Meta-Analysis and Systematic Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(12) 5926–5936

DOI: 10.1177/0300060519882545
journals.sagepub.com/home/imr
SAGE

Effect of hyperthermic intraperitoneal chemotherapy for gastric cancer patients: a meta-analysis of the randomized controlled trials

Yan-Wen Liu, Ying Du* and Bao-An Chen*

Abstract

Objective: To determine the effectiveness and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with advanced gastric cancer and peritoneal metastases.

Methods: PubMed®, CNKI, Web of Science, VIP and WANFANG databases were searched to identify randomized controlled trials (RCTs) that examined the effect of HIPEC on survival, clinical response and adverse events. Patients with advanced gastric cancer and peritoneal metastases were divided into an experimental group and a control group. The statistical results are presented as relative ratio (RR), mean difference (MD) and 95% confidence interval (CI).

Results: Twenty-one RCTs met the inclusion criteria ($n = 1674$ patients). Meta-analysis showed that the 3-year survival rate was significantly higher in the HIPEC group than in the control group (RR 1.61; 95% CI 1.43, 1.82) and the complete response rate was significantly higher in the HIPEC group than in the control group (RR 2.35; 95% CI 1.67, 3.31). HIPEC was also beneficial in terms of decreased CEA (MD −1.79; 95% CI −2.22, −1.35). There was no significant difference in the rate of adverse reactions (RR 1.00; 95% CI 0.87, 1.14).

Conclusions: HIPEC had a beneficial effect on 3-year survival rate and complete response in patients with advanced gastric cancer and peritoneal metastases.

Keywords

Gastric cancer, hyperthermic intraperitoneal chemotherapy, meta-analysis

Date received: 5 March 2019; accepted: 24 September 2019

*These authors contributed equally to this work.

Corresponding author:
Ying Du, Department of Oncology, Zhongda Hospital, School of Medicine, Southeast University, 87 Dingjiaqiao Road, Gulou District, Nanjing 210009, Jiangsu Province, China.
Email: 18761868919@163.com

Department of Oncology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu Province, China

Introduction

Gastric cancer is one of the most common malignant tumours in the world and it is the second leading cause of death from malignant tumours.[1] There are 21 600 new cases of gastric cancer diagnosed in the US every year.[2] The National Cancer Centre of Korea predicts 221 347 new cancer cases and 82 344 cancer deaths in Korea during 2019, of which gastric cancer is one of the most common.[3] In Asia, the countries with the highest incidence of gastric cancer include China, Mongolia, Japan and South Korea.[4] China has the highest incidence of gastric cancer in the world.[5] Early surgical treatment can improve long-term survival, while the prognosis of patients with advanced disease is poor, so early diagnosis is the key to successful treatment of gastric cancer.[6] The 5-year survival rate for patients with advanced gastric cancer in Europe is only 25%.[7]

The peritoneum is a common metastatic site in advanced gastric cancer.[8] The development of peritoneal metastasis begins with the detachment of a single tumour cell from the primary tumour, which then reaches the abdominal cavity and spreads into the peritoneal fluid. Tumour cells reaching the extracellular matrix can bind to integrins and cause degradation, which ultimately results in the invasion of the submesothelial cell layer.[9] The prognosis of patients with peritoneal metastasis from a primary gastric cancer is extremely poor and the median survival time is only 4–6 months.[10] There is currently no consensus on the best way to treat patients with peritoneal metastasis from a primary gastric cancer. Since the 1980s, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has gradually become the main treatment for peritoneal metastasis from gastrointestinal malignancies and the survival time of strictly selected patients has been significantly prolonged.[11] However, this approach remains controversial because the operation is difficult, it is associated with complications and it has a high mortality rate.[12] HIPEC involves the continuous heating and thermostatic infusion of a liquid containing chemotherapy drugs into the abdominal cavity to kill any residual cancer cells in the abdominal cavity that cannot be observed by the naked eye.[13] In 1979, Spratt first used multiple organ resection combined with hyperthermic intraperitoneal chemotherapy to treat a 35-year-old patient with pseudomyxoma peritonei.[14] To evaluate the extent of peritoneal metastasis, the concept of a peritoneal cancer index (PCI) was proposed.[15] The PCI is currently the most widely used evaluation tool used to assess peritoneal metastasis, because it not only reflects the cancer burden, but it also determines to the likely prognosis of patients.[16]The PCI combines the distribution of the tumour cells in 13 abdominal-pelvic regions with lesion size.[17] A previous study has shown a perfect linear relationship between PCI and overall survival.[18]

This present meta-analysis systematically evaluated the published literature in order to investigate the clinical effects of HIPEC used in patients with advanced gastric cancer and peritoneal metastasis.

Materials and methods

Study methods

The methods used in this meta-analysis were in accordance with those proposed by a related meta-analysis.[19]

Search strategy

A systematic search of publications listed in the electronic databases (PubMed®, CNKI, Web of Science, VIP and WANFANG) between January 2004 and July 2018 was conducted using the following search

terms: 'gastric cancer', 'peritoneal metastasis', 'hyperthermic intraperitoneal chemotherapy'. There were no search or language restrictions applied. The list of articles was reviewed independently by all three authors. The reference lists of all selected articles were manually reviewed to identify any additional relevant studies.

Study selection

Studies were eligible for inclusion if they met the following criteria: (i) randomized controlled trial (RCT); (ii) patients had advanced gastric cancer with peritoneal metastasis; (iii) the experimental group received HIPEC therapy, while the control group received systemic chemotherapy only; (iv) PCI score was 0–36; (v) reported outcomes included complete response (CR) rate, 3-year survival rate, serum carcinoembryonic antigen (CEA) level and adverse reactions. The exclusion criteria were as follows: (i) not an RCT; (ii) irrelevant or repetitive research; (iii) incomplete data access; (iv) peritoneal metastatic tumour cells were derived from a variety of primary tumours. After obtaining full reports of the candidate studies, two authors (Y.W.L. & Y.D.) reviewed each article independently. Differences between the two reviewers were resolved by discussion and consensus with the supervisor (B.A.C.).

Data abtraction and quality assessment

Each study was evaluated for quality based on the following characteristics: (i) secure method used for randomization; (ii) allocation concealment; (iii) patient and observer blinding; (iv) loss to follow-up. The quality of the studies was evaluated using Jadad quality scores and classified as low quality (score <4) and high quality (score ≥ 4).[20]

For each study, the following data were extracted: article title; first author's last name; publication year; sample size; the age of the patients; total number for CR or 3-year survival; details of the chemotherapy regimens; curative effects; adverse events; surgery plans; quality evaluation.

Statistical analyses

A meta-analysis was performed via using RevMan software (version 5.0; Cochrane Collaboration, Oxford, UK). Enumeration data are presented as relative risk (RR) with a 95% confidence interval (CI). Measurement data are expressed as the mean difference (MD) with a 95% CI. The difference was considered statistically significant when $P < 0.01$.

Statistical heterogeneity was determined by the P-value and I^2 value in the heterogeneity test results. If homogeneity was found ($P > 0.10$, $I^2 < 50\%$), a fixed-effect model was employed for the meta-analysis. The source of heterogeneity was investigated if $P < 0.10$ and $I^2 > 50\%$ and a random-effect model was used in the absence of significant clinical heterogeneity. Subgroup or descriptive analyses were used in the presence of significant clinical heterogeneity.

Results

The initial database search identified 391 articles, of which 37 were RCTs (Figure 1). Full-text assessment resulted in 21 studies that enrolled a total of 1674 patients with advanced gastric cancer who met the inclusion criteria and were included in this analysis (Table 1).[21–41] Patients receiving HIPEC were classified as the experimental group ($n = 840$) and those receiving chemotherapy alone as the control group ($n = 834$). The studies were stratified according to their quality into a low-quality group (Jadad score <4) and a high-quality group (Jadad score ≥ 4). There were three RCTs in the low-quality group.[26,28,38]

The meta-analysis of the effect of treatment on 3-year survival included 13 RCTs

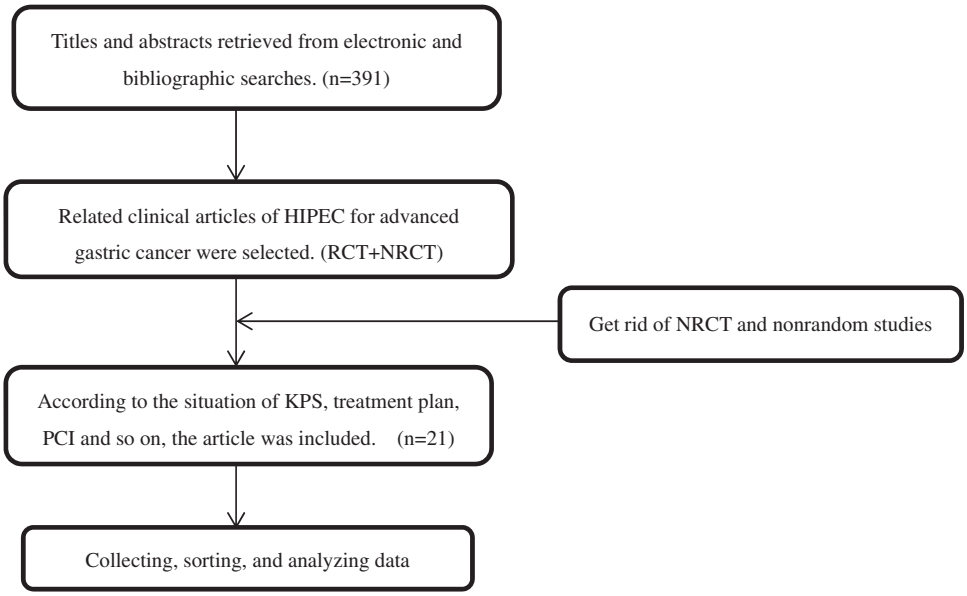

Figure 1. Flowchart of the literature search undertaken in this meta-analysis of the effect of hyperthermic intraperitoneal chemotherapy (HIPEC) for patients with advanced gastric cancer and peritoneal metastasis. RCT, randomized controlled trial; NRCT, nonrandomized controlled trial.

($n = 1142$ patients).[21–28,37–41] The results of the heterogeneity analysis showed that $P > 0.5$ and $I^2 < 50\%$, so there was no heterogeneity between the two study groups. The meta-analysis using a fixed-effect model showed that the 3-year survival rate was significantly higher in the HIPEC group than in the control group (RR 1.61; 95% CI 1.43, 1.82; $P < 0.00001$) (Figure 2).

The meta-analysis of the effect of treatment on CR rate included nine RCTs.[24,29–36] The meta-analysis using a fixed-effect model showed that the CR rate was significantly higher in the HIPEC group than in the control group (RR 2.35; 95% CI 1.67, 3.31; $P < 0.00001$) (Figure 3).

Adverse events included bone marrow suppression, anastomotic leak, bowel fistula, gastrointestinal reactions, kidney damage and liver disfunction. The meta-analysis of the effect of treatment on adverse events included nine RCTs.[23,25,26,35–40] The meta-analysis using a fixed-effect model showed that there was no difference in the rate of adverse events between the two groups (RR 1.00; 95% CI 0.87, 1.14; $P = 0.95$) (Figure 4).

The meta-analysis of the effect of treatment on CEA levels included three RCTs.[25,32,35] There was an acceptable level of statistical heterogeneity between the three studies. The meta-analysis showed that the extent of the decrease in CEA level in the HIPEC group was better than the control group (MD –1.79; 95% CI −2.22, −1.35; $P < 0.00001$) (Figure 5).

Discussion

Although the clinical treatment of gastric cancer has been greatly improved, the prognosis of gastric cancer patients with peritoneal metastasis remains unsatisfactory.[42] At present, peritoneal perfusion chemotherapy, combined with systemic chemotherapy or surgery, is used to improve the prognosis

Table 1. Basic characteristics of the 21 randomized controlled trials that were included in a meta-analysis of the effect of hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with advanced gastric cancer and peritoneal metastasis.[21–41]

Name	Year	Patient number Experimental/ control	Age, years Experimental/control	Karnofsky Performance Status score	HIPEC regimens	Systemic chemotherapy regimens
Zuo[21]	2004	46/36	53/52 (median)	$\geq$ 70	DDP + 5-FU, 1750–2000 ml, 41–43°C, 60 min	CF 100 mg, 5-FU 750 mg, THP 50-60 mg, DDP 20 mg
Cui[22]	2014	48/48	55/56 (mean)	>60	DDP + 5-FU, 3000 ml, 41–43°C, 90 min	PTX 135 mg/m^2, DDP 20 mg/m^2, FT207 0.8–1.0 g/day
Fan[23]	2017	15/15	71.9 ± 5.8/72.4 ± 5.6 (mean ± SD)	ND	DDP + 5-FU, 4000 ml, 43°C, 60 min	L-OHP 130 mg/m^2, FT207 40–60 mg/time
Lu[24]	2016	28/20	52.4 ± 7.9/54.3 ± 6.6 (mean ± SD)	50–80	DDP + 5-FU, 1500–2500ml, 41–44°C, 90 min	L-OHP or TXT and FT207or CDHP and Oxo
Wang[25]	2017	48/48	69.3 ± 7.4/69.5 ± 7.2 (mean ± SD)	ND	DDP + L-OHP, 3000 ml, 41–43°C, 90 min	PTX 135 mg/m^2, DDP 20 mg/m^2, FT207 1.0 g/day
Xu[26]	2017	24/24	52.5 ± 1.4/51.5 ± 2.5 (mean ± SD	ND	DDP + 5-FU, 3000 ml, 45°C, 60 min	ND
Yuan[27]	2017	44/43	55.33 ± 4.75/56.86 ± 4.34 (mean ± SD)	>60	DDP, 2500 ml, 41–44°C, 60 min	L-OHP 135mg/m^2, CF 200 mg/m^2, 5-FU 2600 mg/m^2
Zhu[28]	2008	31/29	54/56 (median)	>60	DDP, 1000 ml, 45°C, 60 min	5-FU 1000 mg/m^2, L-OHP 85 mg/m^2, CF 100 mg/m^2
Chen[29]	2015	40/40	49/48 (mean)	ND	DDP, 41–43°C, 60 min	5-FU 500 mg, DDP 30–40 mg
Chen[30]	2016	30/30	ND	>60	DDP + PTX, 1000 ml, 42.5–43.0°C, 60 min	PTX 135 mg/m^2, DDP 75 mg/m^2
Hong[31]	2016	46/46	62.34 ± 7.37/62.43 ± 7.41 (mean ± SD)	>60	DDP, 3000 ml, 42–43°C, 60 min	L-OHP 135mg/^{2}, CF 200 mg/m^2, 5-FU 2600 mg/m^2

(continued)

Table 1. Continued

Name	Year	Patient number Experimental/ control	Age, years Experimental/control	Karnofsky Performance Status score	HIPEC regimens	Systemic chemotherapy regimens
Hu[32]	2014	20/20	54.75 ± 13.63/ 58.50 ± 12.53 (mean ± SD)	>50	DDP, 3000 ml, 43°C, 60 min	L-OHP 130 mg/m^2, CAPE 2000 mg/m^2
Jin[33]	2017	38/38	ND	ND	DDP + 5-FU + THP, 42–44°C, 90 min	ND
Wang[34]	2016	50/50	62.17 ± 5.54/60.98 ± 5.02 (mean ± SD)	>60	5-FU, 2000 ml, 45°C, 60 min	ND
Wang[35]	2018	32/32	46.4 ± 7.9/44.5 ± 7.3 (mean ± SD)	40–70	TXT, 2000–2500 ml, 41–43°C, 60 min	L-OHP 135mg/m^2, 5-FU 2600 mg/m^2, CF 100 mg/m^2
Zhang[36]	2017	60/60	51.3 ± 8.7/52.6 ± 7.9 (mean ± SD)	>50	ND	ND
Deng[37]	2009	44/41	52/53 (median)	ND	MMC + 5-FU, 3000 ml, 42–43°C, 60–90 min	DDP 15 mg/m^2
Liu[38]	2015	80/70	ND	ND	DDP + 5-FU, 3000 ml, 41–43°C, 90 min	L-OHP 130 mg/m^2, S-1 40 mg/m^2
Yang[39]	2011	34/34	50/51 (median)	>50	DDP + MMC, 6000 ml, 43.0 ± 0.5°C, 60–90 min	ND
Zhang[40]	2013	40/40	ND	ND	MMC + 5-FU, 3000 ml, 45°C, 60–90min	L-OHP 85mg/m^2, CF 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 600 mg/m^2
Zhang[41]	2007	92/120	57/57 (mean)	ND	DDP 100 mg, MMC 30 mg, 2000 ml, 43–45°C, 30 min	DDP 10–15 mg/kg, MMC 0.1–0.15 mg/kg, ADM 0.5–1.0 mg/kg

DDP, cisplatin; 5-FU, 5-fluoruracil; CF, calcium folinate; THP, pirarubicin; PTX, paclitaxel; FT207, tegafur; L-OHP, oxaliplatin; TXT, docetaxel; CDHP, gimeracil; Oxo, oteracil; ND, not declared; CAPE, capecitabine; MMC, mitomycin; S-1, tegafur, gimeracil and oteracil potassium capsules; ADM, adriamycin.

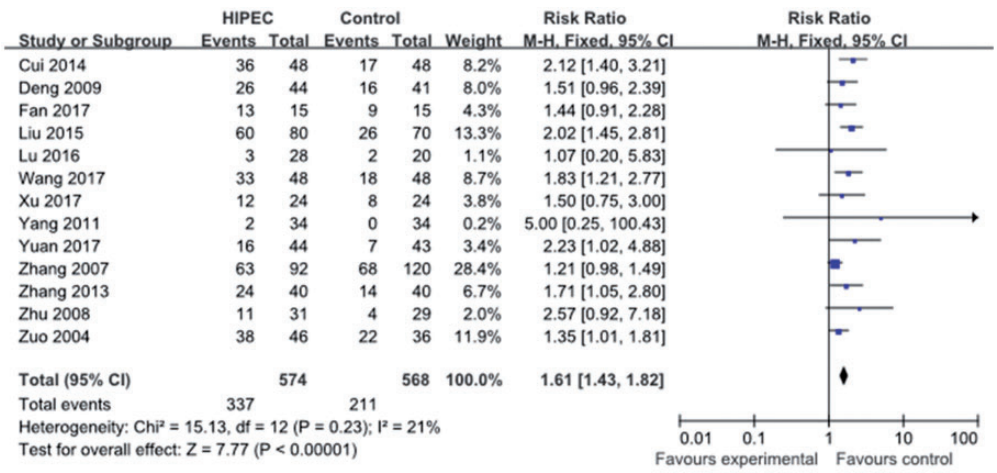

Figure 2. Meta-analysis of the effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on 3-year survival in patients with advanced gastric cancer and peritoneal metastasis.[21–28,37–41]

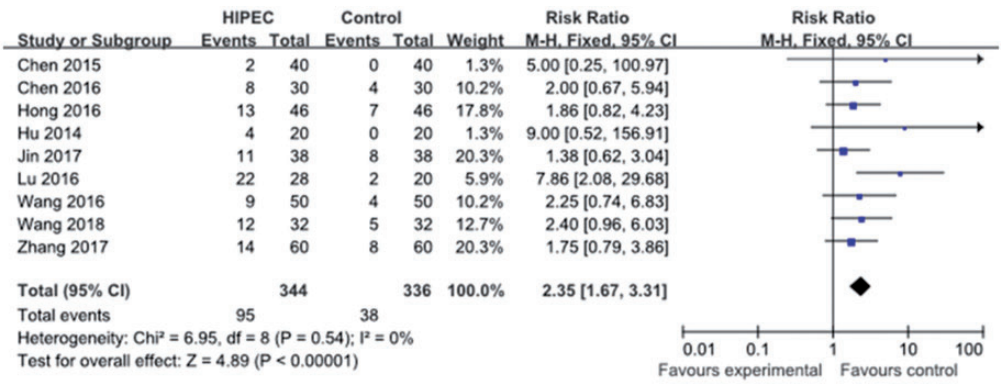

Figure 3. Meta-analysis of the effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on clinical response in patients with advanced gastric cancer and peritoneal metastasis.[24,29–36]

of patients.[43] The combination of cytoreductive surgery and HIPEC is considered to be a promising comprehensive treatment strategy for gastric cancer peritoneal metastases and it has shown good initial results, but there is an urgent need to evaluate this strategy further in RCTs.[44] The optimal therapeutic dose of HIPEC remains to be elucidated and many potential drug regimens for perfusion exist. Studies show that the perfusion of paclitaxel into the abdominal cavity is safe and effective, and it provides significant pharmacological advantages compared with intravenous chemotherapy.[45,46] For example, intraperitoneal perfusion chemotherapy results in higher bioavailability of the drug.[47] The bioavailability of intraperitoneal chemotherapy for docetaxel is two-times that of intravenous chemotherapy.[48]

There have been several RCTs that have investigated combined intraperitoneal chemotherapy and the results showed that the combined treatment group had a better

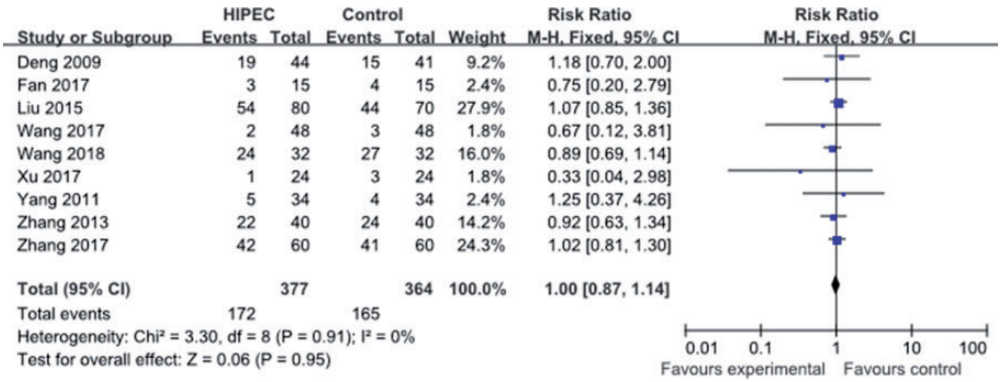

Figure 4. Meta-analysis of the effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on adverse events in patients with advanced gastric cancer and peritoneal metastasis.[23,25,26,35–40]

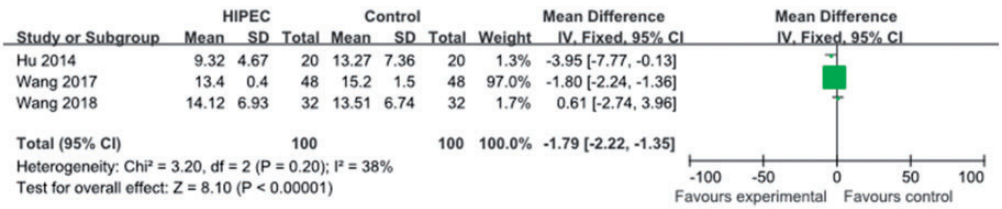

Figure 5. Meta-analysis of the effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on carcinoembryonic antigen levels in patients with advanced gastric cancer and peritoneal metastasis.[25,32,35]

curative effect than single operation or chemotherapy.[49,50] This current meta-analysis demonstrated that the 3-year survival rate, the CR rate and the reductions in CEA level following treatment were all significantly more favourable in the HIPEC group compared with the control group; and there was no difference in the occurrence of adverse events between the two groups. However, it should be noted that there were only three studies that examined the CEA levels after treatment.[25,32,35] In addition, the start and stop times of intervention for patients in each treatment centre were different. A large multi-centre RCT should be undertaken to improve the homogeneity of the data.

In conclusion, this current meta-analysis demonstrated that HIPEC resulted in a higher 3-year survival rate, a higher CR rate and greater reductions in CEA level following treatment than systemic chemotherapy alone in patients with advanced gastric cancer and peritoneal metastases. There was no difference in the occurrence of adverse events between the two treatment groups. As effective treatment of advanced gastric cancer is the key to improving the prognosis of the patient, choosing the most appropriate and effective treatment is likely to have a considerable impact on the patient's long-term outcomes.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

This work was supported by the National Natural Science Foundation of China (no. 81773284).

ORCID iD

Ying Du https://orcid.org/0000-0002-4977-4125

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