Sorafenib in the treatment of radioiodine-refractory differentiated thyroid cancer: a meta-analysis

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Abstract

The advent of biologically targeted agents and increased understanding of thyroid carcinogenesis have generated much interest in the development of biologically targeted therapeutic agents for thyroid cancer. Among them, sorafenib is the most commonly studied drug. The current meta-analysis was carried out to estimate the efficacy and safety of sorafenib administered in radioiodine-refractory differentiated thyroid cancer patients. An electronic search was conducted using PubMed/MEDLINE and EMBASE. Statistical analyses were carried out using either random-effects or fixed-effects models according to heterogeneity. All the statistical analyses were carried out using the Stata version 12.0 software. Seven eligible studies were identified. The final results indicated that 22% of the patients (95% CI: 15–28) achieved a partial response. Hand–foot syndrome, diarrhea, fatigue, rash, weight loss, and hypertension were the most frequently observed adverse effects (AEs) associated with sorafenib use and the incidence of these AEs (all grades) was 80% (95% CI: 68–91), 68% (95% CI: 59–77), 67% (95% CI: 57–78), 66% (95% CI: 50–82), 52% (95% CI: 33–72), and 31% (95% CI: 21–42) respectively. Sixty-two percent (95% CI: 36–89) patients required dose reductions due to toxicity of sorafenib. As far as PR and AEs are concerned, the results of this meta-analysis indicate that sorafenib has a modest effect in patients with radioiodine-refractory differentiated thyroid cancer and the high incidence of AEs associated with this agent may affect the quality of patients' lives. Though the use of sorafenib in the treatment of radioiodine-refractory differentiated thyroid cancer is considered promising by most physicians working in this field, more effective agents with less toxicity and cost are still needed.

Key Words

- ▶ sorafenib
- ▶ tyrosine kinase inhibitors
- ▶ differentiated thyroid cancer
- ▶ meta-analysis
- ▶ molecular targeted therapy

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Introduction

Thyroid carcinoma is the most common endocrine malignancy. While the incidence of most cancers is on the decline, the worldwide incidence of thyroid carcinoma is increasing in both men and women. It has been estimated that in 2013, 60 220 patients will be diagnosed with thyroid carcinoma in the USA and about 1850 will die (Siegel *et al.* 2013). Differentiated thyroid carcinoma

(DTC) is the most common (95%) subtype of thyroid carcinoma accounting for approximately 2% of all malignancies in the USA (Eheman *et al.* 2012). Due to the biological behavior of the tumor, the prognosis of DTC is excellent following conventional treatments based on adequate surgical management and radioactive iodine (RAI) ablation as well as TSH suppression (Dadu & Cabanillas 2012).

However, approximately 10–20% of DTC patients will develop distant metastases and about 50% of them will die within 10 years of diagnosis. It is estimated that 5% of DTC patients will lose ^{131}I avidity and become resistant to RAI, which is a crucial tool for the treatment of DTC. This results in an aggressive behavior and a poor prognosis with long-term overall survival (OS) of only 10% (Regalbuto et al. 2012).

The medical approach for the treatment of advanced or metastatic DTC refractory to conventional treatment was considered particularly challenging. Historically, the role of cytotoxic chemotherapy has been quite limited in these patients due to both limited need and efficacy when used (Sherman 2010). Recently, the knowledge of key mutational events in some genes (mainly focused on *RET/PTC*, *RAS* (*NRAS*, *KRAS*, *HRAS*), *BRAF*, and *EGFR*) has been promulgated widely. These mutations are considered to be connected to a signaling net that is responsible for the carcinogenesis and angiogenesis of thyroid cancer (Albarelli et al. 2012). Moreover, many novel biological agents that target these mutations have been identified and studied, which brings hope to patients with thyroid cancer especially to those with radioiodine-refractory DTC. Among them, sorafenib is the most commonly studied drug.

Sorafenib is an orally active multi-tyrosine kinase inhibitor (TKI) targeting both cell-surface tyrosine kinase receptors and downstream intracellular serine/threonine kinases in the Ras/MAPK cascade. This drug affects tumor cell proliferation and angiogenesis and has recently been approved in the USA by the Food and Drug Administration for the treatment of renal cell and hepatocellular carcinomas (Wilhelm et al. 2006). It is the first compound capable of inhibiting RAF kinases and targeting a panel of tyrosine kinase receptors such as VEGF receptors 1–3 and PDGFRB as well as RET, c-KIT, and FLT3. These characteristics provide the possible molecular rationale for the use of sorafenib in the treatment of all subtypes of thyroid cancer (Duntas & Bernardini 2010).

So far, several clinical trials have been conducted to evaluate the effectiveness and adverse effects (AEs) of sorafenib in patients with radioiodine-refractory DTC, and some reviews of novel targeted therapies available for patients with all types of thyroid cancer are currently being reported. However, to our knowledge, no meta-analysis has been carried out to estimate the efficacy and safety of sorafenib administered in radioiodine-refractory DTC patients. Therefore, the current meta-analysis attempted to analyze and combine the results of these clinical trials to increase the statistical power and improve the estimates of the effects.

Materials and methods

Literature search for identifying related studies

A search for human trials without language restrictions using the bibliographic databases PubMed/MEDLINE and EMBASE was conducted using the terms ‘thyroid cancer’, ‘thyroid carcinoma’, and ‘radioiodine refractory’ as well as the term ‘sorafenib’ and related pharmaceutical names. A list of articles was obtained through extensive crosschecking of the reference lists of all the retrieved articles. Unpublished data and conference proceedings were not included.

Study selection

Two reviewers (Z-L Q and C-T S) independently assessed the eligibility of each article. After screening all the titles and reading the abstracts, full texts of the selected articles were reviewed to determine their eligibility for inclusion in the study. Disagreement between reviewers was resolved by consensus. To be included in the meta-analysis: (1) studies had to use sorafenib; (2) studies had to record necessary data about therapy efficacy and safety; and (3) studies had to be carried out in patients with a diagnosis of radioiodine-refractory DTC. Exclusion criteria were as follows: (1) involvement of malignancy that was not thyroid cancer; (2) use of pharmaceuticals that were not biologically targeted agents; (3) animal and cell studies; and (4) letters, abstracts, reviews, case reports, editorials, and comments.

Data extraction

Data extraction was conducted independently by two investigators (C-T S and Z-L Q) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009). For each relevant study, collected data included the following: first author's name, year of publication, country, trial design, number of enrolled subjects, median age of enrolled subjects, gender composition, drug dose, median treatment duration, median partial response (PR), median stable disease (SD), median progression-free survival (PFS), and OS. To resolve disagreements between reviewers, a third reviewer (Q-Y L) assessed all the discrepant items.

To evaluate the toxicity of sorafenib, the authors calculated the number of events of the following AEs reported in the safety profile section: hand–foot syndrome, diarrhea, fatigue, rash, weight loss, and hypertension. When available, all-grade (1–4) and high-grade (3–4) events according to the Common Terminology

Criteria for Adverse Events (CTCAE Version 3.0; National Cancer Institute, Bethesda, MD, USA) were included in the meta-analysis.

Statistical analyses

For each trial, the rate of PR and stability of disease, PFS, and main AEs were analyzed from the extracted data and 95% CIs were derived. Heterogeneity analysis was carried out by calculating the I^2 , which was interpreted as low (25%), moderate (50%), and high (75%) (Moher *et al.* 2009). According to one review (Berlin 1995), the I^2 index assessed not only heterogeneity in a meta-analysis but also the extent of that heterogeneity. It is considered a more appropriate procedure than Dixon's Q test for assessing whether there is true heterogeneity among the studies in a meta-analysis (Huedo-Medina *et al.* 2006). For the meta-analysis, both fixed-effects (weighted with inverse variance) and random-effects models were considered (DerSimonian & Laird 1986). A random-effects model was chosen when heterogeneity was $>50\%$, while a fixed-effects model was chosen when heterogeneity was $<50\%$. Publication bias was assessed using a standard funnel plot (Copas & Shi 2000). Forest plots were sorted according to the first author's name, year, and country to illustrate the ratio of PR and SD, PFS, and incidence of AEs. All the statistical analyses were carried out using the Stata version 12.0 software (StataCorp. 4905 Lakeway Drive College Station, Texas, 77845, USA).

Results

Study characteristics

The literature search identified 189 potentially relevant articles. After screening titles and abstracts, 176 non-relevant articles were excluded as being for other malignancies, treatment agents, review articles, case reports, abstracts presented at meetings, letters, and commentaries. Following a more detailed review, six articles were excluded because two combined sorafenib with other agents, two mainly referred to molecular mechanisms, two had a duplicate trial, and one included only anaplastic thyroid carcinoma (ATC) cases. The remaining seven trials involving 211 patients fulfilled our inclusion criteria (Gupta-Abramson *et al.* 2008, Kloos *et al.* 2009, Ahmed *et al.* 2011, Chen *et al.* 2011, Capdevila *et al.* 2012, Schneider *et al.* 2012, Marotta *et al.* 2013). The process of study selection is shown as a flow chart in Fig. 1.

The baseline characteristics of each trial are given in Table 1. These seven trials were published between 2008

Figure 1
Flow chart of the study selection process.

and 2013, including two retrospective and five prospective trials. In all, 211 patients (115 men and 96 women, median age: 55–67 years) were identified. All the selected trials involved patients with radioiodine-refractory DTC (four articles (Gupta-Abramson *et al.* 2008, Kloos *et al.* 2009, Ahmed *et al.* 2011, Capdevila *et al.* 2012) also included a small proportion of medullary thyroid carcinoma (MTC) and/or ATC cases and, which were excluded when analyzed). These trials were carried out in six countries: the USA, the UK, China, Italy, the Netherlands, and Spain. All the trials reported an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , except one trial, which included six patients whose ECOG status was 3 (Marotta *et al.* 2013). The dose of sorafenib administered was 400 mg orally twice a day (PO b.i.d.) in all the trials, except in one trial, which used 200 mg PO b.i.d. (Chen *et al.* 2011). The efficacy of each trial is summarized in Table 2, along with the evaluation index including PR, stability of disease, clinical benefits, and PFS and OS rates. High-grade (3–4) events reported in each trial are presented in Table 3.

Efficacy of sorafenib in radioiodine-refractory DTC

The occurrence PR of sorafenib in patients with radioiodine-refractory DTC ranged from 15 to 33%, and no complete response (CR) was reported. SD ranged from 41 to 82%, PFS ranged from 4.5 to 19.6 months, and OS ranged from 10 to 37.5 months. The PR, SD, and PFS were further meta-analyzed for all the radioiodine-refractory DTC patients and the results were 22% (95% CI: 15–28;

Table 1 Baseline characteristics of each trial

References	Country	Trial design	Dose (mg b.i.d)	Number of patients	Type	ECOG	Patients (M+F)/n	Median age (y)	T (m)
Gupta-Abramson et al. (2008)	USA	Phase II: prospective	400	30	27 DTC/1 MTC/2 ATC	0–1	30 (15+15)	63	6.3
Kloos et al. (2009)	USA	Phase II: prospective	400	56	52 DTC/4 ATC	– ^a	56 (31+25)	– ^a	– ^a
					Arm A		19 (11+8)	67	14
					Arm B		22 (10+12)	56	10
					22 PTC		15 (10+5)	61	8
					11 HTC/FTC				2
					4 ATC				
Ahmed et al. (2011)	UK	Phase II: prospective	400	34	19 DTC/15 MTC	0–1	34 (19+15)	55	16.5
Chen et al. (2011)	China	Prospective	200	9	PTC	0–2	9 (7+2)	57	– ^a
Schneider et al. (2012)	The Netherlands	Phase II: prospective	400	31	DTC	0–2	31 (19+12)	64	15
Capdevila et al. (2012)	Spain	Retrospective	400	34	16 DTC/15 MTC/3 ATC	0–2	34 (16+18)	57.3	– ^a
Marotta et al. (2013)	Italy	Retrospective	400	17	DTC	0–3	17 (8+9)	61	–

b.i.d, twice a day; DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma; PTC, papillary thyroid carcinoma; HTC, Hürthle cell thyroid carcinoma; FTC, follicular thyroid carcinoma; ECOG, Eastern Cooperative Oncology Group; M, male; F, female; n, number; y, year; T, median treatment duration; m, month.

^aNot reported in the trial.

$P=0.000$), 52% (95% CI: 44–60; $P=0.000$), and 12.4 months (95% CI: 10.4–14.7; $P=0.000$) respectively (Fig. 2A, B, and C). All of them were pooled using the fixed-effects model according to their heterogeneity. OS was not meta-analyzed because three of the trials did not fulfill the OS criteria.

Safety

The most commonly reported AEs included hand–foot syndrome, diarrhea, and rash. Rare but severe AEs were

observed mainly due to intracranial hemorrhage (Capdevila et al. 2012), cardiac arrest (Marotta et al. 2013), angioedema, small-cell lung cancer, carcinoma of the tongue (Schneider et al. 2012), and grade 5 event of sudden death (Kloos et al. 2009). Meta-analyses of patients with all-grade hand–foot syndrome, diarrhea, fatigue, rash, weight loss, and hypertension revealed that the incidence was 80% (95% CI: 68–91; $P=0.000$), 68% (95% CI: 59–77; $P=0.000$), 67% (95% CI: 57–78; $P=0.000$), 66% (95% CI: 50–82; $P=0.000$), 52% (95% CI: 33–72; $P=0.000$), and 31% (95% CI: 21–42; $P=0.000$)

Table 2 Evaluation indexes reflecting the efficacy of sorafenib in each trial

References	Patients (n)	Type	PR×n/%	SD×n/%	Clinical benefits (%)	PFS (months)	OS (months)
Gupta-Abramson et al. (2008)	27	DTC	7/26	15/56	81	19.6	– ^a
Kloos et al. (2009)	52	41 PTC	6/15	23/56	71	15	– ^a
		33 PTC	5/15	19/57	73	16	23
		8 PTC ^b	1/13	6/75	88	10	37.5
		11 HTC or FTC	0/0	9/82	82	4.5	24.2
Ahmed et al. (2011)	19	DTC	3/16	13/68	84	– ^a	– ^a
Chen et al. (2011)	9	DTC	3/33	4/44	77	9.8	– ^a
Schneider et al. (2012)	31	DTC	8/31	11/42	73	18	34.5
Capdevila et al. (2012)	16	DTC	3/19	8/50	69	13.3	23.6
Marotta et al. (2013)	17	DTC	5/30	7/41	71	9	10

n, number; DTC, differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; HTC, Hürthle cell thyroid carcinoma; FTC, follicular thyroid carcinoma; PR, partial response; SD, stable disease; PFS, progression-free survival; OS, overall survival.

^aNot reported in the trial.

^bPatients treated with chemotherapy before being treated with sorafenib.

Table 3 Grade 3 AEs (>5% frequency) and grade 4 AEs of sorafenib reported in each trial

References	High-grade AEs (%)	Dose reduction (n/%)	Therapy discontinuation due to toxicities (n/%)	Fatalities on therapy ^a (n/%)	Adjustment of thyroid hormone requirements (n/%)
Gupta-Abramson <i>et al.</i> (2008)	Grades 3–4 ^b : hypertension (13), HFS (10), rash (10), weight loss (10), diarrhea (7), and elevated LFTs (7)	14/47	6/20	1/3	10/33
Kloos <i>et al.</i> (2009)	Grade 3: hand or foot pain (12), arthralgia (11), fatigue (16), HFS (7), musculoskeletal chest pain (7), and asymptomatic hyponatremia (5) Grade 4: pericardial effusion and reversible neutropenia	29/52	14/25	24/43	0/0
Ahmed <i>et al.</i> (2011)	Grade 3: HFS (44), other dermatological diseases (6), infection (9), fatigue (9), mucositis (9), arthralgia (9), hypertension (6), and drug hypersensitivity (9) Grade 4: febrile neutropenia and ruptured aortic graft	28/82	2/6	2/6	4/12
Chen <i>et al.</i> (2011)	None	0/0	0/0	1/11	0/0
Schneider <i>et al.</i> (2012)	Grade 3: hypertension (16), HFS (23), rash (16), mucositis (10), weight loss (10), diarrhea (6), and elevated LFTs (7) Grade 4: myocardial infarction and small-cell lung cancer	18/58	7/23	1/3	13/42
Capdevila <i>et al.</i> (2012)	Grade 3: HFS (20), diarrhea (15), alopecia (12), rash (6), fatigue (15), and anorexia (9) Grade 4: HFS and elevated LFTs	12/35	0/0	1/3	0/0
Marotta <i>et al.</i> (2013)	HFS, etc. (details were not reported)	17/100	2/12	5/29	13/76

AEs, adverse effects; TH, thyroid hormone; HFS, hand–foot syndrome; LFTs, liver function tests.

^aFatalities of all causes.

^bHigh-grade AEs were not reported separately in the trial and only grade 3–4 AEs were reported.

respectively (Fig. 3A, B, C, D, E, and F). A meta-analysis was also carried out on the proportion of patients in six trials requiring dose reductions due to the toxicity of sorafenib (one trial was excluded because the initial dose used was already 200 mg PO b.i.d. (Chen *et al.* 2011)) and the incidence was 62% (95% CI: 36–89; $P=0.000$) (Fig. 2D). All of them were pooled using the random-effects model, except diarrhea (which was pooled using the fixed-effects model instead), according to their heterogeneity. Other relative data such as the incidences of therapy discontinuation due to toxicities, fatalities on therapy, and adjustment of thyroid hormone requirements were also obtained and are presented in Table 3.

Discussion

Despite many comprehensive and systematic reviews of the literature on novel targeted therapies available for

patients with all types of thyroid cancer being reported recently (Brose *et al.* 2012, Busaidy & Cabanillas 2012, Kojic *et al.* 2012, Perez *et al.* 2012, Anderson *et al.* 2013), to our knowledge, this is the first meta-analysis conducted to estimate the efficacy and safety of sorafenib administered in radioiodine-refractory DTC patients.

In the current meta-analysis, the pooled PR in patients with radioiodine-refractory DTC was 22%. As has been mentioned above, many other TKIs have been studied in patients with radioiodine-refractory DTC mainly comprising sunitinib, motesanib, pazopanib, and vandetanib (Sherman *et al.* 2008, Bible *et al.* 2010, Carr *et al.* 2010, Leboulleux *et al.* 2012). Among them, pazopanib exhibited confirmed PR in 18 of the 37 patients (49%) with metastatic, rapidly progressive, radioiodine-refractory differentiated thyroid cancer, with the likelihood of response lasting longer than 1 year calculated to be 66% (Bible *et al.* 2010). At the same time, several non-TKIs have

Figure 2

Forest plots illustrating the efficacy of sorafenib in patients with radioiodine-refractory DTC. (A) the ratio of PR; (B) PFS; (C) the ratio of SD; and (D) ES (the incidence of dose reduction due to the adverse effects of sorafenib).

been studied as well, mainly comprising rosiglitazone, vorinostat, thalidomide, celecoxib, and selumetinib (Mrozek *et al.* 2006, Ain *et al.* 2007, Kebebew *et al.* 2009, Woyach *et al.* 2009, Ho *et al.* 2013). Though most of them exhibited modest efficacy, selumetinib, a MAPK kinase (MEK) 1 and MEK 2 inhibitor, increased the uptake of iodine-124 in 12 of the 20 patients (60%). Of these 12 patients, eight reached the dosimetry threshold for radioiodine therapy (five had confirmed partial responses and three had stable disease). All the patients exhibited decreases in serum thyroglobulin levels (mean reduction:

Figure 3

Forest plots illustrating the adverse effects associated with sorafenib. (A) HFS; (B) rash; (C) diarrhea; (D) fatigue; (E) weight loss; and (F) hypertension.

89%), and no toxic effects of grade 3 or higher attributable by the investigators to selumetinib were observed in this trial (Ho *et al.* 2013).

However, currently, a phase III randomized double-blind, multicenter trial evaluating the safety and efficacy of sorafenib (400 mg b.i.d.) vs placebo in patients with locally advanced or metastatic RAI-refractory DTC is underway (DECISION; ClinicalTrials.gov identifier: NCT00984282). The primary results of the trial were presented in the 2013 meeting of the American Society of Clinical Oncology Annual Meeting in Chicago, IL, which highlighted that the PFS in the sorafenib arm was significantly improved by 5 months compared with that in the placebo arm (Brose *et al.* 2013). Dose modifications due to AEs were more common with sorafenib (77.8%) than with placebo (30.1%), 18.8% of the patients discontinued sorafenib therapy due to AEs, and the most frequent serious AEs were secondary malignancies, occurring in 4.3% of the patients receiving sorafenib therapy in this trial (<http://am.asco.org/sorafenib-shows-benefit-refractory-differentiated-thyroid-cancer>, 30 October 2013).

The AEs (all grades) of sorafenib analyzed in the current study included hand-foot syndrome, diarrhea, fatigue, rash, weight loss, and hypertension. Grade 3 and 4 AEs mostly consisted of hand-foot syndrome, diarrhea, hypertension, rash, elevated abnormal liver function tests (LFTs), pericardial effusion, and neutropenia. Because of the limited data, the high-grade AEs were not meta-analyzed. Other rare but severe AEs associated with sorafenib such as eruptive keratoacanthoma-type squamous-cell carcinomas have also been reported (Smith *et al.* 2009).

Several factors had to be considered in the current meta-analysis. First, all the eligible trials lacked randomization and blinding, which might have resulted in an overestimation of the effects. Secondly, the inclusion criteria for each trial were different especially with regard to disease status at entry and previous therapies allowed. Five (Gupta-Abramson *et al.* 2008, Kloos *et al.* 2009, Chen *et al.* 2011, Capdevila *et al.* 2012, Schneider *et al.* 2012) of the seven eligible studies enrolled patients who had evidence of disease progression by the Response Evaluation Criteria in Solid Tumors in the 12 months preceding the initiation of treatment, while one (Ahmed *et al.* 2011) had evidence in the preceding 18 months and the other (Marotta *et al.* 2013) in the preceding 6 months. Five (Gupta-Abramson *et al.* 2008, Kloos *et al.* 2009, Ahmed *et al.* 2011, Capdevila *et al.* 2012, Marotta *et al.* 2013) of the seven eligible studies enrolled patients who had received prior chemotherapy. All the patients had not received prior therapy with TKIs, except two who had received prior

therapy with investigational agents (no specific agents available) and one who had received therapy with a TKI, namely sunitinib (Gupta-Abramson *et al.* 2008, Capdevila *et al.* 2012). These differences in the aspects of inclusion criteria of the eligible studies may increase the heterogeneity. However, considering the fact that almost all the subjects had evidence of disease progression and the proportion of subjects who had received prior chemotherapy or biological therapies was relatively small, it can be assumed that this heterogeneity will not affect the effects greatly. Thirdly, the current meta-analysis was not based on individual patient data, another possible cause for the overestimation of the treatment effects. Finally, as has been mentioned above, there were some disagreements among the authors during the current meta-analysis, which were mainly focused on the eligibility of the trials. The eligibility of Chen's paper (Chen *et al.* 2011) was discussed by CT Shen and ZL Qiu because of its heterogeneity in drug dose and the relatively small number of subjects included. As a result, QY Luo resolved the disagreement and decided to include this trial in the meta-analysis. Though the drug dose used in this trial was 200 mg b.i.d., the other trials had a great proportion of dose reduction, so this may actually decrease the heterogeneity. On the other hand, when dose reduction in the eligible trials was meta-analyzed, this trial was excluded because it had already administered a relatively small dose. The authors actually did not set a limitation to the smallest number of subjects included in each trial, so nine patients were acceptable. The disagreement about prior therapies of the enrolled patients in all the eligible studies has already been discussed above.

In conclusion, as far as PR and AEs are concerned, the results of this meta-analysis indicate that sorafenib has a modest effect in patients with radioiodine-refractory differentiated thyroid cancer and the high incidence of AEs associated with sorafenib may affect the quality of patients' lives. Though the use of this TKI in the treatment of radioiodine-refractory differentiated thyroid cancer is considered promising by many physicians, more effective agents with less toxicity and cost are still needed.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Z-L Qiu and C-T Shen independently assessed the eligibility of each article; C-T Shen and Z-L Qiu independently conducted data extraction according to the PRISMA statement; C-T Shen and Z-L Qiu independently carried out the statistical analyses; Q-Y Luo assessed all the discrepant items to resolve disagreements between C-T Shen and Z-L Qiu; and C-T Shen and Z-L Qiu wrote the paper, supervised by Q-Y Luo.

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