Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Efficacy and safety of apatinib combined with chemotherapy for the treatment of advanced gastric cancer in the Chinese population: a systematic review and meta-analysis

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Objective: To systematically evaluate the efficacy and safety of the combination of apatinib targeted therapy and chemotherapy (CT) in the treatment of patients with advanced gastric cancer (GC).

Materials and methods: Clinical trials were extracted from PubMed, the Cochrane Library, Web of Science, EMBASE, CNKI, and the Wanfang database. Outcome measures, including therapeutic efficacy, quality of life (QOL), and adverse events, were extracted and evaluated.

Results: Nineteen trials, including 1,256 advanced GC patients, were included. The results indicated that, compared with CT alone, the combination of apatinib targeted therapy with CT significantly improved the patients' complete response rate (OR=1.85, 95% CI=1.04–3.28, P=0.04), partial response rate (OR=2.19, 95% CI=1.71–2.80, P<0.00001), overall response (OR=2.57, 95% CI=1.99–3.32, P<0.00001), and disease control rate (OR=3.46, 95% CI=2.57–4.66, P<0.00001). Moreover, the combined therapy exhibited advantages over CT alone in the patients' QOL including the QOL improved rate (OR=1.77, 95% CI=0.94–3.33, P=0.08) and the Karnofsky performance score (OR=1.77, 95% CI=0.94–3.33, P=0.08). The group that received the combined therapy had higher rates of hypertension (OR=5.75, 95% CI=2.22–14.92, P=0.0003), albuminuria (OR=15.42, 95% CI=5.39–44.10, P<0.00001), and hand–foot syndrome (OR=2.09, 95% CI=1.26–3.48, P=0.004), whereas analyses of other adverse events, such as leucopenia, thrombocytopenia, and neutropenia, did not reveal significant differences (P>0.05).

Conclusion: The combination of apatinib targeted therapy and CT is more effective for GC treatment than CT alone. However, this combined treatment could lead to greater rates of hypertension, albuminuria, and hand–foot syndrome. Therefore, the benefits and risks should be considered before treatment.

Keywords: apatinib, target therapy, chemotherapy, gastric cancer, meta-analysis

Introduction

Gastric cancer (GC) is considered the third-leading cause of death among all cancer types and has caused 723,000 deaths across the whole world.[1,2] Currently, the incidence of GC has been significantly increasing, with ~952,000 new cases each year.[2] The People's Republic of China is a high-risk area for GC, and the new cases of GC in this region account for ~42.5% of such cases in the world.[3] Early GC can easily be misdiagnosed because of the small number of symptoms. Most patients with GC have developed to an advanced stage or exhibited metastasis, and the 5-year survival

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rate is <20% at this stage.[1,4] Chemotherapy (CT) is one of the standard treatment regimens for advanced GC. Although CT improves patient survival, most patients eventually relapse and develop resistance to treatment, which is not able to completely eradicate small lesions and metastatic cells.[1,5–7] Thus, more effective and safer treatments are urgently required.

In recent years, the use of molecular targeted therapy has been increasing rapidly, and this approach is considered as a powerful therapeutic method for cancer treatment. The agents used in targeted therapy can precisely identify and attack certain type of cancer cells based on mutations of genes and proteins.[2] Moreover, little damage is done to normal cells; thus, molecular targeted therapy is also called a "biological missile." The clinical application of molecular targeted therapy for malignancies has been reported, and several studies have found that the combination of molecular targeted therapy and CT has better therapeutic effects than treatment with CT alone.[8–13]

Angiogenesis is essential for tumor growth and metastasis, and VEGF and its receptors (VEGFRs) play a crucial role in angiogenesis.[14–16] VEGFR2 is one of 3 VEGFRs and plays a pivotal role in VEGF-mediated cancer angiogenesis.[17] Apatinib is a novel antiangiogenic agent that specifically targets VEGFR2. This small molecule tyrosine kinase inhibitor was approved for the second-line treatment of advanced GC in the People's Republic of China in 2014.[17,18] In several clinical trials, apatinib targeted therapy combined with CT exhibited more prominent therapeutic effects for advanced GC than CT alone.[19–37] However, systematic analyses assessing the therapeutic efficacy of apatinib targeted therapy combined with CT in advanced GC remain scarce. In this study, we conducted a meta-analysis to investigate the treatment effect and safety of apatinib targeted therapy combined with CT in comparison with CT alone for advanced GC to provide a scientific reference for the design of future clinical trials.

Materials and methods

Search strategy and selection criteria

The literature was searched across PubMed, the Cochrane Library, Web of Science, EMBASE, CNKI, and the Wanfang database with key terms "apatinib" combined with "gastric cancer." No language limits were applied. The initial search was performed in January 2018 and updated in March 2018.

Selection criteria: Studies concerning advanced GC patients were involved in our analysis. Patients in the experimental groups received apatinib targeted therapy combined with CT, and patients in the control group were treated with CT alone.

Data extraction and quality assessment

The data were independently extracted by 2 investigators (Honggang Cheng and Aixia Sun). Disagreements were resolved by discussion with a third researcher (Qingbo Guo). All involved studies were summarized as follows: the first author's name, year of publication, study location, tumor stages, number of cases, patient ages, study parameter types, therapeutic regimens, enrollment period, and dosages of apatinib utilized. The included trials' qualities were evaluated based on the Cochrane Handbook.[38]

Outcome definition

The clinical responses included treatment efficacy, quality of life (QOL), and adverse events (AEs). Treatment efficacy was assessed in terms of the complete response rate (CR), partial response rate (PR), stable disease rate (SD), progressive disease rate (PD), overall response rate (ORR, ORR=CR+PR), and disease control rate (DCR, DCR=CR+PR+SD). The patients' QOLs were evaluated using the QOL improved rate (QIR) and the Karnofsky performance score (KPS). AEs, including leukopenia, thrombocytopenia, diarrhea, nausea and vomiting, hypertension, neutropenia, albuminuria, oral mucositis, hand–foot syndrome, weakness, hemoglobin reduction, and myelosuppression, were also assessed.

Statistical analysis

The analyses were performed using Review Manager 5.3 (Cochrane Collaboration, London, UK). $P<0.05$ was taken to indicate that the differences reached statistical significance. Heterogeneity among studies was assessed with the Cochran's Q test to determine the most suitable analysis model, and funnel plots were used to assess the publication biases of the involved studies.[39] $I^2<50\%$ or $P>0.1$ indicated that a study was homogenous. The OR was the principal measurement of the therapeutic effects, and the ORs are presented with the 95% CIs. Sensitivity analyses were conducted to evaluate the influences of the therapeutic regimens, apatinib dosages, sample sizes, and types of involved studies.

Results

Search results

A total of 476 articles were identified in the initial search. After review of the titles and abstracts, 384 articles were excluded because they did not include clinical trials (n=207),

were unrelated studies (n=56), or were duplications or repetitions (n=121). This process left 92 studies as potentially relevant. After detailed assessment of the full texts, case reports and reviews (n=16), and articles without a control group (n=17) or without apatinib and CT combined therapy (n=23) or with insufficient data (n=4) were excluded. Finally, 19 trials[19–37] involving 1,256 advanced GC patients were included in this meta-analysis (Figure 1).

Patient characteristics

After selection, all of the included trials were conducted in the People's Republic of China. In total, 625 advanced GC patients were treated with apatinib in combination with CT, and 631 patients were treated with CT alone. Detailed information about the involved trials and patients is presented in Tables 1 and 2.

Quality assessment

The assessment of bias risk is presented in Figure 2. Fourteen studies were determined to be low risk, and the remaining 5 studies were not true randomized controlled trials. None of the included trials provided clear descriptions of the performance and detection risks. The attrition risks of the involved trials were low; 3 trials were considered to have unclear risk owing to selective reporting.

Therapeutic efficacy assessments

As presented in Figures 3 and 4, Figure S1, and Table 3, the pooled results revealed that the patients who underwent combined therapy exhibited significantly improved CR, PR, ORR, and DCR (CR: OR=1.85, 95% CI=1.04–3.28, P=0.04; PR: OR=2.19, 95% CI=1.71–2.80, $P<0.00001$; ORR: OR=2.57, 95% CI=1.99–3.32, $P<0.00001$; DCR: OR=3.46, 95% CI=2.57–4.66, $P<0.00001$) and significantly decreased PD (OR=0.33, 95% CI=0.25–0.44, $P<0.00001$), whereas the SD was not significantly different from that of the patients who received CT alone (OR=1.09, 95% CI=0.86–1.39, P=0.48). Fixed effect models were used to analyze the OR rate because of low heterogeneity.

QOL assessment

QOL was evaluated in this analysis. The results revealed that the QOL of patients in the combined group was significantly better than that of the control group as indicated by the QIR and KPS, although the former did not reach significance (Figure 5, QIR: OR=1.77, 95% CI=0.94–3.33, P=0.08; KPS: OR=14.99, 95% CI=12.51–17.47, $P<0.00001$).

AEs assessment

The safety of apatinib targeted therapy was evaluated in this meta-analysis. As presented in Figure S2 and

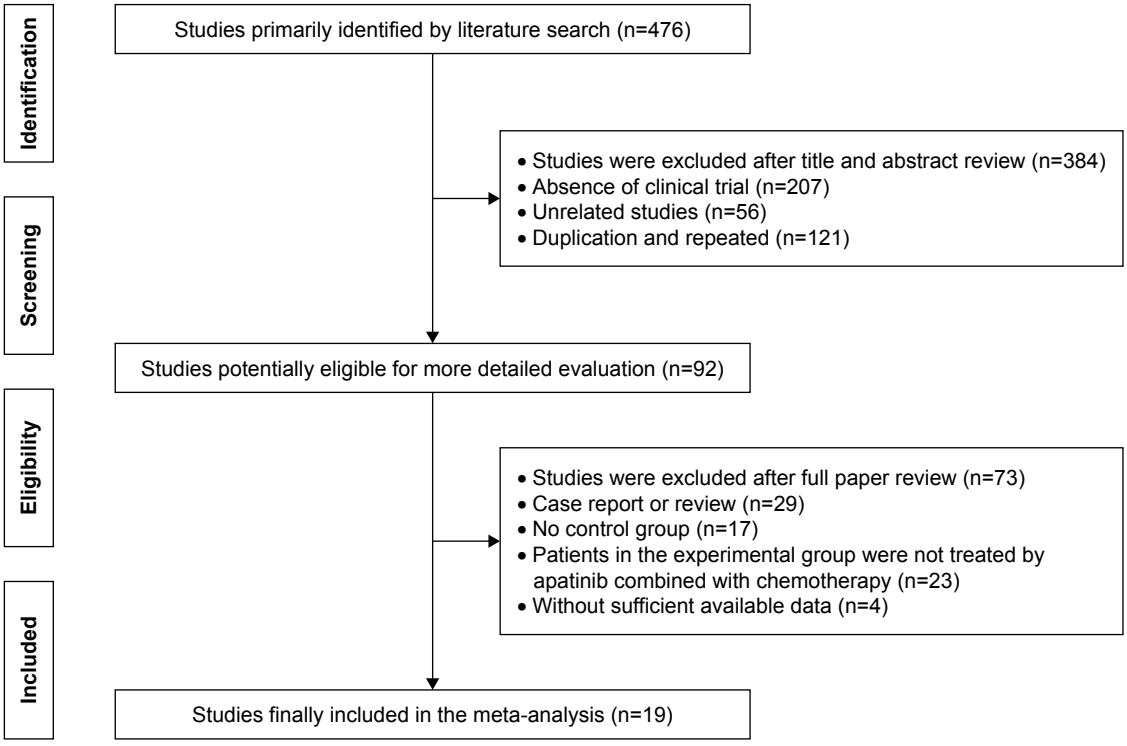

Figure 1 Flow diagram of the selection process.

Table 1 Clinical information from the eligible trials in the meta-analysis

Included studies	Nation	Tumor stage	Patients Con/Exp	Age (year)		Parameter types
				Con	Exp	
Dong et al,[19] 2018	People's Republic of China	ND	41/41	ND	ND	ORR, DCR, KPS, AE
Du,[20] 2017	People's Republic of China	0–2 (ECOG)	40/40	54.6±10.4 (mean)	51.3±10.0 (mean)	ORR, DCR, AE
Duan et al,[21] 2017	People's Republic of China	III–IV	28/32	64.7±9.9 (mean)	63.2±9.5 (mean)	ORR, DCR, AE
Fan et al,[22] 2017	People's Republic of China	III–IV	15/15	≥70 (1)	≥70 (2)	ORR, DCR, QIR, AE
Gao et al,[23] 2017	People's Republic of China	60–80 (KPS)	15/16	ND	ND	ORR, DCR, AE
Hu et al,[24] 2016	People's Republic of China	ND	23/23	58.1±1.2 (mean)	57.8±1.1 (mean)	ORR, DCR, AE
Jing,[25] 2016	People's Republic of China	0–2 (ECOG)	21/21	75.1±3.7 (mean)	74.5±3.7 (mean)	ORR, DCR, AE
Li et al,[26] 2018	People's Republic of China	IV	30/34	55.5±9.5 (mean)	56.0±10.7 (mean)	ORR, DCR
Li and Li,[27] 2017	People's Republic of China	KPS ≥60	35/35	54.3±1.8 (mean)	55.6±1.5 (mean)	ORR, DCR, KPS
Li,[28] 2017	People's Republic of China	0–2 (ECOG)	20/20	48.0±11.5 (mean)	46.5±12.0 (mean)	ORR, DCR, AE
Qian and Ge,[29] 2017	People's Republic of China	IV	42/34	61 (median)	62 (median)	ORR, DCR, AE
Sheng et al,[30] 2017	People's Republic of China	III–IV	59/59	52.2±2.7 (mean)	51.4±2.6 (mean)	ORR, DCR, AE
Wang et al,[31] 2016	People's Republic of China	ND	29/29	58.6±12.0 (mean)	57.2±8.3 (mean)	ORR
Wen et al,[32] 2017	People's Republic of China	III–IV	45/45	62.9±4.3 (mean)	63.3±4.2 (mean)	ORR, DCR, AE
Wu et al,[33] 2017	People's Republic of China	III–IV	14/14	49.3±9.7 (mean)	48.9±9.8 (mean)	ORR, DCR, QIR, AE
Yan et al,[34] 2017	People's Republic of China	IV	75/75	56±6 (mean)	54±6 (mean)	ORR, DCR, AE
Zhan,[35] 2017	People's Republic of China	III–IV	40/40	63.7±3.4 (mean)	64.5±4.1 (mean)	ORR, DCR, QIR, AE
Zhou et al,[36] 2018	People's Republic of China	ND	20/20	61.1±9.5 (mean)	60.2±8.7 (mean)	ORR, DCR, QIR, AE
Zhu et al,[37] 2016	People's Republic of China	0–2 (ECOG)	39/32	60 (median)	56 (median)	ORR, DCR, AE

Notes: Con, control group (CT alone group); Exp, experimental group (apatinib targeted therapy plus CT).
Abbreviations: AE, adverse events; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group score; DCR, disease control rate; KPS, Karnofsky performance score; ND, nondetermined; ORR, overall response rate; QIR, quality of life improved rate.

Table 4, the group that received apatinib targeted therapy plus CT had higher rates of hypertension, albuminuria, and hand–foot syndrome (hypertension: OR=5.75, 95% CI=2.22–14.92, P=0.0003; albuminuria: OR=15.42, 95% CI=5.39–44.10, $P<0.00001$; hand–foot syndrome: OR=2.09, 95% CI=1.26–3.48, P=0.004), whereas analyses of leukopenia, thrombocytopenia, diarrhea, nausea and vomiting, neutropenia, oral mucositis, weak, hemoglobin reduction,

Table 2 Information of apatinib targeted therapy combined with CT

Included studies	Therapeutic regimen		Line	Enrollment period	Dosage of apatinib
	Exp	Con			
Dong et al,[19] 2018	Oxaliplatin+apatinib	Oxaliplatin	ND	2013.1–2013.12	850 mg/time, 3 times/d
Du,[20] 2017	FBC+apatinib	Fluorouracil	ND	2015.3–2017.4	500 mg/time, 1 time/d
Duan et al,[21] 2017	FOLFOX+apatinib	FOLFOX	ND	2015.1–2016.12	850 mg/time, 1 time/d
Fan et al,[22] 2017	S-1+apatinib	S-1	I	2015.1–2016.1	500 mg/time, 1 time/d
Gao et al,[23] 2017	S-1+apatinib	S-1	ND	2015.6–2016.6	500–850 mg/time, 1 time/d
Hu et al,[24] 2016	S-1+apatinib	S-1	I	2015.1–2016.8	800–850 mg/time, 1 time/d
Jing,[25] 2016	S-1+apatinib	S-1	I	2014.11–2015.12	500 mg/time, 1 time/d
Li et al,[26] 2018	FOLFOX+apatinib	FOLFOX	≥III	2014.12–2016.12	250–850 mg/time, 1 time/d
Li and Li,[27] 2017	Oxaliplatin+S-1+apatinib	Oxaliplatin+S-1	≥III	2015.2–2016.2	850 mg/time, 1 time/d
Li,[28] 2017	FBC+apatinib	Fluorouracil	ND	ND	250 mg/time, 1 time/d
Qian and Ge,[29] 2017	Taxanes/platinum/ fluorouracil+apatinib	Taxanes/platinum/ fluorouracil	ND	2015.6–2017.6	500 mg/time, 1 time/d
Sheng et al,[30] 2017	S-1+apatinib	S-1	II	ND	250 mg/time, 2 times/d
Wang et al,[31] 2016	S-1+apatinib	S-1	ND	2015.2–2016.6	850 mg/time, 1 time/d
Wen et al,[32] 2017	Oxaliplatin+S-1+apatinib	Oxaliplatin+S-1	ND	2014.1–2016.4	850 mg/time, 1 time/d
Wu et al,[33] 2017	S-1+apatinib	S-1	II	2015.12–2017.2	500 mg/time, 1 time/d
Yan et al,[34] 2017	Oxaliplatin+S-1+apatinib	Oxaliplatin+S-1	≥III	2015.3–2017.3	850 mg/time, 1 time/d
Zhan,[35] 2017	FOLFIRI+apatinib	FOLFIRI	ND	2011.5–2013.5	425–850 mg/d, 1 time/d
Zhou et al,[36] 2018	S-1+apatinib	S-1	≥II	2015.7–2016.10	850 mg/time, 1 time/d
Zhu et al,[37] 2016	Taxanes/irinotecan/ fluorouracil+apatinib	Taxanes/irinotecan/ fluorouracil	ND	2014.7–2016.7	500 mg/time, 1 time/d

Notes: Con, control group (CT alone group); Exp, experimental group (apatinib targeted therapy plus CT).
Abbreviations: CT, chemotherapy; FBC, fluorouracil-based chemotherapy; FOLFIRI, calcium folinate+irinotecan+5-fluorouracil; FOLFOX, oxaliplatin+calcium folinate+5-fluorouracil; ND, not determined; S-1, gimeracil and oteracil porassium capsules.

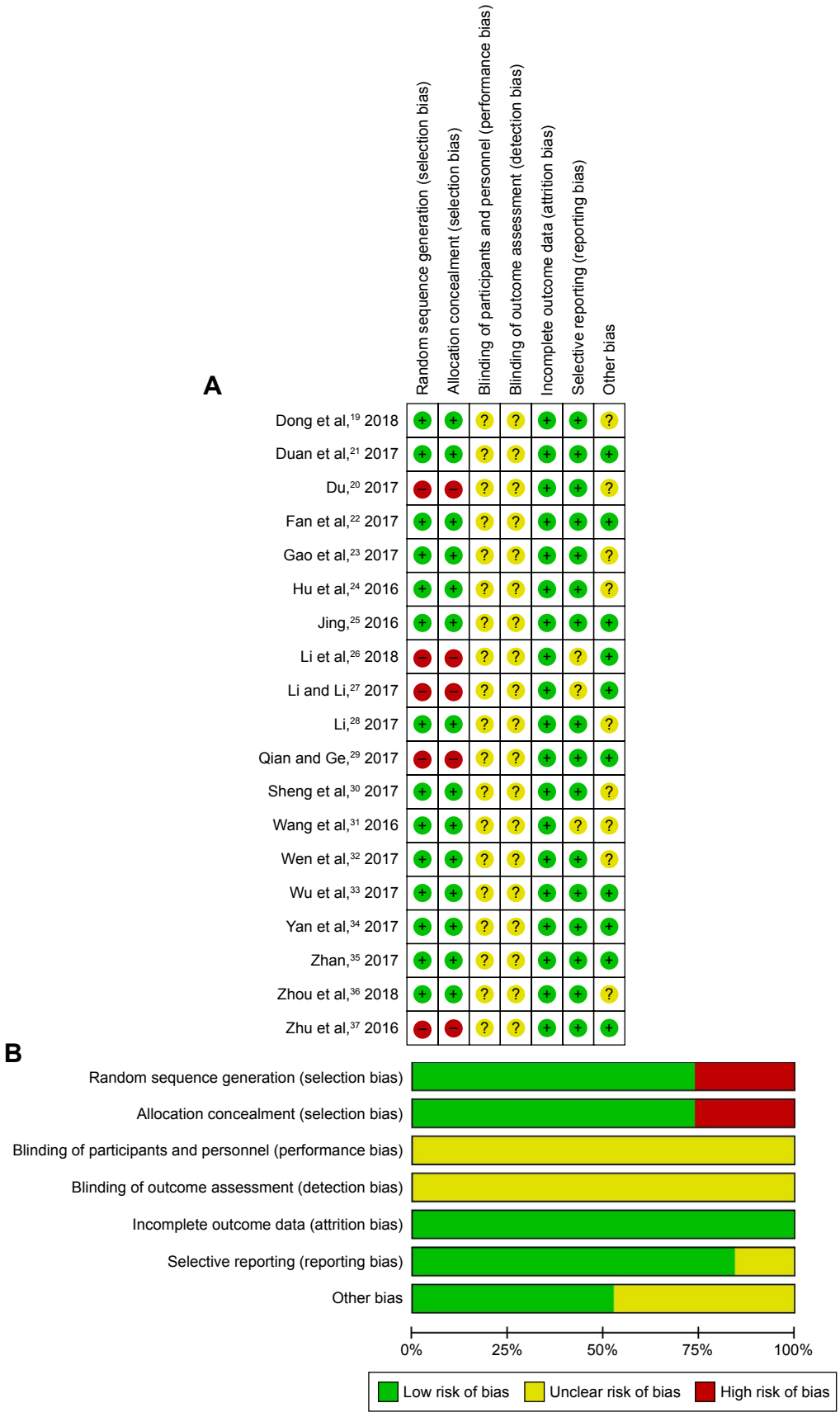

Figure 2 (**A**) Risk of bias summary: review of the authors' judgments about each risk of bias item for the included studies, (**B**) risk of bias graph: review of the authors' judgments about each risk of bias item presented as percentages across all included studies.
Note: Each color represents a different level of bias: red for high risk, green for low risk, and yellow for unclear risk of bias.

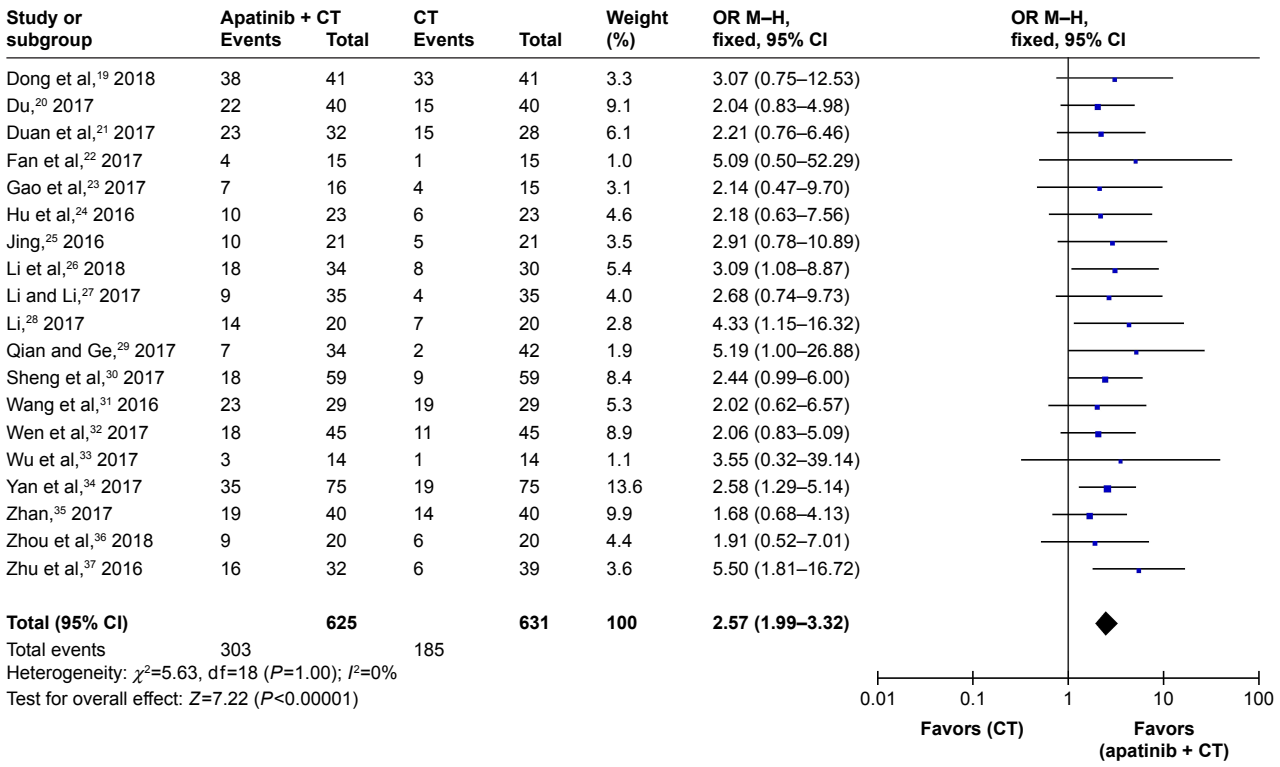

Figure 3 Forest plot of the comparison of the ORR between the experimental and control group.
Notes: Control group, CT alone group; experimental group, apatinib targeted therapy plus CT. The fixed effects meta-analysis model (Mantel–Haenszel method) was used.
Abbreviations: CI, confidence interval; CT, chemotherapy; OR, odds ratio; ORR, overall response rate.

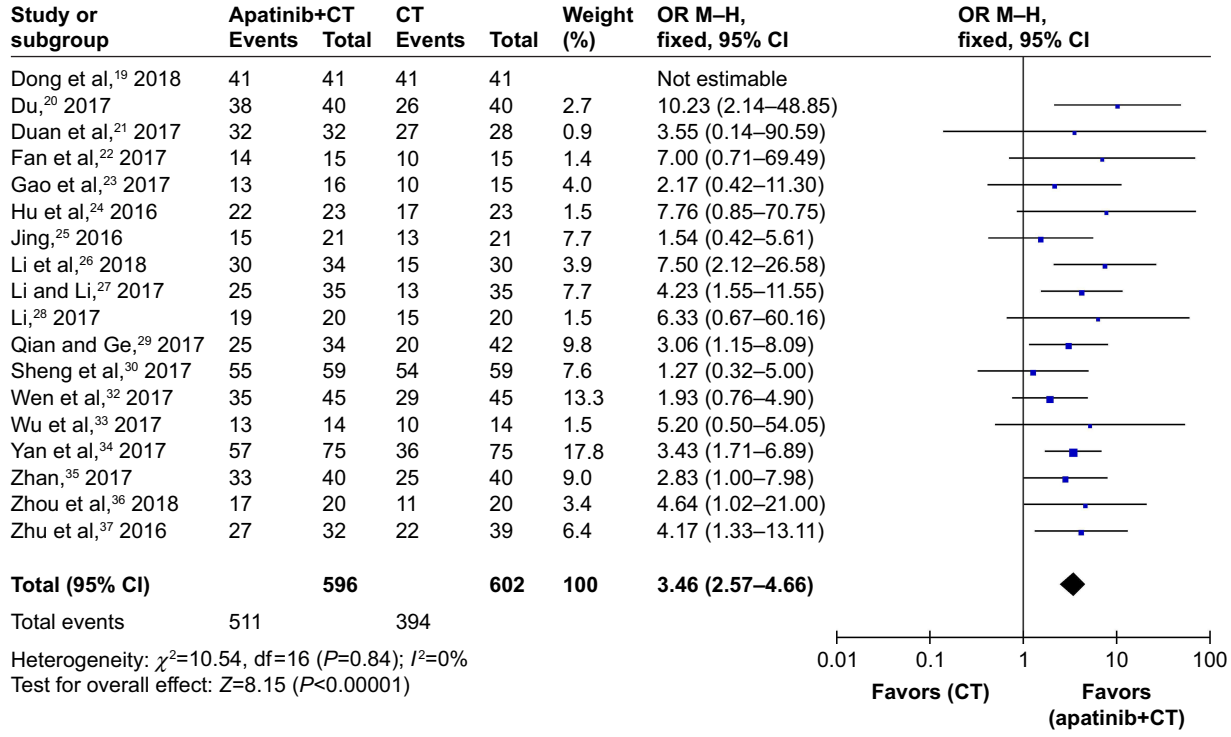

Figure 4 Forest plot of the comparison of the DCR between the experimental and control group.
Notes: Control group, CT alone group; experimental group, apatinib targeted therapy plus CT. The fixed effects meta-analysis model (Mantel–Haenszel method) was used.
Abbreviations: CI, confidence interval; CT, chemotherapy; DCR, disease control rate; OR, odds ratio.

Table 3 Comparison of CR, PR, SD, PD, ORR, and DCR between the experimental and control groups

Parameter	Exp	Con	Analysis method	Heterogeneity		OR	95% CI	*P*-value
	Number of patients (n)	Number of patients (n)		I^2 (%)	*P*-value			
CR	625	631	Fixed	0	0.96	1.85	1.04–3.28	0.04
PR	625	631	Fixed	0	0.89	2.19	1.71–2.80	<0.00001
SD	596	602	Fixed	0	0.59	1.09	0.86–1.39	0.48
PD	596	602	Fixed	0	0.94	0.33	0.25–0.44	<0.00001
ORR	625	631	Fixed	0	1.00	2.57	1.99–3.32	<0.00001
DCR	596	602	Fixed	0	0.84	3.46	2.57–4.66	<0.00001

Notes: Con, control group (CT alone group); Exp, experimental group (apatinib targeted therapy plus CT).
Abbreviations: CR, complete response rates; CT, chemotherapy; DCR, disease control rate; OR, odds ratio; ORR, overall response rate; PD, progressive disease rates; PR, partial response rates; SD, stable disease rates.

and myelosuppression did not reveal significant differences (leukopenia: OR=1.73, 95% CI=0.96–3.10, *P*=0.07; thrombocytopenia: OR=1.31, 95% CI=0.79–2.18, *P*=0.29; diarrhea: OR=0.63, 95% CI=0.36–1.10, *P*=0.10; nausea and vomiting: OR=1.02, 95% CI=0.71–1.46, *P*=0.92; neutropenia: OR=1.33, 95% CI=0.68–2.59, *P*=0.40; oral mucositis: OR=1.19, 95% CI=0.80–1.77, *P*=0.40; weak: OR=1.09, 95% CI=0.70–1.70, *P*=0.70; hemoglobin reduction: OR=2.13, 95% CI=0.69–6.59, *P*=0.19; myelosuppression: OR=0.96, 95% CI=0.57–1.63, *P*=0.89).

Publication bias

The funnel plots drawn for the studies of the primary outcomes (CR, PR, SD, PD, ORR, DCR, and AEs) were approximately symmetrical, which indicated the generally controlled publication bias and reliability of our primary conclusions (Figures 6 and S3 and S4).

Sensitivity analysis

We conducted subgroup analyses to explore the sources of heterogeneity in the ORR and DCR with respect to therapeutic regimens, apatinib dosages, sample sizes, and types of involved studies. As presented in Table 5, our analysis results revealed that no significant differences were found between the different therapeutic regimens, apatinib dosages, sample sizes, and types of studies.

Discussion

In recent years, with the development of tumor molecular biology and epigenetics, increasing numbers of targeted

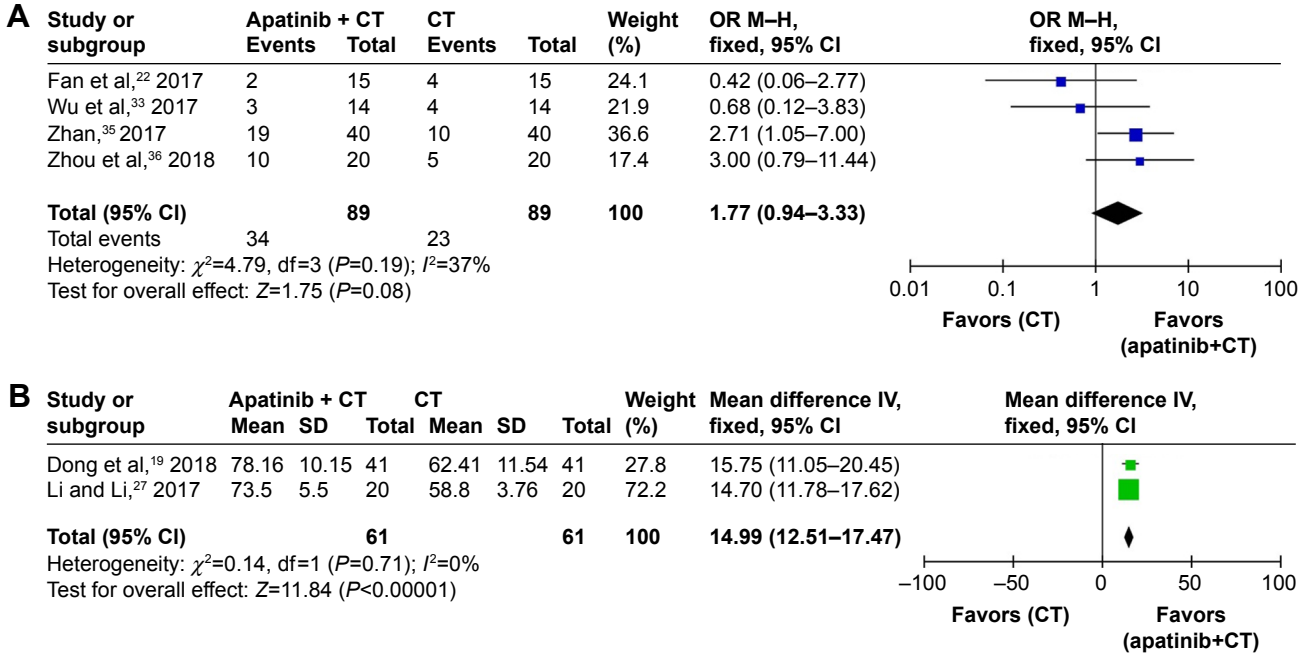

Figure 5 Funnel plot of percentages of the ORR (**A**) and DCR (**B**) between the experimental and control groups.
Abbreviations: CI, confidence interval; CT, chemotherapy; DCR, disease control rate; ORR, overall response rate.

Table 4 Comparison of AEs between the experimental and control groups

AEs	Exp	Con	Analysis method	Heterogeneity		OR	95% CI	*P*-value
	Number of patients (n)	Number of patients (n)		I^2 (%)	*P*-value			
Leukopenia	123	118	Fixed	0	0.67	1.73	0.96–3.10	0.07
Thrombocytopenia	244	239	Fixed	0	0.91	1.31	0.79–2.18	0.29
Diarrhea	252	251	Fixed	0	0.75	0.63	0.36–1.10	0.10
Nausea, vomiting	348	355	Fixed	25	0.21	1.02	0.71–1.46	0.92
Hypertension	392	395	Random	60	0.005	5.75	2.22–14.92	0.0003
Neutropenia	120	120	Fixed	0	0.83	1.33	0.68–2.59	0.40
Albuminuria	175	182	Fixed	0	0.62	15.42	5.39–44.10	<0.00001
Oral mucositis	274	281	Fixed	33	0.16	1.19	0.80–1.77	0.40
Hand–foot syndrome	262	257	Fixed	0	0.57	2.09	1.26–3.48	0.004
Weak	209	208	Fixed	0	0.58	1.09	0.70–1.70	0.70
Hemoglobin reduction	77	72	Random	55	0.08	2.13	0.69–6.59	0.19
Myelosuppression	129	137	Fixed	0	0.79	0.96	0.57–1.63	0.89

Notes: Con, control group (CT alone group); Exp, experimental group (apatinib targeted therapy plus CT).
Abbreviations: AE, adverse event; CT, chemotherapy; OR, odds ratio.

agents, such as gefitinib, erlotinib, apatinib, etc, have been used to improve treatment effects for patients with malignancies.[40–43] As components of the important signaling pathway of cancer angiogenesis, VEGF and VEGFR are closely related to cancer invasiveness. Researchers have confirmed that the expressions of VEGF and VEGFR are associated with poor prognosis in GC.[44,45] Upon binding to its receptors, the activated VEGF family promotes the proliferation of vascular cells for the development of new blood vessels in tumor tissues and then ensures oxygen and nutrient supplies and causes tumor growth and metastasis.[14,46] Therefore, anti-VEGFR target drugs are considered promising prospects for the treatment of advanced GC.

The VEGFR family includes VEGFR-1, VEGFR-2, and VEGFR-3.[16] Among these receptors, VEGFR2 plays an essential role in VEGF-mediated tumor angiogenesis.[14,17] When it associates with VEGF, the dimerization of VEGFR2 causes the autophosphorylation of intracellular tyrosine kinase domains, which leads to the activation of the PLC-γ–Raf kinase–MEK–MAP kinase pathway, which in turn enhances endothelial cell proliferation.[14,15] Apatinib is a new inhibitor of VEGFR-2 tyrosine kinase that targets the intracellular ATP binding site of the receptor.[17] Several studies have reported that the addition of apatinib can be beneficial for patients with advanced GC.[42,43] Although there are statistical analyses of published clinical trials, the exact therapeutic effects have not been systematically evaluated and demonstrated due to sample size variability among these trials. Additionally, the different applied protocols in the different clinical trials may have led to different therapeutic effects. In the present research, we performed an extensive online search followed by rigorous contrasting and combining data

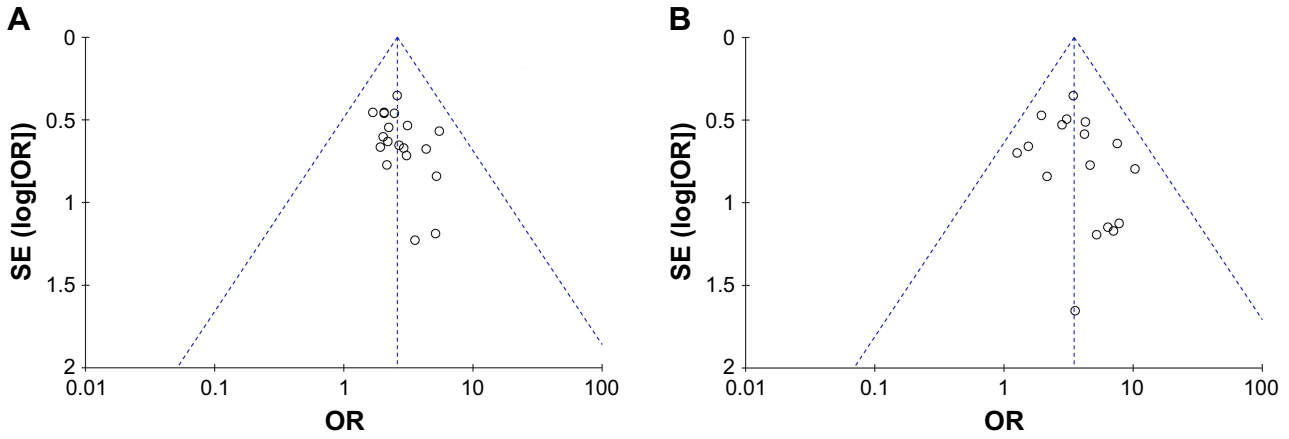

Figure 6 Forest plot of the comparison of the QIR (**A**) and KPS (**B**) between the experimental and control groups.
Notes: Control group, CT alone group; experimental group, apatinib targeted therapy plus CT. The fixed effects meta-analysis model (Mantel–Haenszel method) was used.
Abbreviations: CI, confidence interval; CT, chemotherapy; KPS, Karnofsky performance score; QIR, quality of life improved rate.

Table 5 Subgroup analyses of ORR and DCR between the experimental and control groups

Parameter	Factors at study level	Exp	Con	Analysis method	Heterogeneity		OR	95% CI	*P*-value
		Number of patients (n)	Number of patients (n)		I^2 (%)	*P*-value			
ORR	**Therapeutic regimen**								
	Apatinib+FOLFOX	66	58	Fixed	0	0.66	2.63	1.24–5.56	0.01
	Apatinib+S-1+oxaliplatin	155	155	Fixed	0	0.91	2.42	1.46–4.01	0.0006
	Apatinib+FBC	60	60	Fixed	0	0.35	2.58	1.24–5.39	0.01
	Apatinib+S-1	197	196	Fixed	0	1.00	2.40	1.51–3.82	0.0002
	Dosage of apatinib								
	850 mg/d	236	232	Fixed	0	1.00	2.29	1.53–3.43	<0.0001
	500 mg/d	215	230	Fixed	0	0.84	3.07	1.94–4.88	<0.00001
	Study sample size								
	>50	496	503	Fixed	0	0.96	2.52	1.89–3.37	<0.00001
	<50	129	128	Fixed	0	0.97	2.75	1.57–4.79	0.0004
	Type of control trials								
	RCT	450	445	Fixed	0	1.00	2.38	1.77–3.22	<0.00001
	Non-RCT	175	186	Fixed	0	0.68	3.16	1.92–5.20	<0.00001
DCR	**Therapeutic regimen**								
	Apatinib+FOLFOX	66	58	Fixed	0	0.67	6.74	2.07–21.95	0.002
	Apatinib+S-1+oxaliplatin	155	155	Fixed	0	0.49	3.07	1.89–5.00	<0.00001
	Apatinib+FBC	60	60	Fixed	0	0.73	8.80	2.45–31.70	0.0009
	Apatinib+S-1	168	167	Fixed	0	0.63	2.78	1.51–5.10	0.0010
	Dosage of apatinib								
	850 mg/d	207	203	Fixed	0	0.79	3.21	2.03–5.07	<0.00001
	500 mg/d	215	230	Fixed	0	0.43	3.32	2.02–5.48	<0.00001
	Study sample size								
	>50	467	474	Fixed	0	0.61	3.43	2.45–4.79	<0.00001
	<50	129	128	Fixed	0	0.78	3.58	1.86–6.90	0.0001
	Type of control trials								
	RCT	421	416	Fixed	0	0.89	2.88	1.98–4.18	<0.00001
	Non-RCT	175	186	Fixed	0	0.68	4.79	2.89–7.92	<0.00001

Notes: Con, control group (CT alone group); Exp, experimental group (apatinib targeted therapy plus CT).
Abbreviations: CI, confidence interval; CT, chemotherapy; DCR, disease control rate; FBC, fluorouracil-based chemotherapy; FOLFOX, oxaliplatin+calcium folinate+5-fluorouracil; OR, odds ratio; ORR, overall response rate; QIR, quality of life improved rate; RCT, randomized controlled trial; S-1, gimeracil and oteracil porassium capsules.

analyses in terms of categorization to provide a clear and systematical conclusion.

Our meta-analysis revealed that apatinib targeted therapy combined with CT is associated with a favorable efficacy compared with CT alone. Compared with the patients who were treated with CT alone, the patients who were treated with combined therapy exhibited markedly increased CR, PR, ORR, and DCR ($P<0.05$). The patients' QOL was also evaluated in this analysis, and the QOL was significantly improved after combined therapy. These results indicated that apatinib targeted therapy increased the curative effect of CT by inhibiting tumor angiogenesis and thereby improving the patients' life qualities.

Safety is the top priority of clinical treatment, and it is also the key factor for the development of apatinib targeted therapy. Regarding AEs and severe toxicities, our analysis revealed that there were no significant differences in most of the AE indicators between the 2 groups. The group receiving CT plus apatinib targeted therapy had higher rates of hypertension, proteinuria, and hand–foot syndrome, which are usually controllable events and do not require permanent discontinuation of therapy.

Some factors may influence the therapeutic effects of apatinib targeted therapy. In our subgroup analysis, no differences were found between the different therapeutic regimens, apatinib dosages, sample sizes, and types of studies. However, currently published studies that have probed the influences of these factors on the curative effect of apatinib targeted therapy are still insufficient; thus, these issues should be further researched and explored. Furthermore, the determination of the optimal therapeutic strategy will be valuable for GC treatment. Recently, many novel treatment strategies, such as targeted therapy and immunotherapy, have been developed for the treatment of malignancies. Several

studies have found that combined treatment with targeted therapy and immunotherapy for malignant tumors has better therapeutic effects than single therapy.[47,48] Therefore, the combination of targeted therapy with an immunotherapy, such as chimeric antigen receptor-modified T cells, T-cell receptor-modified T cells, etc,[49,50] may be the new direction for the future development of advanced GC treatment.

There are some limitations in our analysis. First, the number of GC patients included in this study is not sufficiently large, and the follow-up time was short. Apart from that, the different trials evaluated the treatment efficacy using different outcomes, so it was difficult to summarize the results on the same scale, which led to shrunken statistical sample sizes. Third, our data were partly extracted from published papers rather than original patient records, which mean that we were not able to avoid analytical bias based on the information presented in the articles. Due to the above limitations, future studies and generated data will be valuable to further verify the safety and efficacy of apatinib targeted therapy.

Conclusion

In summary, our study confirmed that apatinib targeted therapy combined with CT is an effective treatment for advanced GC patients. Apatinib targeted therapy markedly enhances the treatment efficacy of CT for advanced GC. However, this combined treatment could lead to greater rates of hypertension, albuminuria, and hand–foot syndrome. Therefore, the benefits and risks should be considered before treatment.

Author contributions

All authors contributed toward data analysis, drafting, and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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