34/33                 | 55/12 | 31–77 | B34 B33                   | No                  | AsO3 (10 mg/d), 14 days + TACE | 4               |
| 2  | Zhuang XL (38)   | 2006 (Chinese)  | 62/56                 | 44/18 | 36/20 | 26–76                     | A28 B32 C2          | TACE (Epi-ADM 30 mg + AsO3 10 mg, iv, 28 days) | 4               |
| 3  | Zhang XB (55)    | 2011 (Chinese)  | 30/30                 | 36/25 | 26–78 | 31–68                     | A3 B32 C4           | TACE (Epi-ADM 40 mg) | 2               |
| 4  | Zhou YT (42)     | 2007 (Chinese)  | 41/45                 | 36/65 | 27–75 | 23–74                     | A35 B6 B37 B8       | TACE (Epi-ADM 30 mg) | 3               |
| 5  | Meng YL (26)     | 2013 (Chinese)  | 30/30                 | 34/16 | 19–11 | 11–28                     | NA NA               | TACE (Adriamycin 20 mg/m² + AsO3 50 mg + 125I 8 g), 10–30 mL, 28 days | 4               |
| 6  | Cui Z (31)       | 2006 (Chinese)  | 26/29                 | 7/25  | 21–54 | 39–65                     | A19 B7              | TACE (Epi-ADM 30 mg, 14 days) | 4               |
| 7  | Zheng S (29)     | 2013 (Chinese)  | 30/34                 | 32/76 | 18–26 | 28–76                     | NA NA               | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 8  | Qi X (38)        | 2003 (Chinese)  | 34/30                 | 10/5  | 25/46 | 8–38                      | A24 B2 C4           | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 9  | Lu XD (36)       | 2006 (Chinese)  | 27/25                 | 24/3  | 23–72 | 35–71                     | A/B A/B             | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 10 | Yan TH (32)      | 2013 (Chinese)  | 30/32                 | 32/8  | 19–26 | 29–74                     | A25 B5              | TACE (Epi-ADM 20 mg, ac) | 4               |
| 11 | Zhu GH (35)      | 2010 (Chinese)  | 16/15                 | 27/4  | 27–82 | NA NA                     | No                  | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 12 | Xie YR (41)      | 2007 (Chinese)  | 33/32                 | 28/8  | 21–70 | NA NA                     | No                  | TACE (Epi-ADM 10 mg, ac) | 4               |
| 13 | Hu Q (37)        | 2014 (Chinese)  | 28/25                 | 21/7  | 17–80 | 31–60                     | NA NA               | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 14 | Meng YL (40)     | 2015 (Chinese)  | 30/30                 | 27/3  | 36–76 | 36–76                     | A/B A/B             | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 15 | Xiang W (33)     | 2014 (Chinese)  | 27/28                 | 22/5  | 35/75 | 60.2 ± 10.50              | 58.76 ± 10.78       | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 16 | Xing R (28)      | 2012 (Chinese)  | 23/28                 | 18/5  | 23/32 | 55.43 ± 10.49             | 54.84 ± 8.24        | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 17 | Guan UK (25)     | 2014 (Chinese)  | 40/40                 | 32/8  | 55/35 | 33–61                     | A17 B6              | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 18 | Huang LJ (24)    | 2015 (Chinese)  | 15/15                 | 13/2  | 11/4  | 57.80 ± 9.56              | 57.92 ± 12.38       | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 19 | Wang SM (30)     | 2012 (Chinese)  | 30/30                 | 26/3  | 25/55 | 54.72 ± 10.77             | 57.04 ± 9.46        | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 20 | Gao CK (20)      | 2015 (Chinese)  | 78/78                 | 48/30 | 5/27  | 22–74                     | NA NA               | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 21 | Nan DF (21)      | 2015 (Chinese)  | 75/81                 | 9/67  | 45–76 | NA B65 C15               | No                  | TACE (AsO3 25 mg, ac) | 4               |
| 22 | Yang BJ (19)     | 2015 (Chinese)  | 40/40                 | 21/19 | 22/18 | 59.1 ± 2.03               | 61.50 ± 1.80        | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 23 | Bao L (30)       | 2015 (English)  | 70/69                 | 58/12 | 62/7  | 36 (<55)                  | 31 (<55)            | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 24 | Hui W (34)       | 2015 (English)  | 61/64                 | 51/10 | 55/9  | 33–71                     | A62 B9              | TACE (Epi-ADM 10 mg, 14 days) | 4               |
| 25 | Hu HT (33)       | 2017 (English)  | 30/30                 | 22/8  | 19/11 | 51.7 ± 9.2               | 52.4 ± 12.3         | TACE (Epi-ADM 10 mg, 14 days) | 4               |

The TACE-related chemotherapeutic agents are summarized in brackets: (5-FU = fluorouracil, ADM = adriamycin, Epi-ADM = epirubicin, DOX = doxorubicin, CBP = carboplatin, HDT = hydroxyamptotenin, 125I = iodine-125, 5-FU = 5-fluorouracil, ADM = adriamycin, THP = thriamycin, DDP = cisplatin, MMC = mitomycin, CAP = chloromycin, OX1 = oxaxiplatin, LBP = lobaplatin). ac = arterial chemoembolization, ap = arterial perfusion, AsO3 = arsenic trioxide, C = control group for TACE alone, E = experimental group for AsO3 and TACE, iv = intravenous drip, NA = not applicable, TACE = transarterial chemoembolization.
drugs. Only in the 4 trials, all patients were diagnosed PHC with pulmonary metastasis and intervened by the intravenous drip of As$_2$O$_3$. We also performed a subgroup analysis of some outcome measure basing on intervened methods of As$_2$O$_3$ and presence or absence of pulmonary metastasis, if the heterogeneity was significant.

### 3.3. Quality assessment of the included studies

We used the Cochrane Collaboration’s tool to evaluate the quality of the included studies and found that 25 studies were randomized. The results of the quality assessment can be seen in Table 2. A major problem we found was that, although the participants were randomized into 2 groups in each trial, most of the trials did not present the details of sequence generation (10 RCTs), allocation concealment (19 RCTs), and blinding methods (22 RCTs). Therefore, the corresponding risks of bias could not be excluded. Furthermore, as a result of inadequate information was given, the judgment for “other sources of bias” also was “unclear” for most included trials (22 RCTs).

### 3.4. Quantitative analyses

#### 3.4.1. Clinical benefit rate

The clinical benefit rate (CBR) was reported in 23 studies. The pooled CBR was significantly higher in the As$_2$O$_3$ & TACE group compared with the TACE group (RR: 1.24, 95% CI: 1.12–1.37, $Z = 4.13$, $P = .000$). Notably, the significant heterogeneity was detected among the studies ($P = .000$, $I^2 = 71.1\%$). In the subgroup analysis according to intervened methods of As$_2$O$_3$, statistically significant differences of CBR were obtained from intravenous drip group (RR: 1.65, 95% CI: 1.21–2.26, $Z = 3.12$, $P = .002$) and arterial chemoembolization with other drugs in TACE group (RR: 1.17, 95% CI: 1.09–1.26, $Z = 4.19$, $P = .000$), however, no statistically significant differences of CBR were obtained from arterial perfusion group (RR: 1.07, 95% CI: 0.94–1.22, $Z = 0.97$, $P = .330$) and arterial chemoembolization without other drugs group (RR: 1.22, 95% CI: 0.98–1.52, $Z = 1.77$, $P = .077$) (Fig. 2). Heterogeneity between studies for each subgroup indicated that the reason of significant heterogeneity for all studies is the high heterogeneity for intravenous drip group ($P = .000$, $I^2 = 90.2\%$), and the heterogeneity for other groups were not detected ($P > .1$, $I^2 = 0.0\%$). Furthermore, in order to explore the reason of high heterogeneity for intravenous drip group, we distinguished 2 subgroups based on presence or absence of pulmonary metastasis in intravenous drip group with the high heterogeneity. Similar positive results were obtained from both the absence of pulmonary metastasis group (RR: 1.15, 95% CI: 1.06–1.25, $Z = 3.22$, $P = .001$) with no heterogeneity between studies ($P = .919$, $I^2 = 0.0\%$) and presence of pulmonary metastasis group (RR: 4.55, 95% CI: 2.69–7.68, $Z = 5.65$, $P = .000$) with no heterogeneity between studies ($P = .191$, $I^2 = 36.8\%$) (Fig. 3).

#### 3.4.2. Clinical effective rate

The clinical effective rate (CER) was reported in 24 studies. The pooled CER was significantly higher in the As$_2$O$_3$ & TACE group compared with the TACE group (RR: 1.35, 95% CI: 1.17–1.55, $Z = 4.23$, $P = .000$). Notably, the significant heterogeneity was detected among the studies ($P = .029$, $I^2 = 38.6\%$). In the subgroup analysis according to intervened methods of As$_2$O$_3$, statistically significant differences of CER were obtained from intravenous drip group (RR: 1.64, 95% CI: 1.18–2.29, $Z = 2.91$, $P = .004$) and arterial chemoembolization with other drugs in TACE group (RR: 1.65, 95% CI: 1.21–2.26, $Z = 3.12$, $P = .002$) and arterial chemoembolization with other drugs in TACE group (RR: 1.17, 95% CI: 1.09–1.26, $Z = 4.19$, $P = .000$), however, no statistically significant differences of CBR were obtained from arterial perfusion group (RR: 1.07, 95% CI: 0.94–1.22, $Z = 0.97$, $P = .330$) and arterial chemoembolization without other drugs group (RR: 1.22, 95% CI: 0.98–1.52, $Z = 1.77$, $P = .077$) (Fig. 2). Heterogeneity between studies for each subgroup indicated that the reason of significant heterogeneity for all studies is the high heterogeneity for intravenous drip group ($P = .000$, $I^2 = 90.2\%$), and the heterogeneity for other groups were not detected ($P > .1$, $I^2 = 0.0\%$). Furthermore, in order to explore the reason of high heterogeneity for intravenous drip group, we distinguished 2 subgroups based on presence or absence of pulmonary metastasis in intravenous drip group with the high heterogeneity. Similar positive results were obtained from both the absence of pulmonary metastasis group (RR: 1.15, 95% CI: 1.06–1.25, $Z = 3.22$, $P = .001$) with no heterogeneity between studies ($P = .919$, $I^2 = 0.0\%$) and presence of pulmonary metastasis group (RR: 4.55, 95% CI: 2.69–7.68, $Z = 5.65$, $P = .000$) with no heterogeneity between studies ($P = .191$, $I^2 = 36.8\%$) (Fig. 3).
1.39, 95% CI: 1.18–1.65, Z = 3.87, P = .000), however, no statistically significant differences of CBR were obtained from arterial perfusion group (RR: 1.22, 95% CI: 0.91–1.65, Z = 1.32, P = .187) and arterial chemoembolization without other drugs group (RR: 1.20, 95% CI: 0.80–1.79, Z = 0.90, P = .370) (Fig. 4).

Heterogeneity between studies for each subgroup indicated that the reason of significant heterogeneity for all studies is the high heterogeneity for intravenous drip group (P = .034, I² = 50.2%) and arterial perfusion group (P = .074, I² = 61.6%), however, the heterogeneity for arterial chemoembolization with other drugs in TACE group (P = .56, I² = 0.0%) and arterial chemoembolization without other drugs group (P = .308, I² = 3.8%) was not significant. Furthermore, in order to explore the reason of high heterogeneity for intravenous drip group, we distinguished 2 subgroups based on presence or absence of pulmonary metastasis in intravenous drip group with the high heterogeneity. Similar positive results were obtained from both the absence of pulmonary metastasis group (RR: 1.40, 95% CI: 1.18–1.65, Z = 3.92, P = .000) with no heterogeneity between studies (P = .835, I² = 0.0%) and presence of pulmonary metastasis group (RR: 15.73, 95% CI: 3.83–64.60, Z = 3.82, P = .000) with no heterogeneity between studies (P = .993, I² = 0.0%) (Fig. 5).

The high heterogeneity for arterial perfusion group may be due to different ratio of patients for Child-Pugh Classification or different TACE drugs or different sample number. Due to including only 3 studies for arterial perfusion group, the reason of high heterogeneity cannot be explored.

3.4.3. Survival rate. The half-year survival rates were reported in 6 studies. The relative risk of half-year survival rates from As2O3 & TACE group compared with the TACE group was 1.08 (95% CI: 1.02–1.14, Z = 2.54, P = .011), with no heterogeneity between studies (I² = 0%, P = .825). A total of 13 studies reported the 1-year survival rates, and the quantitative synthesis was conducted. A higher pooled result was obtained from the As2O3 & TACE group compared with the TACE group (RR: 1.36, 95% CI: 1.23–1.50, Z = 6.21, P = .000), and no evidence of heterogeneity was identified (I² = 1.1%, P = .435). There were 6 studies providing data on 2-year survival rates, and the relative risk of 2-year survival rates was obtained from the As2O3 & TACE group compared with the TACE group (RR: 1.45, 95% CI: 1.20–1.75, Z = 3.85, P = .000), and no evidence of heterogeneity was identified (I² = 0.0%, P = .588). Similar relative risk of 3-year survival rates (RR: 1.38, 95% CI: 1.06–1.79, Z = 2.38, P = .017)
was obtained from only 3 studies with no heterogeneity ($I^2 = 8.8\%$, $P = .334$) (Fig. 6).

### 3.4.4. Life quality

The Karnofsky performance score (KPS) was used to evaluate life quality for included patients. A total of 12 studies reported KPS, and the meta-synthesis was conducted using the fixed-effects model. The results for the superior of As$_2$O$_3$ & TACE therapy were obtained from both the patients with improvement of KPS scores (RR: 1.31, 95% CI: 1.14–1.50, $Z = 3.90$, $P = .000$) with no heterogeneity between studies ($P = .552$, $I^2 = 0.0\%$) and the patients with maintaining of KPS scores (RR: 1.00, 95% CI: 0.83–1.22, $Z = 0.05$, $P = .963$) with no heterogeneity between studies ($P = .285$, $I^2 = 16.2\%$). Notably, the relative risk of improvement of KPS scores in 2 studies with pulmonary metastasis$^{[26,29]}$ was significantly higher than in other studies without pulmonary metastasis (Fig. 7).

### 3.4.5. Adverse events

There were 18 studies that clearly described adverse reactions in the As$_2$O$_3$ & TACE group and the TACE group. The most common adverse events in the treatment of PHC were leukopenia, thrombocytopenia, myelosuppression, liver dysfunction, nausea, febrile reactions, ache, and retention of sodium and water. However, some adverse events from these studies were selected reported by quantitative results. We conducted meta-synthesis for these some adverse events according to quantitative synthesis with existing data, and the results were shown in Table 3. Notably, the relative risk of leukopenia was obtained from the As$_2$O$_3$ & TACE group compared with the TACE group (RR: 1.44, 95% CI: 1.03–2.02), and the significant difference of retention of sodium and water was obtained from the As$_2$O$_3$ & TACE group compared with the TACE group (RR: 16.616, 95% CI: 8.01–34.486). There was no obvious difference in occurrence rate of other adverse events between 2 groups in each study, and no severe syndrome or treatment-related death was reported by all included studies (Table 3).

### 3.5. Publication bias

We respectively performed the funnel plots of CER, CBR, 1-year survival rates, and improving KPS (Fig. 8), which suggested the possible presence of publication bias due to visually asymmetry. Furthermore, the Egger test and Harbord modified test also suggested significant asymmetry of funnel plots for CBR, CER and improving KPS ($P < .05$), however, the publication bias of 1-year survival rates was not identified using Egger test and Harbord modified test ($P > .05$). Using a “trim” method to make an adjusted estimation of Egger test and Harbord modified test, we found that the publication biases of CBR, CER, and improving KPS were not identified after removing the studies with pulmonary metastasis ($P > .05$) (Table 4).

### 4. Discussion

#### 4.1. Principal findings

This systematic review and meta-analysis suggest that As$_2$O$_3$ & TACE therapy achieves better therapeutic results compared with alone TACE on both short-term effects (CBR and CER) and long-
term effects (survival rates and life quality). In PHC patients without pulmonary metastasis, the adjuvant As$_2$O$_3$ therapy using intravenous drip or arterial chemoembolization with other drugs achieved more effective results for short-term effect than alone TACE, with no difference between 2 administration methods of As$_2$O$_3$, however, the other 2 methods using arterial perfusion or arterial chemoembolization without other drugs was not superior to alone TACE. Notably, the intravenous drip of As$_2$O$_3$ & TACE was extremely significant superior to alone TACE for short-term effect and long-term effect in PHC patients with pulmonary metastasis. Those observations were robust through different subgroup analyses we performed. Moreover, we found that the relative risk of leucopenia and retention of sodium and water was obviously raised in patients with As$_2$O$_3$ & TACE therapy. However, those adverse events were relieved with symptomatic treatments in the included studies, which proved the safety of As$_2$O$_3$ for a long-term use.

4.2. Strengths and limitations of study

A contemporaneous and exhaustive search strategy was included in this study, which permitted us to pool data from 1886 subjects in our initial and basic analysis. We also made a contact with all authors in included studies and some excluded studies, so that we were able to acquire some data from the last point of follow-up, and made certain that we had not missed the potentially eligible trials, or embraced data from the exactly same study at 2 different points of follow-up. Furthermore, strengths of this study include accurate and comprehensive quantitative analysis, administering to exploring the reasons of high heterogeneity, and publication bias. Finally, the better administration approach of adjuvant As$_2$O$_3$ and the most effective patient for using As$_2$O$_3$ & TACE therapy were identified from the included studies.

Despite our efforts to provide an accurate and comprehensive analysis, limitations of our meta-analysis need to be addressed. First, all included studies were conducted in China, because As$_2$O$_3$ was only approved for palliative treatment for the patients with unresectable PHC by China Food and Drug Administration. Although we found the authors of included studies came from different cities and provinces of China, the results may still not be generalizable to a wider population all over the world, which may have produced a potential bias of publication. Second, most studies included in this systematic review had a low-moderate methodological quality. Most of the included studies did not
describe how the random allocation sequence was generated and how the blinding of outcome assessment was performed, which implied that the corresponding risks of bias could not be ruled out. All studies included in this paper used an "A + B versus B" design in which patients were randomized to receive either As2O3 & TACE therapy or alone TACE, and there was no rigorous control for the placebo effect. Third, none of the included studies were formally registered with the WHO International Clinical Trials Registry Platform. Therefore, the protocols were not available to confirm that the studies were free of selective reporting. Finally, individual adverse events data were not reported comprehensively and quantitatively by many of the trials we identified, and the sample size in some included studies was small. Thus, we were not able to definitely assess the balance of benefits and harms if As2O3 combined with TACE was to be adopted in the general PHC population. Therefore, the results and conclusions in this study should be interpreted with caution due to those limitations of this study and characteristics of the published literature identified, and it will be necessary to carry out high-quality, multicenter studies with large sample sizes that are regularly reported to provide for evidence-based medicine in the future.

4.3. Comparison with other studies

Recent studies demonstrated that the surgical resection for PHC has a positive effect on a minority of patients; however, the majority patients with untreated nonsurgical PHC die from tumor progression (63.2%) and liver failure (31.1%) in a brief period time relatively. Meanwhile, the survival rate, on average, was 3 months, as well as 7.8% for survival rates for 1-year.[3,44] It is much harder for PHC patients to put up with the systemic chemotherapy for their hepatic function can easily get impaired as a consequence of the underlying cirrhosis, and such condition is often accompanied by hypersplenism and peripheral cytopenia.[45] TACE is an alternative approach to intra-arterial chemoinfusion that relies on embolization, and take an apparent effect on allowing the synergistic influence of increased local levels of chemotherapeutic agents and occlusion of the artery which supplies nutrients for a tumor.[46] Lo et al.[47] made an assessment for the similar cohort of PHC patients. The study, based on analysis, demonstrated that the survival rates of 1-year for TACE are 57% versus 32% respectively in the regulated team that received symptomatic therapy, and 2-year survival rates of 31% versus 11%, respectively. Therefore, TACE has been discovered to own the clinical therapeutic effect to a significant degree, and at the same time, its therapeutic effect can reduce systemic toxicity across hepatic malignancies, compared with systemic chemotherapy.[48] TACE is also being combined with systemic therapies, such as sorafenib.[2,3] Sorafenib is currently approved as the only systemic therapy for PHC by American Food and Drug Administration, and inhibits angiogenesis by targeting the vascular endothelial growth factor receptor 2 (VEGFR2) and platelet-derived growth factor receptor (PDGFR) pathway.[49]
The exploratory phase II trial of 307 patients randomized tested the efficacy of TACE plus sorafenib in patients with intermediate stage HCC, and demonstrated the CERs for patients in the sorafenib and placebo groups with post-baseline scans were respectively 56% and 41%, and the CBRs were 89% and 76%, respectively. However, our meta-analysis suggests that CER for As2O3 & TACE group of 51% versus 35% in alone TACE group, and CBR of 83% and 63%, respectively. Although these data suggested that TACE combined with systemic therapies either sorafenib or As2O3 significantly improved similar clinical efficacy in advanced HCC patients, the price of sorafenib is much higher than that of As2O3.

A large number of studies in vivo and in vitro have shown As2O3 has a strong antitumor activity for hepatic carcinoma in recent years. The possible mechanisms for antitumor effects of As2O3 were as follows: induction of tumor cell apoptosis was achieved by regulating expression of apoptotic-related proteins; reduction of tumor angiogenesis was achieved by inhibiting of the vascular endothelial growth factor receptor (VEGFR); inhibition of tumor cell proliferation was achieved by regulating expression of cycle related proteins; reduction of tumor angiogenesis was achieved by inhibiting of the vascular endothelial growth factor receptor (VEGFR). However, 2 clinical phase II trial of As2O3 therapy in PHC patient demonstrated 1-year survival rate of 30%, CER of 7%, CBR of 76%, and improvement of life quality of 22.5%, which revealed that single-agent As2O3 had a less clinically therapeutic effect than alone TACE for PHC patient.

Two recent meta-analysis reviews of As2O3 combined with TACE studies had suggested this strategy achieved better therapeutic results compared with alone TACE in the treatment of PHC. One of the meta-analysis reviews only reported that As2O3 combined with TACE had significant effects in improving CER, decreasing alpha-fetoprotein, increasing 1-year survival rate, and improving life quality of PHC patients, and with some unknown high heterogeneity and possible publication bias. Another meta-analysis review further supported the superiority of As2O3 & TACE therapy on increasing CER, CBR, and 1-year survival rates.
Figure 7. Forest plot on KPS scores of As$_2$O$_3$ & TACE and alone TACE in treating PHC. PHC=primary hepatic carcinoma, TACE=transarterial chemoembolization.

Table 3

Meta-analysis for adverse events of As$_2$O$_3$ & TACE group compared with TACE group.

| Study (reference) | Number of study | Number of events/total | Risk ratio M-H, fixed (95% CI) | Test for overall effect | Test for heterogeneity |
|-------------------|-----------------|------------------------|-------------------------------|------------------------|-----------------------|
| Leukopenia[^37,42,39,33,28,25,34] | 9 | 66/287 47/297 | 1.441 (1.030, 2.016) | Z=2.13, P=0.033 | I$^2$=0.0% |
| Thrombopenia[^37,43,31,33,29,24] | 7 | 43/162 37/174 | 1.254 (0.840, 1.872) | Z=1.11, P=0.269 | I$^2$=10.6% |
| Myelosuppression[^41,30,21,19] | 5 | 86/170 90/261 | 0.921 (0.796, 1.067) | Z=1.00, P=0.374 | I$^2$=10.6% |
| Liver dysfunction[^41,35,24,20,21,34] | 6 | 138/298 137/310 | 1.054 (0.851, 1.305) | Z=0.48, P=0.629 | I$^2$=47.2% |
| Nausea[^37,32,41,28,24,30,20,34] | 8 | 114/304 113/309 | 1.308 (0.868, 2.041) | Z=0.41, P=0.685 | I$^2$=0.0% |
| Febrile reactions[^32,41,30,20,19] | 5 | 100/211 96/212 | 1.032 (0.872, 1.223) | Z=0.37, P=0.713 | I$^2$=0.0% |
| Ache[^41,28,30,20,21,19] | 6 | 115/244 129/286 | 0.912 (0.795, 1.067) | Z=1.09, P=0.374 | I$^2$=0.0% |
| Retention of sodium and water[^35,26,29,31,34] | 5 | 108/177 5/187 | 16.616 (8.006, 34.486) | Z=7.54, P=0.000 | I$^2$=0.0% |

As$_2$O$_3$=arsenic trioxide, CI=confidence intervals, M-H=Mantel-Haenszel, TACE=transarterial chemoembolization.
Table 4

An estimates of publication bias by “trim” method.

| Estimates of publication bias | Number of study | Egger test | Harbord modified test |
|------------------------------|-----------------|------------|-----------------------|
| Clinical benefit rate        |                 |            |                       |
| All included studies         | 23              | \(P = 0.000\) | \(P = 0.001\)         |
| Studies without pulmonary metastasis | 19             | \(P = 0.365\) | \(P = 0.571\)         |
| Clinical effective rate      |                 |            |                       |
| All included studies         | 24              | \(P = 0.003\) | \(P = 0.004\)         |
| Studies without pulmonary metastasis | 20          | \(P = 0.171\) | \(P = 0.309\)         |
| 1-year survival rates        |                 |            |                       |
| All included studies         | 13              | \(P = 0.123\) | \(P = 0.295\)         |
| Studies without pulmonary metastasis | 12          | \(P = 0.165\) | \(P = 0.311\)         |
| Improving KPS                |                 |            |                       |
| All included studies         | 11              | \(P = 0.012\) | \(P = 0.018\)         |
| Studies without pulmonary metastasis | 9            | \(P = 0.239\) | \(P = 0.455\)         |

KPS = Karnofsky performance scale.
survival rate, however, \(\text{As}_2\text{O}_3\) & TACE therapy was not superior to alone TACE for improving life quality. Although subgroup analysis was performed in that review, the heterogeneity of each subgroup was still obvious, and without no explanation.[13] In addition, compared with our meta-analysis, the included studies were not exhaustive and in-depth analysis, especially crude and qualitative conclusion of adverse events.

5. Conclusions
These data provide moderate and appropriate quality and evidence that \(\text{As}_2\text{O}_3\) & TACE therapy achieves better therapeutic results compared with alone TACE on both short-term effect and long-term effect, and both intravenous drip and arterial chemoembolization with other drugs were good adjuvant options for clinical therapy of PHC. Especially, the intravenous drip of \(\text{As}_2\text{O}_3\) & TACE was extremely significant superior to alone TACE for clinical effect in PHC patients with pulmonary metastasis. As the exactly limited trials operated in Chinese PHC population succeeded to demonstrate a significant profit of \(\text{As}_2\text{O}_3\) & TACE therapy, these data should not be applied to the exact populations outside of China. Considering that any programmes on account of such the interference will concern about healthy topics and themes. There are of greater confidence in the estimate of influence and more precious information on the benefit of \(\text{As}_2\text{O}_3\) & TACE therapy before such a tactic can be recommended as a method of treating unresectable PHC. It appears that the advantages of adjuvant \(\text{As}_2\text{O}_3\) therapy combined with TACE in PHC individuals will outweigh alone TACE therapy, especially in PHC populations with pulmonary metastasis. Nevertheless, there are urgent requirements for the consequences from more researches in various geographical populations to amplify the evidence foundation. On the other hand, there are some multicenter randomized controlled clinical study in progress in China, countries that wish to apply Western medicine combined with Chinese medicine to treat PHC should think about properly randomized designs to implement so as to improve our related knowledge.

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Author contributions
Peng Song, Peng Chen, and Hongyu Li contributed to conception and design. All authors were involved in analysis and interpretation of the data. Peng Song and Yang Hai contributed to systematic literature search and study selection. Longhe Zhao and Wantong Ma contributed to data extraction and risk of bias assessment. Peng Song and Qinjian Xie designed and conducted the statistical analysis. Peng Song and Xin Wang drafted the manuscript. All authors approved the final version.

Conceptualization: Peng Song, Hongyu Li.

Data curation: Peng Song, Yang Hai, Wantong Ma, Longhe Zhao, Yingdong Li.

Software: Peng Song, Wantong Ma, Longhe Zhao, Yingdong Li.

Writing – original draft: Peng Song, Xin Wang.

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