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Original Article

Comparative efficacy and adverse reactions of apatinib-chemotherapy combinations versus chemotherapy alone for treatment of advanced colorectal cancer: a meta-analysis of randomized controlled trials

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Abstract: Objective: Apatinib mesylate is the first small-molecule anti-angiogenic agent that has been shown to be effective and well-tolerated for treatment of advanced gastric cancer, and has shown encouraging efficacy for treatment of advanced colorectal cancer (CRC). However, previous studies reported diverse efficacy and safety results of apatinib for treatment of advanced CRC. This meta-analysis aimed to compare the efficacy and safety of apatinib plus chemotherapy (trial group) versus chemotherapy alone (control group) for treatment of advanced CRC. Methods: A joint search was performed in electronic databases to retrieve randomized clinical trials (RCTs) reporting the efficacy and adverse reactions of apatinib in the treatment of advanced CRC. The pooled survival, treatment responses, and safety were estimated and compared between the trial and control groups. Results: A total of 7 eligible RCTs involving 539 colorectal cancer patients were enrolled. Meta-analysis showed significantly higher overall response rate (risk ratio (*RR*) = 1.46, $P < 0.00001$), disease control rate (*RR* = 1.24, $P < 0.00001$), complete response (*RR* = 1.72, $P = 0.01$), PR (*RR* = 1.43, $P = 0.001$), overall survival (mean difference (*MD*) = 3.89, $P = 0.0006$), and progression-free survival (*MD* = 2.94, $P < 0.00001$) and lower progressive disease (*RR* = 0.37, $P < 0.00001$) in the trial group than in the control group; however, there were no significant differences between the two groups in terms of stable disease (*RR* = 0.89, $P = 0.38$) or incidence of adverse reactions (*RR* = 1.01, $P = 0.92$). Conclusion: Apatinib plus chemotherapy shows a higher efficacy and comparable safety for treatment of advanced CRC in relative to chemotherapy alone.

Keywords: Colorectal cancer, apatinib, efficacy, safety, meta-analysis

Introduction

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related mortality in the world [1]. In 2020, there were 1.88 million new patients diagnosed with CRC and more than 0.9 million deaths occurred due to this malignancy globally [2]. The 5-year survival rate is estimated to be 64% among all CRC patients; however, the 5-year survival rate is only 12% in patients with metastatic CRC [3]. Early-stage CRC may present no apparent symptoms, while hematochezia, abdominal pain, abdominal mass and ileus may develop following progression [4]. Most patients with CRC are at an advanced stage upon definitive diagnosis, and hepatic metastasis is detected in approximately 15% of patients with CRC at diagnosis, which misses the best timing for surgical treatment [5].

During the past decade, great improvements have been achieved in the survival of patients with CRC, and emerging treatments extend the overall survival (OS) to 3 years [6]. Currently, chemotherapy remains the standard treatment

for metastatic CRC, and the addition of anti-vascular endothelial growth factor (VEGF) has been proven to prolong the survival period [7]. The National Comprehensive Cancer Network (NCCN) guidelines recommend multi-targeted tyrosine kinase inhibitors (TKIs) as the standard third-line treatment for metastatic CRC, such as regorafenib, fruquintinib, and trifluridine and tipiracil hydrochloride (TAS-102) [8]. Nevertheless, acquired resistance may rapidly occur and result in disease progression in a portion of patients with CRC [9]. To date, there have been no standard fourth- or higher-line treatments for CRC [6].

Recently, small-molecule anti-angiogenic agents have been shown to be effective for the treatment of CRC [10]. Apatinib mesylate, the first small-molecule anti-angiogenic agent, has been shown to be safe and effective for the treatment of advanced gastric cancer [11]. Since apatinib mesylate was approved for treatment of advanced metastatic gastric cancer by China Food and Drug Administration (CFDA) in 2014, this agent, given by oral administration, has shown clinical benefits among patients with advanced gastric cancer [12-14]. As a specific small-molecule, anti-angiogenic TKI targeting VEGF receptor (VEGFR)-2, apatinib has been found to be active against multiple solid cancers through highly selectively blocking VEGF signaling and suppressing platelet-derived growth factor receptors (PDGFRs), c-Kit and c-Src expression [14-17]. Recently, apatinib was found to suppress the growth of CRC cells [18, 19], and clinical studies have shown encouraging efficacy of apatinib for treatment of advanced CRC [20]. However, the efficacy and adverse reactions of apatinib for treatment of advanced CRC vary in studies. This meta-analysis aimed to compare the efficacy and safety of apatinib-chemotherapy combinations versus chemotherapy alone for treatment of advanced CRC, so as to provide insight into the clinical treatment of advanced CRC with apatinib.

Methods

Literature search strategy

A joint search was performed in electronic international and national databases, including PubMed, The Cochrane Library, Scopus, Embase, Web of Science, China Biology Medicine disc (CBM, http://www.sinomed.ac.cn), China National Knowledge Infrastructure (CNKI, http://www.cnki.net), China Science and Technology Journal Database (VIP Database, http://csi1.cqvip.com/) and Wanfang Database (https://www.wanfangdata.com.cn), using mesh terms of “apatinib” and “colorectal cancer” until January 2022. We retrieved English and Chinese publications pertaining to the clinical efficacy and safety of apatinib for treatment of CRC. The inclusion criteria involved (1) Randomized controlled trials (RCTs); (2) English or Chinese publications; (3) Patients with cytological or pathological diagnosis of CRC, and without obvious abnormal routine blood tests, liver or kidney functions or electrocardiogram (ECG) prior to enrollment, or vital organ dysfunction; (4) Patients in the trial group received apatinib-chemotherapy combinations, while patients in the control group received chemotherapy alone; (5) The survival, treatment responses and safety were reported, including progression-free survival (PFS), OS, complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall response rate (ORR), disease control rate (DCR), and incidence of adverse reactions. Publications meeting the following criteria were excluded from the study: (1) Patients without definitive diagnosis of CRC; (2) Non-RCTs; (3) Animal experiments, gene assays or *in vitro* studies; (4) Review, conference articles, correspondence, letters, case reports, descriptive studies, or repeated publications; (5) Incomplete outcome measures.

Literature screening and data extraction

Literature screening and data extraction were performed independently by two investigators. All data were cross-checked, and the final decision was made following addition of a third investigator if there was a disagreement between the two investigators. The following data were extracted from the publications: (1) Title, author, year, and source of publications; (2) Interventions given to the trial and control groups; (3) Type of the study and publication bias; (4) Outcome measures and results.

Assessment of risk of bias in RCTs

The risk of bias was evaluated using the Cochrane tool, and the assessment items

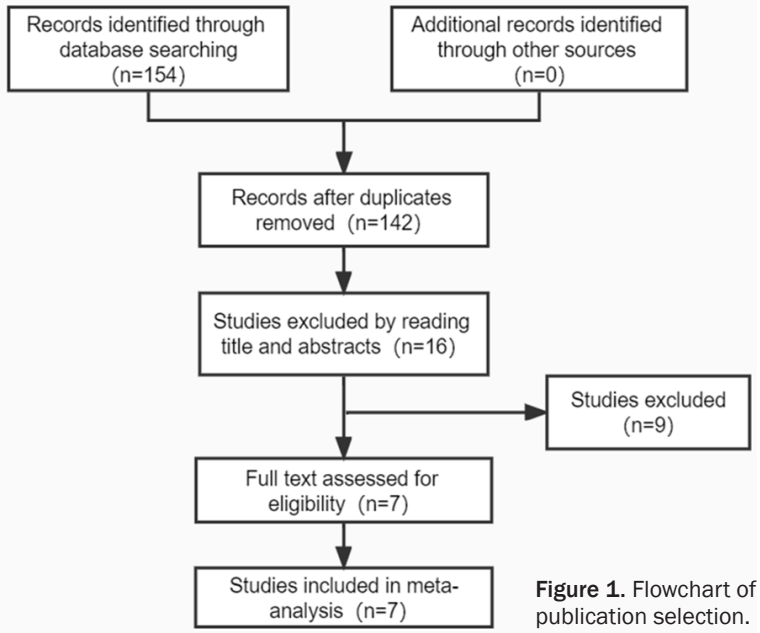

Figure 1. Flowchart of publication selection.

included randomization process, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential threats to validity [21].

Meta-analysis

The treatment responses and safety were analyzed by risk ratio (RR) as efficacy statistics, and the survival was analyzed by mean difference (MD) as efficacy statistics. The effect sizes were expressed as a 95% confidence interval (*CI*), and the differences were considered significant at $P < 0.05$. The heterogeneity of the included studies was determined using the chi-square test and I^2 statistic. A P value of > 0.1 and I^2 value of < 50% was defined as no heterogeneity, and a fixed-effects model was employed for pooled analyses, while a P value of 0.1 and greater and I^2 value of 50% and greater was defined as a heterogeneity, and a random-effects model was employed for pooled analyses. All statistical analysis was performed using the software RevMan version 5.3 (Revman International, Inc.; New York, NY, USA), and a P value of < 0.05 was considered significant.

Ethical statement

This study was approved by the Ethical Review Committee of Sanming First Hospital (approval number: Ming (2022) 3). All procedures were performed according to the international and national guidelines for human studies.

Results

Study characteristics

A total of 154 publications were initially screened, and 7 eligible studies involving 539 CRC patients that met the inclusion and exclusion criteria were finally enrolled in the meta-analysis (**Figure 1**). **Table 1** describes the characteristics of included studies.

Risk of bias

The risk of bias was evaluated in the 7 included RCTs using the Cochrane tool, which was shown in **Figure 2**.

Meta-analysis

Overall response rate (ORR): The included 7 studies all reported ORR [22-28], and no heterogeneity was identified ($P = 0.71$, $I^2 = 0$); therefore, a fixed-effects model was employed for pooled analyses. Meta-analysis showed a significantly higher ORR in the trial group than in the control group (*RR* = 1.46, 95% *CI*: 1.25 to 1.69, $P < 0.00001$) (**Figure 3**).

Disease control rate (DCR): The included 7 studies all reported DCR [22-28], and no heterogeneity was detected ($P = 0.83$, $I^2 = 0$); therefore, a fixed-effects model was employed for pooled analyses. Meta-analysis showed a significantly higher DCR in the trial group than in the control group (*RR* = 1.24, 95% *CI*: 1.14 to 1.35, $P < 0.00001$) (**Figure 4**).

Complete response (CR): The included 7 studies all reported CR [22-28], and no heterogeneity was found ($P = 0.43$, $I^2 = 0$); therefore, a fixed-effects model was employed for pooled analyses. Meta-analysis showed significantly higher CR in the trial group than in the control group (*RR* = 1.72, 95% *CI*: 1.12 to 2.65, $P = 0.01$) (**Figure 5**).

Table 1. Characteristics of included randomized clinical trials

Reference	Diagnosis	Study area	No. of patients (trial/control group)	Treatment		Outcome measures
				Trial group	Control group	
[22]	Stage III-IV colorectal cancer	Ningxiang, Hunan Province, China	98 (49/49)	Apatinib (500 mg, QD) plus XELOX regimen	XELOX regimen	CR, PR, SD, PD, DCR, ORR, incidence of adverse reactions
[23]	Stage IIIB-IV colorectal cancer	Jinhua, Zhejiang Province, China	120 (60/60)	Apatinib (500 mg, QD) combined with oxaliplatin + capecitabine	Oxaliplatin + capecitabine	OS, PFS, CR, PR, SD, PD, DCR, OSS, incidence of adverse reactions
[24]	Advanced colorectal cancer	Luoyang, Henan Province, China	50 (25/25)	Apatinib (500 mg, QD) combined with oxaliplatin + capecitabine	Oxaliplatin + capecitabine	OS, median survival, CR, PR, SD, PD, DCR, ORR, incidence of adverse reactions
[25]	Advanced colorectal cancer	Zaozhuang, Shandong Province, China	80 (40/40)	oxaliplatin + capecitabine + irinotecan, calcium folinate	Oxaliplatin + capecitabine + irinotecan, calcium folinate	CR, PR, SD, PD, OSS, incidence of adverse reactions
[26]	Advanced colorectal cancer	Cenxi, Guangxi Province, China	50 (25/25)	Apatinib (500 mg, QD) combined with oxaliplatin + capecitabine	Oxaliplatin + capecitabine	CR, PR, SD, PD, DCR, ORR, incidence of adverse reactions
[27]	Advanced colorectal cancer	Nanping, Fujian Province, China	66 (33/33)	Apatinib (500 mg, QD) combined with oxaliplatin + capecitabine	Oxaliplatin + capecitabine	OS, PFS, CR, PR, SD, PD, ORR, DCR, incidence of adverse reactions
[28]	Advanced colorectal cancer	Hefei, Anhui Province, China	75 (30/35)	Apatinib (500 mg, QD) combined with oxaliplatin + capecitabine	Oxaliplatin + capecitabine	CR, PR, SD, PD, ORR, DCR

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; XELOX regimen, capecitabine plus oxaliplatin; QD, once daily.

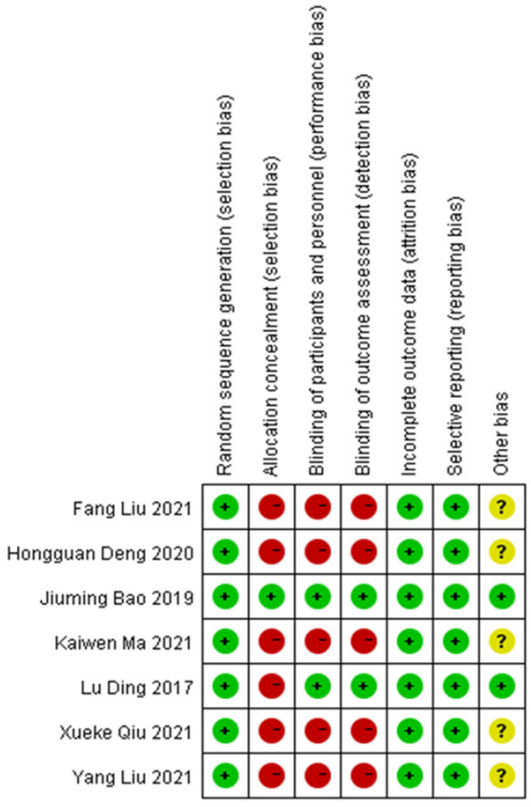

Figure 2. Risk of bias in included randomized control trials.

Partial response (PR): The included 7 studies all reported PR [22-28], and no heterogeneity was detected (P = 0.98, I^2 = 0); therefore, a fixed-effects model was employed for pooled analyses. Meta-analysis showed significantly higher PR in the trial group than in the control group (*RR* = 1.43, 95% *CI*: 1.15 to 1.77, P = 0.001) (**Figure 6**).

Stable disease (SD): The included 7 studies all reported SD [22-28], and no heterogeneity was detected (P = 0.91, I^2 = 0); therefore, a fixed-effects model was employed for pooled analyses. Meta-analysis showed comparable SD between the two groups (*RR* = 0.89, 95% *CI*: 0.69 to 1.15, P = 0.38) (**Figure 7**).

Progressive disease (PD): The included 7 studies all reported PD [22-28], and no heterogeneity was detected (P = 0.79, I^2 = 0); therefore, a fixed-effects model was employed for pooled analyses. Meta-analysis showed significantly lower PD in the trial group than in the control group (*RR* = 0.37, 95% *CI*: 0.25 to 0.56, P < 0.00001) (**Figure 8**).

Overall survival (OS): Of the included 7 publications, only two studies reported OS [23, 27],

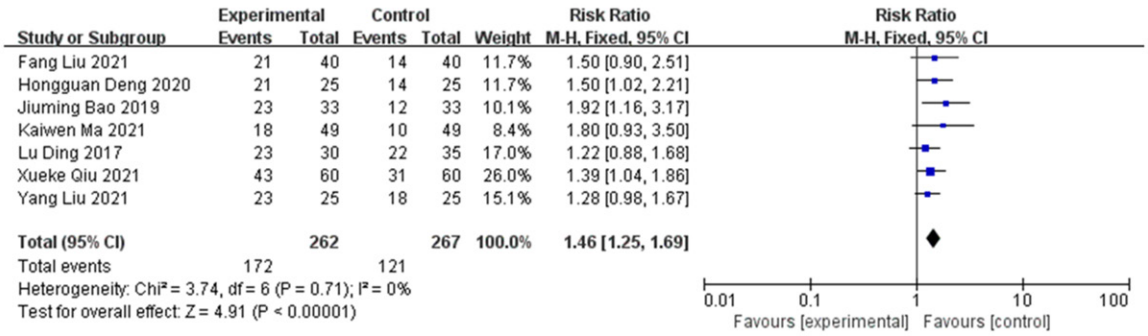

Figure 3. Forest plot of overall response rate among colorectal cancer patients.

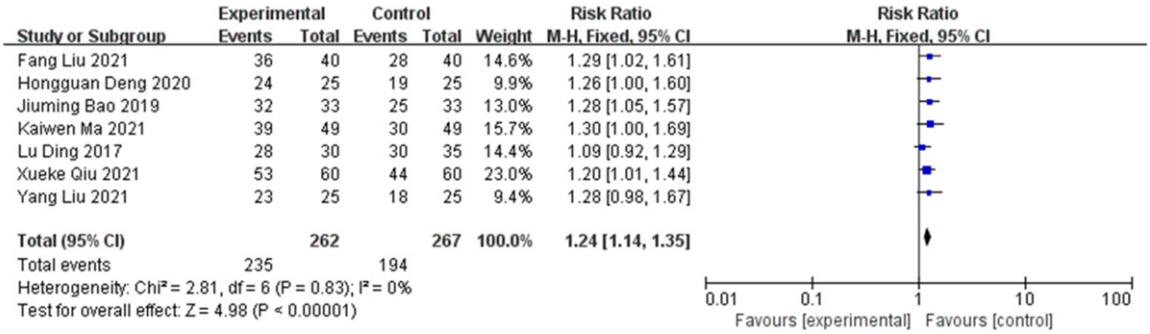

Figure 4. Forest plot of disease control rate among colorectal cancer patients.

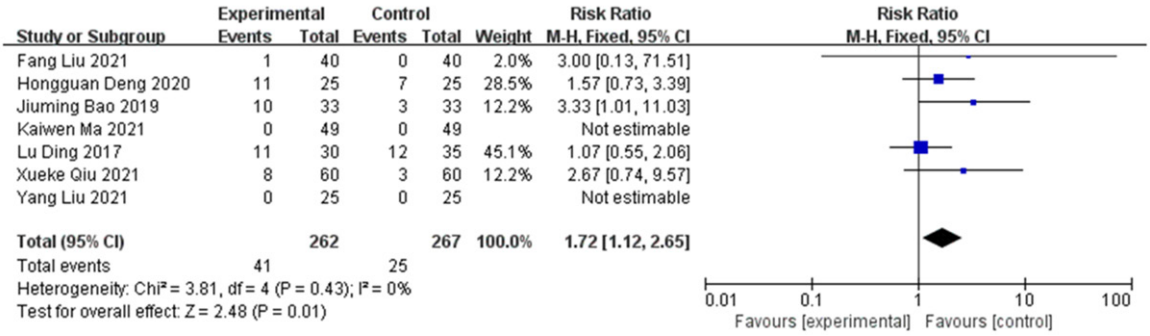

Figure 5. Forest plot of complete response among colorectal cancer patients.

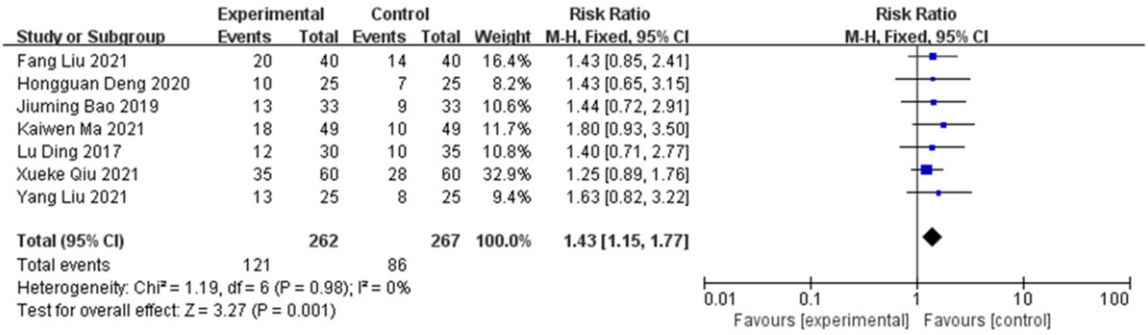

Figure 6. Forest plot of partial response among colorectal cancer patients.

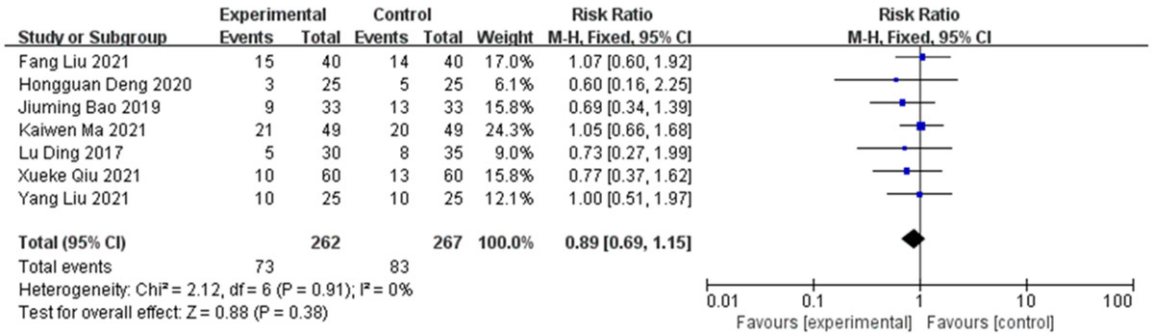

Figure 7. Forest plot of stable disease among colorectal cancer patients.

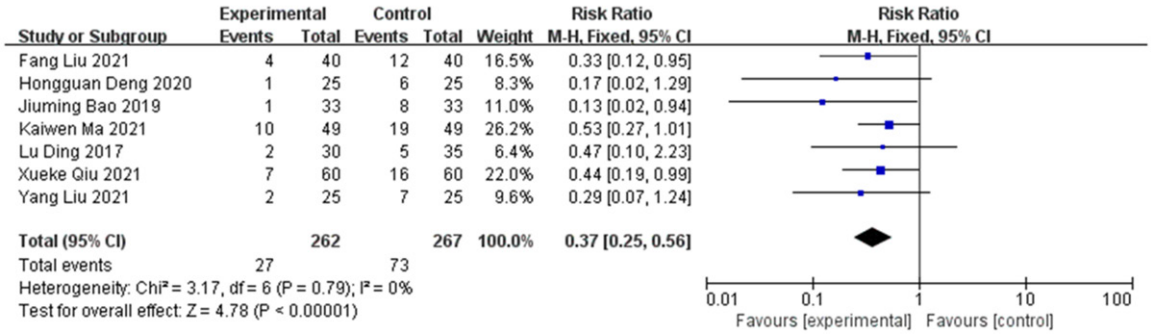

Figure 8. Forest plot of progressive disease among colorectal cancer patients.

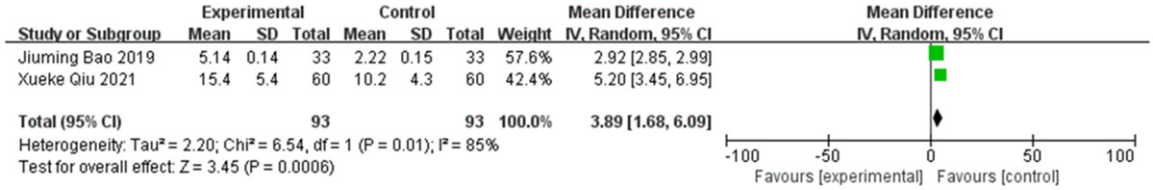

Figure 9. Forest plot of overall survival among colorectal cancer patients.

and there was a heterogeneity among included studies (P = 0.01, I^2 = 85%); therefore, a random-effects model was employed for pooled analyses. Meta-analysis showed significantly greater OS in the trial group than in the control group (*MD* = 3.89, 95% *CI*: 1.68 to 6.09, P = 0.0006) (**Figure 9**).

Progression-free survival (PFS): Of the included 7 publications, only two studies reported PFS [23, 27], and there was a heterogeneity in the included studies (P = 0.13, I^2 = 57%); therefore, a random-effects model was employed for pooled analyses. Meta-analysis showed significantly greater PFS in the trial group than in the control group (*MD* = 2.94, 95% *CI*: 2.36 to 3.52, P < 0.00001) (**Figure 10**).

Incidence of adverse reactions: Of the included 7 publications, six studies reported incidence of adverse reactions associated with chemotherapy [22-26], and no heterogeneity was detected (P = 0.63, I^2 = 0); therefore, a fixed-effects model was employed for pooled analyses. Meta-analysis showed no significant difference in the incidence of adverse reactions between the two groups (*RR* = 1.01, 95% *CI*: 0.8 to 1.28, P = 0.92) (**Figure 11**).

Discussion

It is well known that colorectal cancer (CRC) is a highly heterogeneous malignancy, and has diverse treatment outcomes and prognoses [1]. 5-fluorouracil-based combination therapy

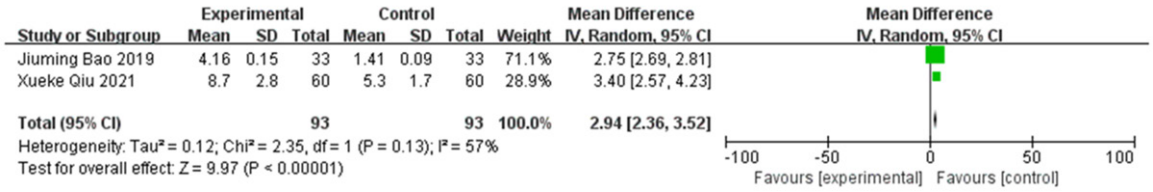

Figure 10. Forest plot of progression-free survival among colorectal cancer patients.

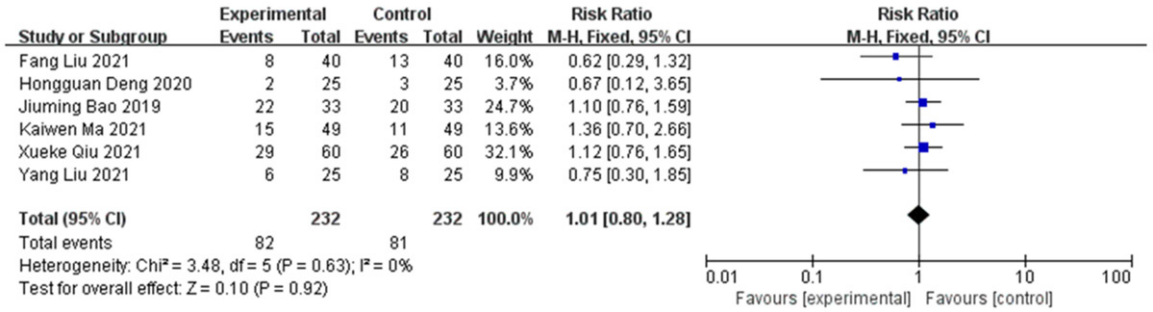

Figure 11. Forest plot of incidence of adverse reactions among colorectal cancer patients.

with targeted drugs as a first-line treatment has achieved progression-free survival (PFS) of more than 10 months and overall survival (OS) of approximately 30 months among CRC patients; however, progressive disease (PD) still occurs [7]. Since the overall response of the late-line therapy remains unsatisfactory, targeted drugs that are effective to extend OS are urgently needed for CRC patients [29].

Angiogenesis is an important marker for tumor development and progression [30]. VEGF and VEGFR signaling pathways have been found to be indispensable in tumor growth and metastasis [31]. Elevated vascular density has been reported to correlate with recurrence and metastasis in patients with CRC [32]. Since VEGF and VEGFR are lowly expressed in normal tissues and moderately/highly detected in CRC tissues, and VEGF/VEGFR expression correlates positively with angiogenesis, inhibition of the VEGF/VEGFR signaling is accepted as a promising therapeutic target for advanced CRC [33]. Apatinib is found to suppress tumor growth through specific suppression of the VEGF/VEGFR2 signaling and inhibition of vascular endothelial cell proliferation [11]. Currently, apatinib has been approved for the third-line treatment of advanced gastric adenocarcinoma or adenocarcinoma of the esophagogastric junction in China [14]. In addition, apatinib was found to be active against showed cholangiocarcinoma, hepatocellular carcinoma, CRC and lung cancer [34], which encourages the evaluation of the anti-tumor activity against CRC.

This study retrieved all potential RCTs pertaining to apatinib for the treatment of advanced CRC, and 7 eligible studies were included in the final analysis. Apatinib-chemotherapy combinations were found to improve ORR, DCR, CR and PR and reduce PD relative to chemotherapy alone among CRC patients ($P < 0.01$); however, comparable SD was measured between the two groups ($P > 0.05$). It is therefore considered that apatinib-chemotherapy combinations improve the clinical efficacy among CRC patients.

In the current study, we found comparable incidence of adverse reactions between apatinib combined with chemotherapy and chemotherapy alone ($P > 0.05$). In addition, the type and severity of treatment-related adverse reactions were comparable between the two groups, which mainly included grade I/II headache, weakness and diarrhea. These side effects were alleviated following timely management, indicating that apatinib combined with chemotherapy is well tolerated for treatment of CRC.

In addition, apatinib combined with chemotherapy was reported to improve PFS and OS among CRC patients; however, only two studies were enrolled in this meta-analysis [23, 27]. Further multicenter RCTs to evaluate the long-term efficacy and safety of apatinib-chemotherapy combinations are warranted.

This study aimed to assess the adverse reactoins and efficacy of apatinib for treatment of advanced CRC based on English and Chinese publications. However, the present study has some limitations. (1) There have been a few RCTs published, and several RCTs had a small sample size; (2) Absence of multicenter RCTs; (3) All included studies were performed in Chinese populations, and the findings may be not feasible in other populations.

In summary, the results of this meta-analysis demonstrate that apatinib-chemotherapy combinations present a higher efficacy and comparable adverse events relative to chemotherapy alone among advanced CRC patients. Further large, multicenter RCTs to investigate the long-term efficacy and safety of apatinib combined with chemotherapy for advanced CRC seem justified.

Acknowledgements

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Disclosure of conflict of interest

None.

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