

# Meta-analysis on the risk of fatal adverse events by bevacizumab, cetuximab, and panitumumab in 31 randomized trials including 25,000 patients with colorectal carcinoma

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## Abstract

**Background:** Targeted drugs including bevacizumab, cetuximab, and panitumumab have been widely used during the management of patients diagnosed with colorectal carcinoma, especially as palliative treatment. The present meta-analysis was performed to evaluate the fatal adverse events (FAEs) of targeted drugs including bevacizumab, cetuximab, and panitumumab in patients with colorectal cancer.

**Patients and methods:** Studies of prospective, randomized, and controlled feature from EMBASE, Medline, and Cochrane Library, which reported FAEs potentially associated with bevacizumab, cetuximab, and panitumumab were adopted. Clinical characteristics and FAEs were collected from the enrolled literatures, with the quality of which been evaluated. Pooled analysis of FAEs, caused by each agent as first line, second/further line, and adjuvant treatment were performed with relative risks (RRs) and their corresponding 95% confidence intervals (CIs) in software RevMan 5.3.

**Results:** Thirty-one studies including 25,939 patients were brought into the final analysis. The RR and its 95% CI of the FAEs among all the agents including bevacizumab, cetuximab, and panitumumab was 1.07 (95% CI, 0.89–1.29;  $P = .50$ ). The RRs and their 95% CIs of the FAEs as first line, second or further line, and adjuvant treatment related to bevacizumab were 0.91 (95% CI, 0.62–1.32;  $P = .61$ ), 1.14 (95% CI, 0.57–2.28;  $P = .71$ ), and 1.10 (95% CI, 0.67–1.79;  $P = .72$ ). The RRs and their 95% CIs of the FAEs as first line, second or further line, and adjuvant treatment related to cetuximab were 1.02 (95% CI, 0.60–1.76;  $P = .93$ ), 2.51 (95% CI, 0.49–12.88;  $P = .27$ ), and 2.40 (95% CI, 1.00–5.77;  $P = .05$ ). The RRs and their 95% CIs of the FAEs as first line, second or further line treatment related to panitumumab were 1.40 (95% CI, 0.89–2.18;  $P = .14$ ) and 0.68 (95% CI, 0.43–1.09;  $P = .11$ ), respectively.

**Conclusions:** The present meta-analysis did not show any significantly increased RR of FAEs belonging to bevacizumab, cetuximab, or panitumumab, whether as first line, second/further line, or adjuvant treatment among patients with colorectal carcinoma comparing to placebo or blank treatment.

**Abbreviations:** AE = adverse events, B = bevacizumab, BSC = best supportive care, C = cetuximab, CI = confidence interval, CT = chemotherapy, ECOG PS = Eastern Cooperative Oncology Group, performance status, FAE = fatal adverse event, FOLFIRI = irinotecan + fluorouracil + leucovorin, FOLFOX = oxaliplatin + fluorouracil + leucovorin, IFL = irinotecan + fluorouracil + leucovorin, MOF = multiple organ failure, N/R = not reported, NCCN = National Comprehensive Cancer Network, NSCLC = non-small cell lung cancer, P = panitumumab, PHD = physical health deterioration, PL = placebo, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = relative risk, XELIRI = irinotecan + capecitabine, XELOX = oxaliplatin + capecitabine.

**Keywords:** bevacizumab, cetuximab, colorectal cancer, fatal adverse events, panitumumab

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QZ and HH contributed equally to the article and should be considered as co-corresponding authors.

The ethical approval was waived as the present study being a systematic review. This article does not contain any studies with animals performed by any of the authors.

Informed consent was not available in the present study as it was a systematic review.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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## 1. Introduction

Colorectal cancer is one of the most common malignancies worldwide, accounting for 10.2% (1,846,200) of the new cases and 9.2% (883,200) of the deaths in 2018.<sup>[1]</sup> Currently, the treatment strategy of colorectal cancer has been established with the alternative including surgery, chemotherapy, radiotherapy, and targeted therapy in recent years. However, approximately 50% to 60% of patients diagnosed with colorectal cancer developed metastatic disease,<sup>[2,3]</sup> and 80% to 90% of which had unresectable liver metastases.<sup>[4–6]</sup> In terms of the systematic treatment of the metastatic colorectal cancer, the panel of National Comprehensive Cancer Network (NCCN) recommended five chemotherapeutic regimens, including FOLFOX,<sup>[7]</sup> FOLFIRI,<sup>[8]</sup> XELOX,<sup>[9,10]</sup> 5-FU/LV,<sup>[11]</sup> and FOLFOXIRI<sup>[12,13]</sup> based on the relative clinical trials. In particular, targeted agents including bevacizumab, cetuximab, and panitumumab have been deemed as the standard choices, in combination with chemotherapy on the basis of their encouraging results, which prolonged the overall survival of patients with metastatic disease up to 3 years in selected population.<sup>[14]</sup>

With the wide use of the monoclonal antibodies including bevacizumab, cetuximab, and panitumumab in the systematic therapy in patients with colorectal cancer, the safety of the agents has raised the attention of the clinical physicians. The addition of bevacizumab was associated with significantly increased risk of fatal adverse events (FAEs) among patients with special tumor types including non-small cell lung cancer (NSCLC), pancreatic cancer, prostate cancer, and ovarian cancer (RR was 1.29, 95% confidence intervals (CI): 1.05–1.57,  $P=.01$ ).<sup>[15]</sup> Likewise, cetuximab was suggested with an increased risk of severe adverse events in patients with colorectal carcinoma (70.0% versus 51.23%,  $P<.001$ ).<sup>[16]</sup> However, few analyses have been conducted to explore the FAEs of the monoclonal antibodies including bevacizumab, cetuximab, and panitumumab, in patients with colorectal carcinoma.

Thus, the present meta-analysis was designed to identify the relative risks (RR) of FAEs in colorectal cancer patients treated with bevacizumab, cetuximab, and panitumumab comparing to placebo/blank, in an attempt to provide some potential evidence for clinicians during the treatment of colorectal carcinoma.

## 2. Patients and methods

### 2.1. Literature search

Databases including EMBASE, MEDLINE, and Cochrane Library were reviewed with the main key words “Bevacizumab,” “Cetuximab,” and “Panitumumab” as MeSH terms. Literature review was conducted up to December 31, 2018, without restrictions on start time. The searching procedure was limited to original, published, prospective, randomized, placebo/blank controlled clinical trials, which had been fully published in English. The present meta-analysis was performed in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. The pooled analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>[17]</sup>

### 2.2. Inclusion and exclusion criteria

Inclusion criteria:

1. Prospective, randomized, placebo/blank controlled clinical trials related to bevacizumab, cetuximab, or panitumumab in patients with colorectal carcinoma;
2. Participants were randomly assigned to receive one of the agents (bevacizumab, cetuximab, or panitumumab) as experiment or placebo/blank treatment in the group control in the including studies;
3. FAEs, in both of the arms were reported with or without etiology specified.

Exclusion criteria:

1. Agents (bevacizumab, cetuximab, or panitumumab) used in the researches were not the comparative ones.
2. Case reports, basic experiments, review publication, and correspondences were excluded;
3. All the meeting abstracts were excluded because of the potential publication bias.

### 2.3. Data extraction

Data extraction was conducted by two independent investigators (JXC, JHW). Available data was extracted from all the screened studies with the items as below: first author's name, publication year, sample size of the study, median age, treatment status, European Cooperative Oncology Group Performance Status (ECOG PS), available agents (bevacizumab, cetuximab, or panitumumab), regimens adopted in both of the arms, and the number of FAEs. Administered doses and treatment time of targeted agents were also specified. All the objective FAEs, with or without reasons specified, rather than drug-caused FAEs according to researchers' judgment, were recorded. Any discrepancies between the two investigators were resolved by consensus with a third participant (TN).

### 2.4. Quality assessment of included studies

Quality assessment of the included studies was performed by the two reviewers (JXC, JHW) with the criteria of Cochrane Collaboration's tool for assessing risk of bias of RCTs. The items adopted for the evaluation were listed below: random sequence generation, allocation concealment, binding of participants and personnel, binding of outcome assessments, incomplete outcome data, selective reporting and other bias, all of which were presented with figure format.

### 2.5. Statistical analysis

RRs and their corresponding 95% CIs of FAEs in patients treated with drugs (bevacizumab, cetuximab, or panitumumab) comparing to placebo were considered as the primary objective in the present study. We also explored the RRs of the FAEs related to the agents in the cases of first-line, second or further line, or adjuvant treatment comparing to the control. In addition, etiology-specified FAEs were extracted and classified on the basis of physiology system or symptoms to illuminate the difference between the group experiment and the control. Pooled analysis of RRs was developed with software RevMan 5.3 (Cochrane Collaboration, USA). Between-study heterogeneity was estimated with  $I^2$  test.  $P$ -value  $>.1$  and  $I^2 < 50\%$  were considered as no substantial heterogeneity. Random effect model or fixed effect model was adopted for the pooled analysis of heterogeneous data or homogeneous one, respectively. A  $P$ -value  $<.05$  was supposed

to be statistically significant. Potential publication bias was detected by funnel plot with software RevMan 5.3.

### 3. Results

#### 3.1. Search results

With an integrative review, there were 971 potential literatures totally searched in databases including MEDLINE, EMBASE, and Cochrane Library. About 542 publications were removed because of duplications. Two hundred ninety-three studies were excluded further because of the inconformity of prospective, randomized, placebo/blank controlled feature. With the inclusion criteria, 53 papers were finally considered for further assessment. After reviewed with full texts, 14 researches were conclusively eliminated because of the reasons including negatively reported of FAEs ( $n=9$ ), unspecified classification of adverse events ( $n=3$ ), nature of research protocol ( $n=1$ ), and unmatched comparison of the groups ( $n=1$ ). Finally, a total of 31 original researches included in 39 literatures were considered eligible for the eventual analysis. A flow diagram which detailed the selective procedure of included studies was shown in Figure 1.

#### 3.2. Quality assessment of the included studies

After quality evaluation was conducted within the criteria of Cochrane Collaboration's tool, which was designed for assessing risk of bias of RCTs, it was revealed that most of the included RCTs accord with the evaluation criterion including allocation concealment, random sequence generation, binding of participants and personnel, and binding of outcome assessments, results of which were shown in Figures 2 and 3.

#### 3.3. Population characteristics

A total of 25,939 patients enrolled in 31 studies were considered available in the present pooled analysis. The investigative agents in the satisfactory clinical trials include bevacizumab ( $n=15$ ), cetuximab ( $n=10$ ), and panitumumab ( $n=6$ ). All the patients included in the present study possessed a good performance status (PS) as 0, 1, and 2. The baseline characteristics of the included literature were presented in Tables 1 and 2.

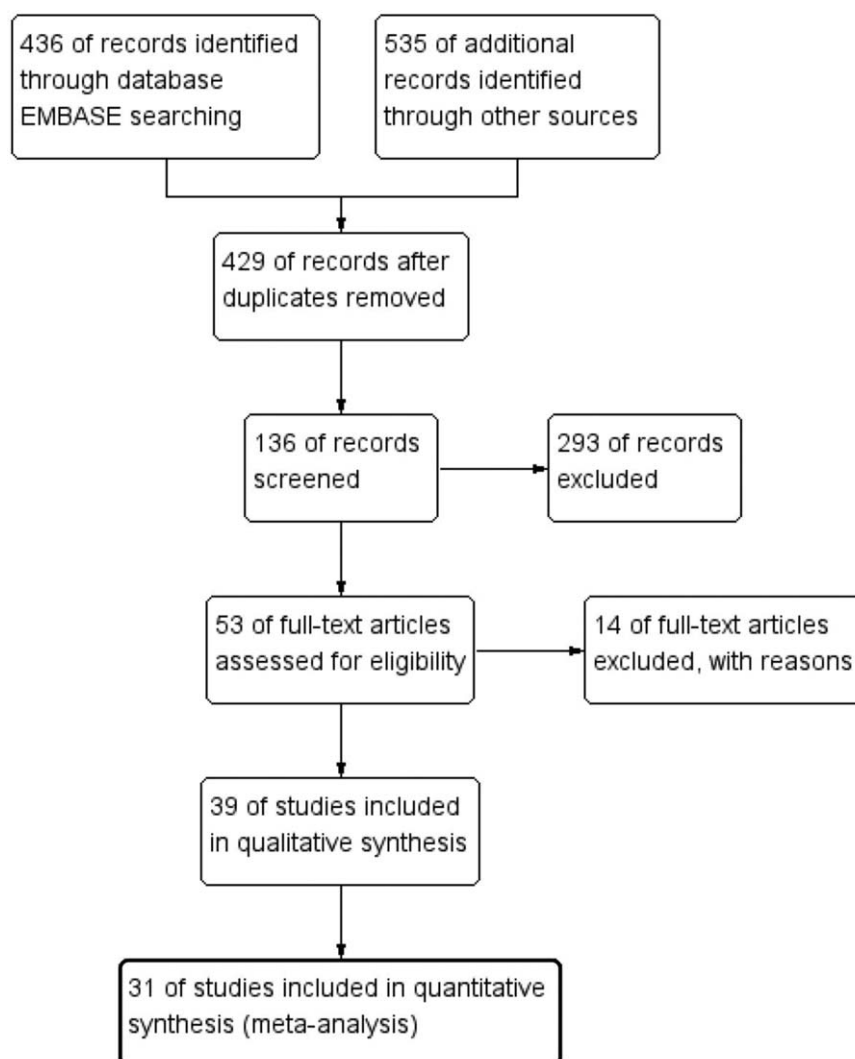


Figure 1. Study selection procedure with PRISMA flow diagram.

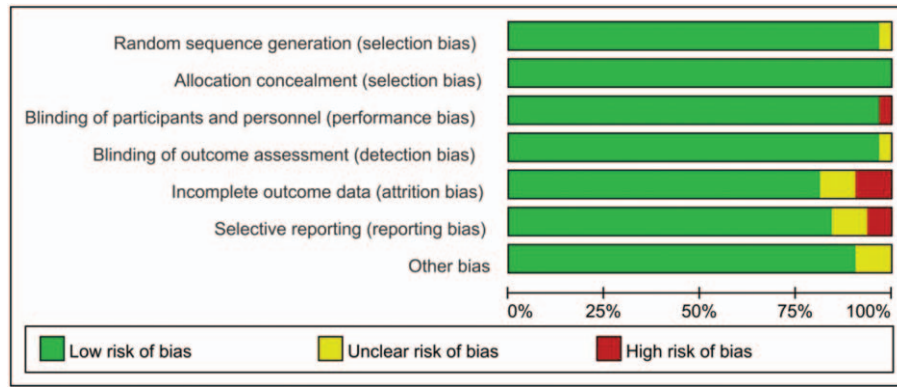


Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages among all the included studies.

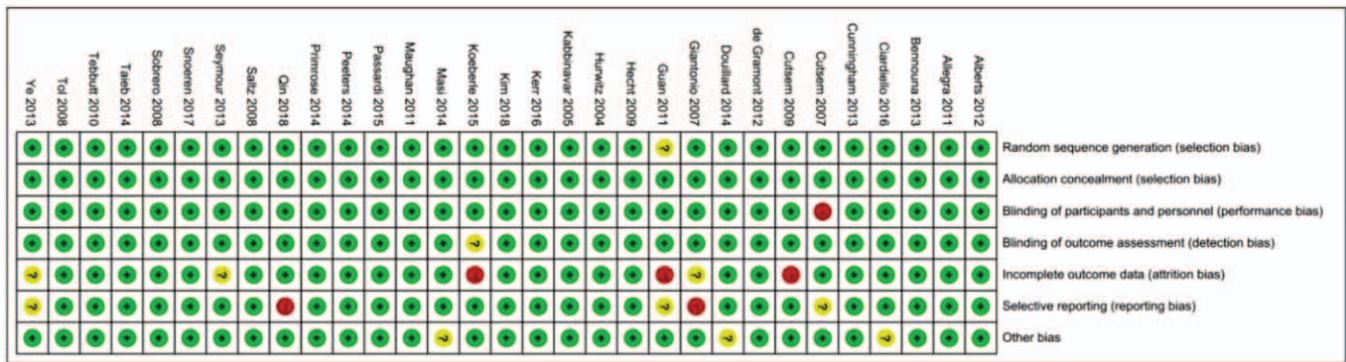


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Table 1

Baseline characteristics of the researches included in the present study.

Author Year	No. of patients	Median age	Treatment status	ECOG PS (0/1/2/3/unknown)	Drug	Regimen	No. of events	AE criterion
Snoeren 2017 <sup>[18]</sup>	39/38	62/61	Adjuvant	17/6/16, 13/11/14	B	Arm 1: XELOX + B Arm 2: XELOX	1/1	NCI CTC version 3.0
Kerr 2016 <sup>[19]</sup>	973/968	65/65	Adjuvant	0/1, unspecified	B	Arm 1: Capecitabine + B Arm 2: Capecitabine	15/8	NCI CTC version 3.0
Masi 2014 <sup>[20]</sup>	92/92	62/66.5	Second or further	82/16/2, 82/17/1	B	Arm 1: CT + B Arm 2: CT (FOLFOX6/FOLFIRI)	1/0	NCI CTC version 3.0
Koeberle 2015 <sup>[21]</sup>	131/131	63/65	Maintenance	97/34/0, 91/40/0	B	Arm 1: B Arm 2: Observation	0/0	NCI CTC version 3.0
Cunningham 2013 <sup>[22]</sup>	140/140	76/77	First line	70/58/10/0/2, 60/67/11/1/1	B	Arm 1: Capecitabine + B Arm 2: Capecitabine	9/14	NCI CTC version 3.0
Bennouna 2013 <sup>[23]</sup>	409/411	63/63	Second or further	179/209/19,178/212/19	B	Arm 1: CT + B Arm 2: Capecitabine	11/11	NCI CTC version 3.0
de Gramont 2012 <sup>[24]</sup>	1155/1151	58/58	Adjuvant	987/166, 994/156	B	Arm 1: FOLFOX4 + B Arm 2: CT (FOLFOX/FOLFIRI/XELOX/XELIRI)	6/9	NCI CTC version 3.0
Guan 2011 <sup>[25]</sup>	139/64	53/50	First line	66/73, 23/41	B	Arm 1: mFL + B Arm 2: FOLFOX4	2/1	NCI CTC version 3.0
Allegra 2011 <sup>[26]</sup>	1334/1338	N/R	Adjuvant	1075/259, 1089/249	B	Arm 1: FOLFOX6 + B Arm 2: mFL	12/13	N/R

(continued)

**Table 1**  
**(continued).**

Author Year	No. of patients	Median age	Treatment status	ECOG PS (0/1/2/3/unknown)	Drug	Regimen	No. of events	AE criterion
Tebbutt 2010 <sup>[27]</sup>	157/156	67/69	First line	91/54/12, 90/59/7	B	Arm 2: FOLFOX6 Arm 1: Capecitabine + B	9/7	NCI CTC version 3.0
Saltz 2008 <sup>[28]</sup>	699/701	60/60	First line	405/289/1, 418/281/0	B	Arm 2: Capecitabine Arm 1: CT + B	14/11	NCI CTC version 3.0
Giantonio 2007 <sup>[29]</sup>	286/291	*62/60.8	Second or further	140/134/12, 149/125/17	B	Arm 2: CT (FOLFOX4/XELOX) Arm 1: FOLFOX4 + B	5/4	NCI CTC version 3.0
Kabbinavar 2005 <sup>[30]</sup>	100/104	*71.3/ 70.7	First line	29/64/8, 28/67/6	B	Arm 2: FOLFOX4 Arm 1: Fluorouracil + Leucovorin + B	5/14	NCI CTC version 2.0
Hurwitz 2004 <sup>[31]</sup>	402/411	*59.5/ 59.2	First line	233/165/4, 226/181/4	B	Arm 2: Fluorouracil + Leucovorin + PL Arm 1: IFL + B	10/11	NCI CTC version 2.0
Passardi 2015 <sup>[32]</sup>	176/194	66/66	First line	144/32, 154/40	B	Arm 2: IFL + Placebo Arm 1: CT + B	4/0	NCI CTC version 3.0
Qin 2018 <sup>[33]</sup>	193/200	56/56	First line	63/130, 66/134	C	Arm 2: CT (FOLFOX4/FOLFIRI) Arm 1: FOLFOX4 + C	8/5	NCI CTC version 3.0
Ciardello 2016 <sup>[34]</sup>	74/79	64/63	Second or further	0/1, unspecified	C	Arm 2: FOLFOX4 Arm 1: FOLFOX + C	0/0	NCI CTC version 3.0
Taieb 2014 <sup>[35]</sup>	791/811	60/60	Adjuvant	621/139/1/30, 637/136/3/35	C	Arm 2: FOLFOX Arm 1: FOLFOX + C	7/3	NCI CTC version 3.0
Primrose 2014 <sup>[36]</sup>	129/128	63/64	Perioperative	0/1, unspecified	C	Arm 2: FOLFOX Arm 1: CT + C	3/1	N/R
Ye 2013 <sup>[37]</sup>	70/68	57/59	First line	58/12, 54/14	C	Arm 2: CT (FOLFOX/FOLFIRI/XELOX) Arm 1: CT + C	0/0	NCI CTC version 3.0
Alberts 2012 <sup>[38]</sup>	931/894	58/58	Adjuvant	0/1/2, unspecified	C	Arm 2: CT (FOLFOX6/FOLFIRI) Arm 1: FOLFOX6 + C	10/4	NCI CTC version 3.0
Maughan 2011 <sup>[39]</sup>	815/815	63/63	First line	376/377/62, 375/378/62	C	Arm 2: FOLFOX6 Arm 1: Oxaliplatin + Fluorouracil + C	9/10	NCI CTC version 3.0
Cutsem 2009 <sup>[40]</sup>	599/599	61/62	First line	330/246/21, 318/260/21	C	Arm 2: Oxaliplatin + Fluorouracil Arm 1: FOLFIRI + C	0/0	NCI CTC version 2.0
Tol 2008 <sup>[41]</sup>	192/197	61.5/62	First line	122/65/5, 115/79/3	C	Arm 2: FOLFIRI Arm 1: XELOX + B + C	8/11	NCI CTC version 3.0
Sobrero 2008 <sup>[42]</sup>	648/650	61/62	Second or further	608/35/5, 611/35/4	C	Arm 2: XELOX + B Arm 1: Irinotecan + C	57/40	NCI CTC version 2.0
Kim 2018 <sup>[43]</sup>	189/188	62/60	Second or further	71/100/18, 65/107/16	P	Arm 2: Irinotecan Arm 1: BSC + P	8/15	N/R
Peeters 2014 <sup>[44]</sup>	591/595	60/61	Second or further	512/29, 506/36	P	Arm 2: BSC Arm 1: FOLFIRI + P	12/17	NCI CTC version 3.0
Douillard 2014 <sup>[45]</sup>	546/550	62/61	First line	518/28, 521/28	P	Arm 2: FOLFIRI Arm 1: FOLFOX4 + P	33/27	NCI CTC version 3.0
Seymour 2013 <sup>[46]</sup>	230/230	64/63	Second or further	217/13, 217/13	P	Arm 2: FOLFOX4 Arm 1: Irinotecan + P	12/14	NCI CTC version 3.0
Hecht 2009 <sup>[47]</sup>	528/525	60/61	First line	321/207, 313/212	P	Arm 2: Irinotecan Arm 1: CT + P	15/8	NCI CTC version 3.0
Cutsem 2007 <sup>[48]</sup>	231/232	62/63	Second or further	107/94/29/1, 80/115/35/2	P	Arm 2: CT (FOLFOX/FOLFIRI) Arm 1: BSC + P  Arm 2: BSC	0/0	N/R

AE = adverse events, B = bevacizumab, BSC = best supportive care, C = cetuximab, CT = chemotherapy, ECOG PS = Eastern Cooperative Oncology Group, performance status, FOLFIRI = irinotecan + fluorouracil + leucovorin, FOLFOX = oxaliplatin + fluorouracil + leucovorin, IFL = irinotecan + fluorouracil + leucovorin, N/R = not reported, P = panitumumab, PL = placebo, XELIRI = irinotecan + capecitabine, XELOX = oxaliplatin + capecitabine.

\* Mean.

**Table 2****Administered doses and treatment time of targeted agents included in the present study.**

Author Year	No. of patients	Median age	Treatment status	Drug	Administered doses and treatment time of targeted agents
Snoeren 2017 <sup>[18]</sup>	77 (39/38)	62/61	Adjuvant	B	7.5 mg/kg infusion on day 1 for a duration of 8 cycles followed by bevacizumab alone (7.5 mg/kg every 3 weeks) for another 8 cycles.
Kerr 2016 <sup>[19]</sup>	1941 (973/968)	65/65	Adjuvant	B	7.5 mg/kg bevacizumab by intravenous infusion over 90 min on day 1 of each cycle, repeated every 3 weeks for a total of 16 cycles
Masi 2014 <sup>[20]</sup>	184 (92/92)	62/66.5	Second or Further	B	Continuation of bevacizumab at 2.5 mg/kg per week equivalent (either 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg every 3 weeks, intravenously)
Koeberle 2015 <sup>[21]</sup>	262 (131/131)	63/65	Maintenance	B	Continuation of bevacizumab 7.5 mg/kg intravenously every 3 weeks
Cunningham 2013 <sup>[22]</sup>	280 (140/140)	76/77	First line	B	Bevacizumab (7.5 mg/kg intravenously on day 1), given every 3 weeks until disease progression
Bennouna 2013 <sup>[23]</sup>	820 (409/411)	63/63	Second or Further	B	Continuation of bevacizumab at 2.5 mg/kg per week equivalent (either 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg every 3 weeks, intravenously)
de Gramont 2012 <sup>[24]</sup>	2306 (1155/1151)	58/58	Adjuvant	B	Bevacizumab 5 mg/kg followed by bevacizumab monotherapy 7.5 mg/kg every 3 weeks (eight cycles), or bevacizumab 7.5 mg/kg every 3 weeks for eight cycles followed by bevacizumab monotherapy 7.5 mg/kg every 3 weeks (eight cycles)
Guan 2011 <sup>[25]</sup>	203 (139/64)	53/50	First line	B	Bevacizumab (5 mg/kg) administered intravenously on day 1 every 2 weeks until disease progression
Allegra 2011 <sup>[26]</sup>	2672 (1334/1338)	NR	Adjuvant	B	5 mg/kg on day 1 every 2 weeks for 1 year
Tebbutt 2010 <sup>[27]</sup>	313 (157/156)	67/69	First line	B	Bevacizumab on day 1 at 7.5 mg/kg every 3 weeks until disease progression
Saltz 2008 <sup>[28]</sup>	1400 (699/701)	60/60	First line	B	7.5 mg/kg on day 1 of a 3-week cycle until disease progression or for 48 weeks
Giantonio 2007 <sup>[29]</sup>	577 (286/291)	*62/60.8	Second or Further	B	10 mg/kg on day 1 of a 2-week cycle until disease progression
Kabbinavar 2005 <sup>[30]</sup>	204 (100/104)	*71.3/ 70.7	First line	B	Bevacizumab 5 mg/kg administered every 2 weeks until disease progression
Hurwitz 2004 <sup>[31]</sup>	813 (402/411)	*59.5/ 59.2	First line	B	5 mg/kg every 2 weeks until disease progression or unacceptable adverse effects occurred or for a maximum of 96 weeks
Passardi 2015 <sup>[32]</sup>	370 (176/194)	66/66	First line	B	5 mg/kg on day 1 of each 2-week cycle until disease progression, withdrawal of consent or unacceptable toxicity
Qin 2018 <sup>[33]</sup>	393 (193/200)	56/56	First line	C	Cetuximab was administered every 7 days at an initial dose of 400 mg/m <sup>2</sup> at 5 milligram per minute (mg/min) and 250 mg/m <sup>2</sup> at 10 mg/min for subsequent infusions until progression of disease, withdrawal of consent, or unacceptable toxicity to cetuximab
Ciardello 2016 <sup>[34]</sup>	153 (74/79)	64/63	Second or Further	C	Cetuximab 500 mg/m <sup>2</sup> i.v. over 120 min for the first dose, over 90 min for the second and over 60 min for the subsequent doses. Treatment was repeated every 2 weeks until disease progression, unacceptable toxicity or patient refusal
Taieb 2014 <sup>[35]</sup>	1602 (791/811)	60/60	Adjuvant	C	Weekly cetuximab, which was given on day 1, 400 mg/m <sup>2</sup> (2 h infusion) the first week, then every week at 250 mg/m <sup>2</sup> (1 h infusion) for subsequent infusions. Treatment was continued for 12 cycles
Primrose 2014 <sup>[36]</sup>	257 (129/128)	63/64	Perioperative	C	Cetuximab was given as an intravenous dose of 500 mg/m <sup>2</sup> every 2 weeks or a loading dose of 400 mg/m <sup>2</sup> followed by a weekly infusion of 250 mg/m <sup>2</sup> , for 12 weeks
Ye 2013 <sup>[37]</sup>	138 (70/68)	57/59	First line	C	Cetuximab once per week (with an initial loading dose of 400 mg/m <sup>2</sup> and thereafter 250 mg/m <sup>2</sup> ) or once every 2 weeks (500 mg/m <sup>2</sup> on day 1 and once every 2 weeks thereafter), continued until tumor response indicated suitability for surgery or until disease progression or unacceptable toxicity
Alberts 2012 <sup>[38]</sup>	1825 (931/894)	58/58	Adjuvant	C	Cetuximab 400 mg/m <sup>2</sup> over 2 h on day 1 of cycle 1, then 250 mg/m <sup>2</sup> over 1 hour on day 8 (cycle 1) and day 1 and 8 each of cycles 2 through 12
Maughan 2011 <sup>[39]</sup>	1630 (815/815)	63/63	First line	C	Cetuximab was given as an initial intravenous dose of 400 mg/m <sup>2</sup> over 2 h and subsequently at 250 mg/m <sup>2</sup> over 1 h once a week. Treatment was continued until disease progression, development of cumulative toxic effects, or patient choice
Cutsem 2009 <sup>[40]</sup>	1198 (599/599)	61/62	First line	C	Cetuximab in an initial 120-minute infusion on day 1 of 400 mg/m <sup>2</sup> , followed by 60-minute infusions of cetuximab at a dose of 250 mg/m <sup>2</sup> , once weekly, continued until disease progression, unacceptable toxic effects, or withdrawal of consent occurred
Tol 2008 <sup>[41]</sup>	389 (192/197)	61.5/62	First line	C	400 mg/m <sup>2</sup> of cetuximab, given intravenously on day 1 of the first treatment cycle, followed by 250 mg/m <sup>2</sup> of cetuximab given weekly thereafter, Treatment was continued until the occurrence of disease progression, death, or unacceptable adverse event
Sobrero 2008 <sup>[42]</sup>	1298 (648/650)	61/62	Second or Further	C	Cetuximab 400 mg/m <sup>2</sup> day 1 followed by 250 mg/m <sup>2</sup> weekly, treatment continued until disease progression or unacceptable toxicity
Kim 2018 <sup>[43]</sup>	377 (189/188)	62/60	Second or Further	P	Panitumumab 6.0 mg/kg intravenously on day 1 of each 14-day cycle, treatment continued until disease progression, consent withdrawal, or panitumumab intolerance
Peeters 2014 <sup>[44]</sup>	1186 (591/595)	60/61	Second or Further	P	Panitumumab 6 mg/kg; intravenous infusion on day 1 of a 2-week cycle, treatments were administered bi-weekly until disease progression, consent withdrawal, or unacceptable toxicity
Douillard 2014 <sup>[45]</sup>	1096 (546/550)	62/61	First line	P	Panitumumab 6.0 mg/kg every 2 weeks, continued until disease progression, consent withdrawal, or unacceptable toxicity
Seymour 2013 <sup>[46]</sup>	460 (230/230)	64/63	Second or Further	P	Panitumumab 9 mg/kg every 3 weeks, treatment continued until disease progression or unacceptable toxicity
Hecht 2009 <sup>[47]</sup>	1053 (528/525)	60/61	First line	P	Panitumumab 6 mg/kg every 2 weeks, treatment continued until disease progression, consent withdrawal, or panitumumab intolerance
Cutsem 2007 <sup>[48]</sup>	463 (231/232)	62/63	Second or Further	P	Panitumumab was administered by a 60-minute intravenous infusion at 6 mg/kg once every 2 weeks until patients progressed or unacceptable toxicity developed

B = bevacizumab, C = cetuximab, P = panitumumab.

### 3.4. Relative risk of FAEs

A pooled analysis of the RR of the FAEs in patients treated with bevacizumab, cetuximab, and panitumumab comparing to placebo or blank in the control was performed in the 31 prospective, randomized, controlled clinical trials. The RR and its 95% CI of the FAEs among all the agents including bevacizumab, cetuximab, and panitumumab was 1.07 (95% CI, 0.89–1.29;  $P=.50$ ). The RRs and their 95% CIs of the FAEs related to bevacizumab, cetuximab, and panitumumab were 1.01 (95% CI, 0.76–1.33;  $P=.96$ ), 1.41 (95% CI, 0.91–2.17;  $P=.12$ ), and 0.99 (95% CI, 0.72–1.36;  $P=.95$ ), respectively (Fig. 4).

Results of the heterogeneity evaluation among all the including researches did not show statistical heterogeneity ( $I^2=0\%$ ,  $P=.37$ ). Likewise, heterogeneity was not detected in patients treated with bevacizumab ( $I^2=0\%$ ,  $P=.57$ ), cetuximab ( $I^2=0\%$ ,  $P=.51$ ), or panitumumab ( $I^2=33\%$ ,  $P=.20$ )

### 3.5. Relative risk of FAEs in different treatment status

We evaluated the RRs of FAEs treated with agents (bevacizumab, cetuximab, panitumumab) or placebo/blank as first line, second or further line, and adjuvant treatment separately, to specify the influence of therapeutic status on the incidence of FAEs. As a

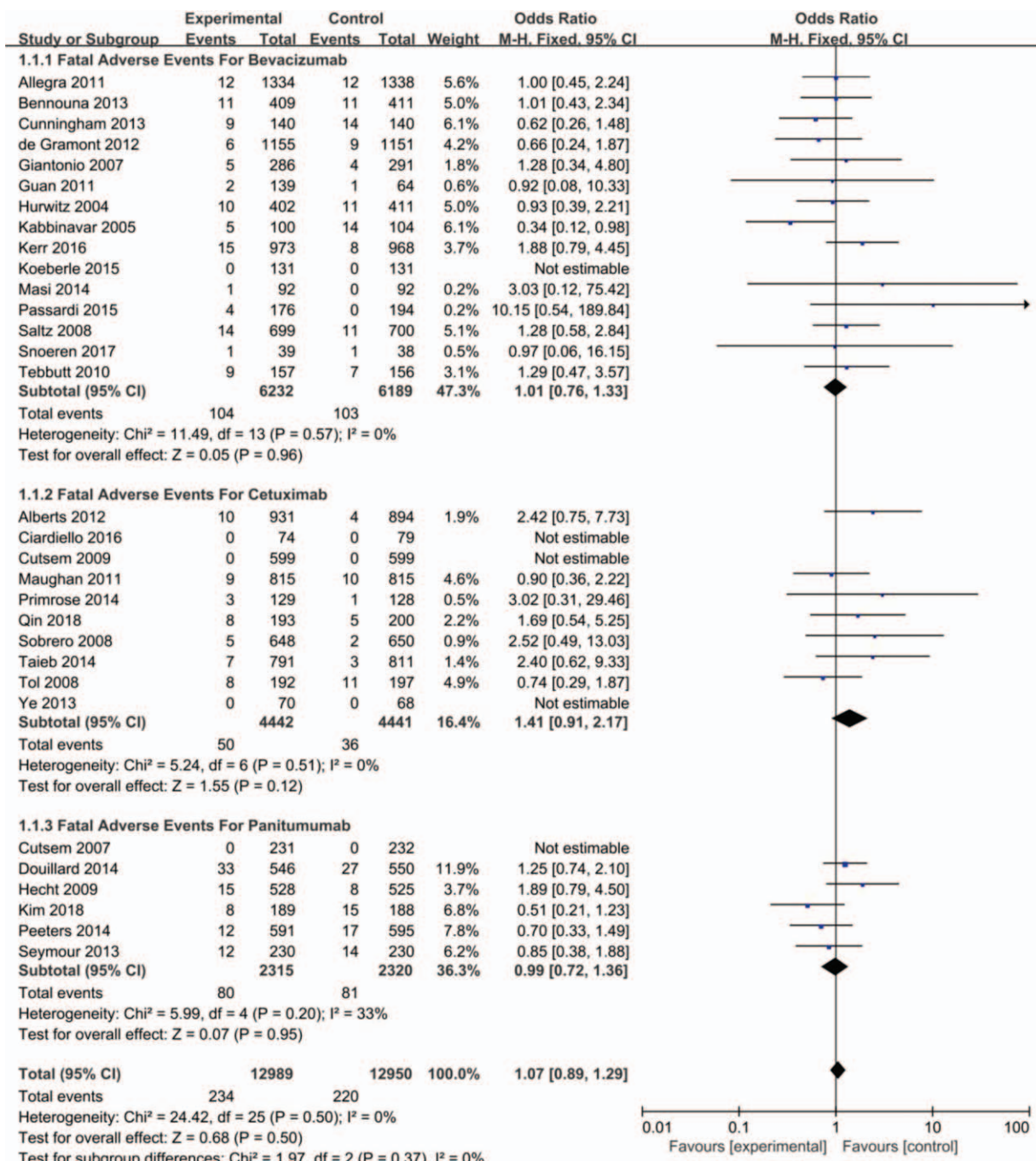


Figure 4. Forest plot of FAEs in patients treated with bevacizumab, cetuximab, and panitumumab (group experiment) comparing to placebo/blank (group control).

result, the RRs and their 95% CIs of the FAEs as first line, second or further line, and adjuvant treatment related to bevacizumab were 0.91 (95% CI, 0.62–1.32;  $P = .61$ ), 1.14 (95% CI, 0.57–2.28;  $P = .71$ ), and 1.10 (95% CI, 0.67–1.79;  $P = .72$ ), respectively (Fig. 5). The RRs and their 95% CIs of the FAEs as first line, second or further line, and adjuvant treatment related to cetuximab were 1.02 (95% CI, 0.60–1.76;  $P = .93$ ), 2.51 (95% CI, 0.49–12.88;  $P = .27$ ), and 2.40 (95% CI, 1.00–5.77;  $P = .05$ ), respectively (Fig. 6). The RRs and their 95% CIs of the FAEs as first line, second or further line treatment related to panitumumab were 1.40 (95% CI, 0.89–2.18;  $P = .14$ ) and 0.68 (95% CI, 0.43–1.09;  $P = .11$ ), respectively (Fig. 7)

### 3.6. Specific FAEs

Individual specified causes of FAEs were presented in Figure 8. As it showed, there were 67 cases of FAEs and 62 cases of those specified in the group experiment and the control, respectively. However, there were 71.4% of FAEs in the group experiment and 71.8% of those remaining unspecified etiology. For the FAEs specified in the present study, we classified them according to physiology system or symptoms. FAEs included in cardiovascular system covered heart arrhythmia, myocardial infarction, aortic dissection, venous/artery thrombosis, cardiac failure, cardiac arrest, myocardial ischemia, pulmonary embolism, and circula-

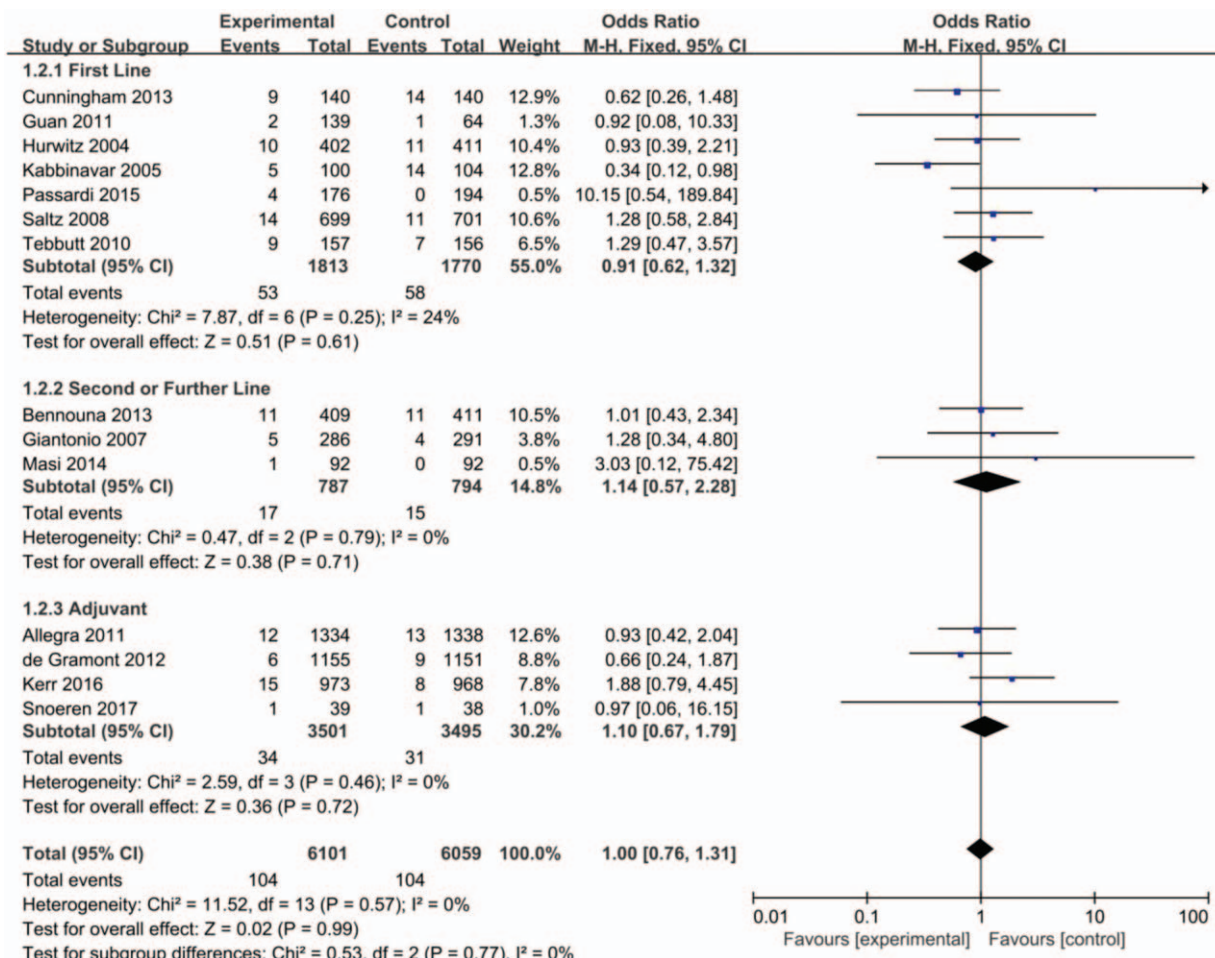
tory failure, while digestive system covered mucositis, gastrointestinal perforation, hepatic failure, diarrhea, enteritis, gastrointestinal necrosis, and ileus, hematologic system covered agranulocytosis and severe anemia, respiratory system covered respiratory failure, pneumonia, pulmonary fibrosis, interstitial lung disease, and dyspnea, central nervous system covered encephalorrhagia and central nervous system ischemia. As a result, the most common FAEs in the group experiment concentrated upon cardiovascular system (29.9% versus 29.0%), digestive system (17.9% versus 19.4%), and multiple organ failure (16.4% versus 16.1%), respectively.

### 3.7. Publication bias

Result of funnel plot did not show significant publication bias (Fig. 9).

## 4. Discussion

The present meta-analysis did not show a significantly increased risk of FAEs among patients with colorectal carcinoma enrolled in prospective, randomized, controlled clinical trials who received bevacizumab, cetuximab, or panitumumab therapy compared to placebo or blank treatment. Furthermore, the statistical differences were not detected either, in patients who



**Figure 5.** Forest plot of FAEs in patients treated with bevacizumab (group experiment) comparing to placebo/blank (group control) as first line, second or further line, and adjuvant treatment.



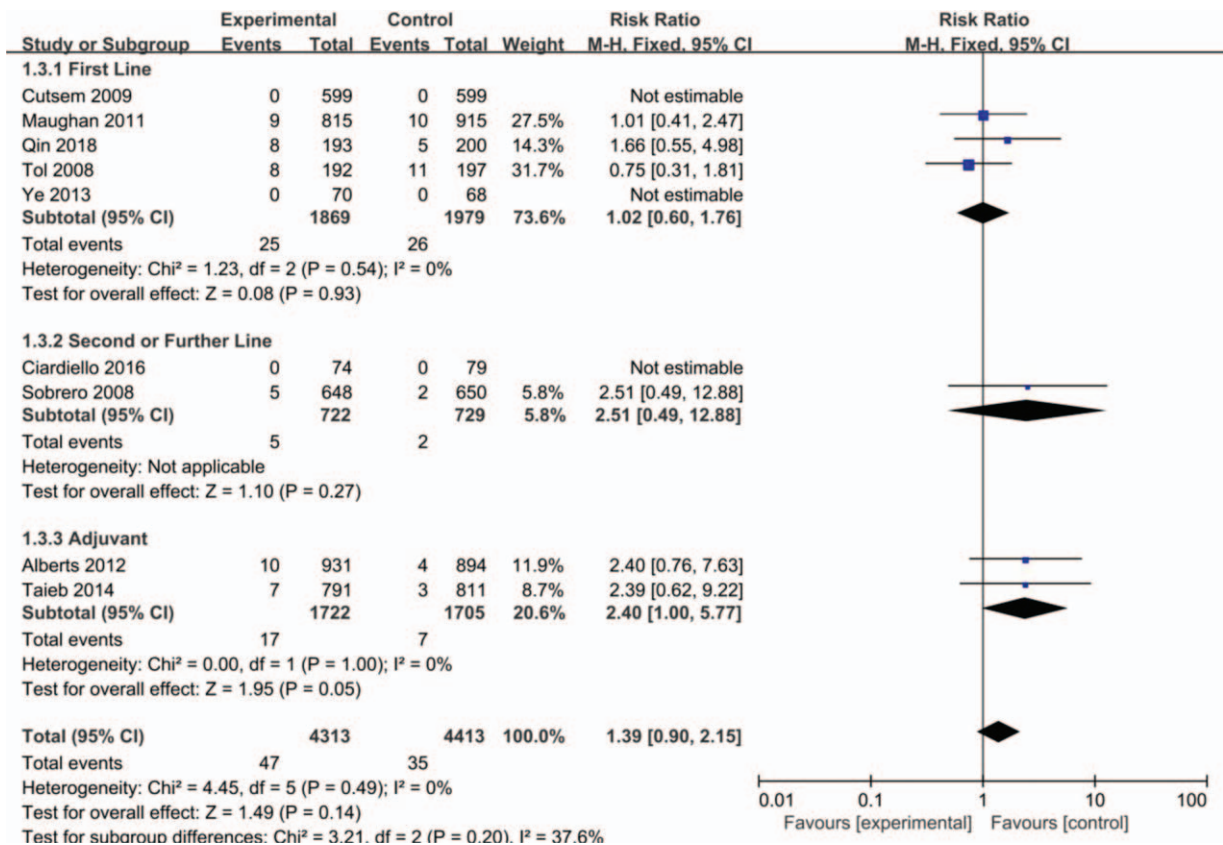


Figure 6. Forest plot of FAEs in patients treated with cetuximab (group experiment) comparing to placebo/blank (group control) as first line, second or further line, and adjuvant treatment.

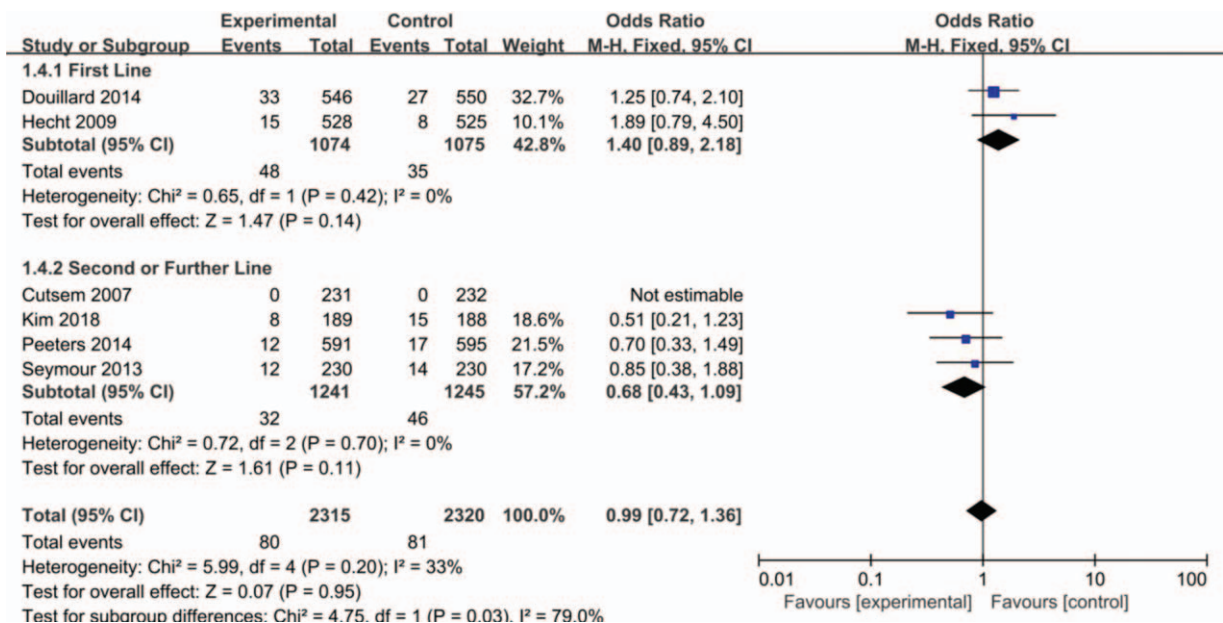


Figure 7. Forest plot of FAEs in patients treated with panitumumab (group experiment) comparing to placebo/blank (group control) as first line, second or further line treatment.

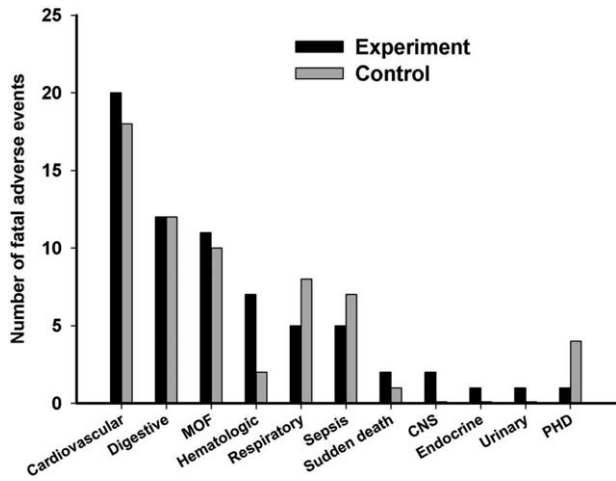


Figure 8. FAEs specified by types.

received the agents as first line, second/further line, or adjuvant treatment.

Targeted agents including cetuximab (KRAS/NRAS wild type and left-side tumors only), panitumumab (KRAS/NRAS wild type and left-side tumors only), and bevacizumab have been emerged as the standard options with or without chemotherapy for the systematic treatment in patients with metastatic colorectal carcinoma. Selected patients with colorectal cancer were benefited from the wide use and the price reduction of the agents, which might make it more extensive in clinical practice. However, anti-tumor therapy with targeted drugs is a double edged sword. The efficacy, rather than safety of the drugs, always played a significant role in the decision-making of the patients, which might lead to the potential incidence of severe and even

FAEs during the treatment. Hence, the proper understanding of the adverse events may help to make the decision more objective. According to the results of the present meta-analysis, the administration of monoclonal antibodies including bevacizumab, cetuximab, or panitumumab did not increase the RR of FAEs comparing to placebo/blank in the treatment of colorectal carcinoma.

There have been a few meta-analyses conducted to evaluate the RRs or incidence of the severe/fatal adverse events of bevacizumab, cetuximab, and panitumumab in patients with solid tumors. The anti-VEGFR antibody bevacizumab was showed to be in association with a significant increase in the risk of high-grade adverse events, including hypertension (RR 5.67, 95% CI 3.02–10.65), proteinuria (RR 10.09, 95% CI 4.79–21.27), bleeding (RR 3.45, 95% CI 2.25–5.30), cardiac toxicity (RR 2.15, 95% CI 1.29–3.59), and neutropenic fever (RR 1.51, 95% CI 1.15–2.00) among patients with advanced-stage breast cancer.<sup>[49]</sup> However, the dose of bevacizumab used in breast cancer in the included studies (10–15 mg/kg) was much more bigger than colorectal cancer in the present analysis (5 mg/kg).<sup>[49]</sup> The difference of dose between the cancer types might lead to the diversity of the RRs. Another pooled analysis of the adverse events including fatal ones of bevacizumab was conducted in patients with NSCLC.<sup>[50]</sup> The pooled result of nine clinical trials (bevacizumab 2.5–5 mg/kg) showed that the addition of bevacizumab to therapy in advanced NSCLC increased the RRs of proteinuria (RR=7.55), hypertension (RR=5.34), and hemorrhagic events (RR=2.61), however, rather than arterial/venous thromboembolic events ( $P=.35$ ,  $P=.92$ ), gastrointestinal perforation ( $P=.60$ ), or FAEs ( $P=.29$ ).<sup>[50]</sup> The pooled result of FAEs was similar to our own estimates in the current study. This implied that the dose of bevacizumab used in different tumor types might lead to the discrepant risk of FAEs. However, in an earlier published meta-analysis including 34 researches with different tumor types, the

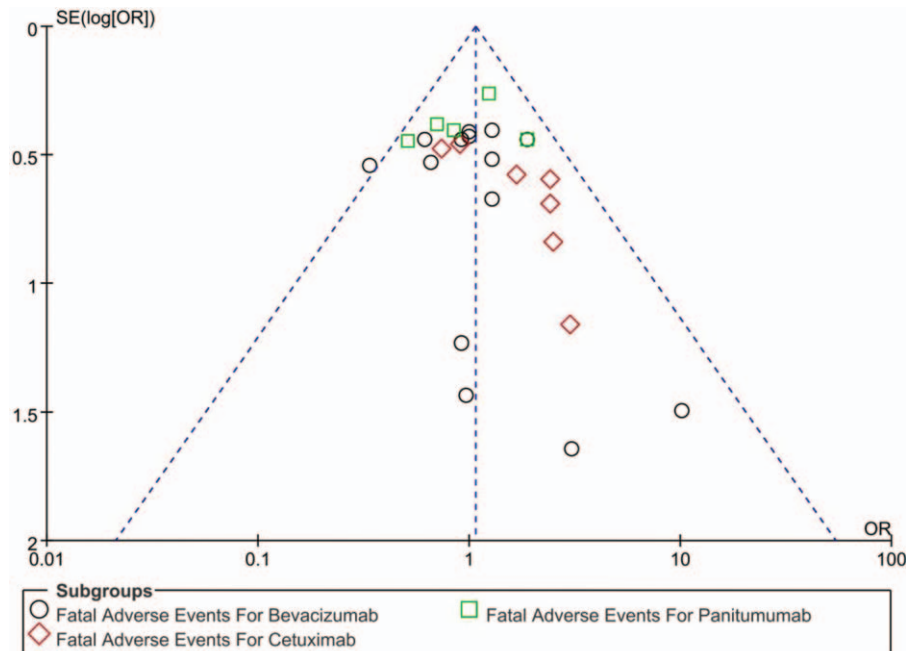


Figure 9. Funnel plot for publication bias.

pooled results of the RRs induced by bevacizumab showed that the addition of bevacizumab was associated with an increased risk of FAEs among patients with pancreatic cancer (RR=1.83, 95% CI, 1.07–3.14), prostate cancer (RR=3.34, 95% CI, 1.35–8.25), and ovarian cancer (RR=2.35, 95% CI, 1.03–5.33), but not in colorectal carcinoma (RR=1.29, 95% CI, 0.84–1.99).<sup>[15]</sup> Owing to that the dose of bevacizumab was similar between the included literatures (2.5–5 mg/kg),<sup>[15]</sup> tumor types might play another important role in the RRs of FAEs.

The RRs of FAEs with cetuximab has been former assessed by another meta-analysis,<sup>[16]</sup> the result of which showed that cetuximab was not associated with increased risk of FAEs (odds ratio, 1.41; 95% CI, 0.99–2.03; incidence, 1.8% versus 1.3%). The present updating analysis with the addition of another four researches still supported the conclusion that there was no evidence of an increased risk of FAEs with cetuximab in patients with colorectal carcinoma. However, another pooled analysis revealed that the incidence of grade 3/4 adverse events, including skin toxicity (RR=20.76, 95% CI, 3.87–111.33,  $P=.000$ ), diarrhea (RR=1.48, 95% CI, 1.33–1.64,  $P=.000$ ), hypertension (RR=1.69, 95% CI, 1.17–2.46,  $P=.006$ ), anorexia (RR=1.57, 95% CI, 1.18–2.10,  $P=.002$ ), and mucositis/stomatitis (RR=2.69, 95% CI, 1.90–3.80,  $P=.000$ ), was statistically higher in the combined therapy group (chemotherapy plus cetuximab) than in the chemotherapy-only group, while without the RRs or incidence of FAEs reported.<sup>[15]</sup> Interestingly, the result of a recent phase II clinical trial suggested that severe early skin reactions caused by cetuximab predicted favorable overall survival for patients treated with cetuximab plus chemotherapy without impairing quality of life (hazard ratio, 0.48; 95% CI, 0.21–0.97;  $P=.04$ ).<sup>[52]</sup> However, the conclusion of the above study might be limited by its relatively small sample size ( $n=140$ ) and the deficiency of control group, which hampered part of the statistical analyses. Thus, future studies are required to build on the findings of the study. Besides, with the clinical experience, we do suggest that the severe skin reactions really harm the quality of life in selected patients. There was a recently published meta-analysis conducted to evaluate the different toxicities between cetuximab and panitumumab, the results of which revealed that cetuximab was associated with fewer high grade (grade 3–4) skin toxicities (RR, 0.62, 95% CI 0.53–0.62), frequent high grade acne-like rash (RR, 1.24, 95% CI 1.04–1.48), and paronychia (RR, 1.36, 95% CI 1.1–1.7) than panitumumab.<sup>[53]</sup> However, in the present study, the results of pooled analysis did not reveal any increased risk of FAEs of panitumumab or cetuximab comparing to placebo or blank, which had not been reported before. In addition, we further investigated the influence of treatment status including first line, second/further line, and adjuvant therapy on the risk of FAEs, the results of which did not show any evidence of increased risk of FAEs by bevacizumab, cetuximab, or panitumumab as first line, second/further line, or adjuvant treatment in patients with colorectal cancer. Although the FAEs not specified in the majority of the included literatures, we still identified the specified ones by physiology system or symptoms. The limited outcome did not reveal any differences between the targeted agents and placebo either.

There were several limitations existing in the present meta-analysis. First, and most obviously, was heterogeneity, which was caused by the diversity of dose of drugs (bevacizumab, cetuximab, and panitumumab), as well as the different chemotherapy regimens combined in the present study. We tried to conduct a meta-regression to reduce that. However, the

relevant coefficient seemed to be untoward to specify, especially among studies with various chemotherapeutic regimens used in the enrolled literatures. It seems difficult to figure out whether there existed potential synergistic side-effects between targeted agents and different chemotherapy regimens. In addition, the diversity of duration of drugs exposure came with another potential heterogeneity, which may lead to another bias in the pooled assessment of relative risks. Finally, most of the FAEs (71.6%) were not etiology specified in the present study. Lacking of the essential information may bring with some potential bewilderment to readers. However, we could not establish more convinced results with the limitations.

In conclusion, the present meta-analysis did not show a significantly increased relative risk of FAEs belonging to bevacizumab, cetuximab, or panitumumab, whether as first line, second/further line, or adjuvant treatment among patients with colorectal carcinoma comparing to placebo or blank treatment.

### Author contributions

JXC designed the study and wrote this manuscript. JHW retrieved database and reviewed the studies. TN reviewed the included studies. QHZ and HJH reviewed the manuscript and supervised the conduction of the present study. JXC and JHW extracted data and performed the analysis. All of the authors have read and approved the final manuscript.

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