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ORIGINAL RESEARCH

Risk of bleeding associated with antiangiogenic monoclonal antibodies bevacizumab and ramucirumab: a meta-analysis of 85 randomized controlled trials

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Aim: Bevacizumab and ramucirumab are antiangiogenic monoclonal antibodies, which target vascular endothelial growth factor-A and vascular endothelial growth factor receptor-2, respectively, used in various cancers. Bleeding events have been described with these two agents. We conducted an up-to-date meta-analysis to determine the relative risk (RR) associated with the use of antiangiogenic monoclonal antibodies, bevacizumab and ramucirumab.

Methods: This meta-analysis of randomized controlled trials was performed after searching PubMed, American Society for Clinical Oncology Abstracts, European Society for Medical Oncology Abstracts, and the proceedings of major conferences for relevant clinical trials. RR and 95% CIs were calculated by random-effects or fixed-effects models for all-grade and high-grade bleeding events related to the angiogenesis inhibitors.

Results: Eighty-five randomized controlled trials were selected for the meta-analysis, covering 46,630 patients. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade (RR: 2.38, 95% CI: 2.09–2.71, $p<0.00001$) and high-grade (RR: 1.71, 95% CI: 1.48–1.97, $p<0.00001$) bleeding compared with control arms. In the subgroup analysis, bevacizumab significantly increased the risk of all-grade (RR: 2.73, 95% CI: 2.24–3.33, $p<0.00001$) and high-grade bleeding (RR: 1.98, 95% CI: 1.68–2.34, $p<0.00001$), but ramucirumab only increased the risk of all-grade bleeding (RR: 1.94, 95% CI: 1.76–2.13, $p<0.00001$) and no difference was observed for the risk of high-grade bleeding (RR: 1.04, 95% CI: 0.78–1.39, $p=0.79$) compared with the control group. For lung cancer patients, bevacizumab significantly increased the risk of all-grade (RR: 4.72, 95% CI: 1.99–11.19, $p=0.0004$) and high-grade pulmonary hemorrhage (RR: 3.97, 95% CI: 1.70–9.29, $p=0.001$), but no significant differences in the risk of all-grade (RR: 1.09, 95% CI: 0.76–1.57, $p=0.64$) and high-grade (RR: 1.22, 95% CI: 0.35–4.21, $p=0.75$) pulmonary hemorrhage were observed for ramucirumab. The increased risk of all-grade and high-grade bleeding was also observed in colorectal cancer or non-colorectal tumors and low-dose or high-dose angiogenesis inhibitors.

Conclusion: Antiangiogenic monoclonal antibodies are associated with a significant increase in the risk of all-grade and high-grade bleeding. Ramucirumab may be different from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients.

Keywords: bevacizumab, ramucirumab, antiangiogenic monoclonal antibodies, bleeding, meta-analysis

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Introduction

Angiogenesis is a complex biological process that plays an important role in sustaining growth, invasion, and the metastatic potential of tumors, and this process is mainly driven by vascular endothelial growth factor (VEGF).[1,2] One of the VEGF family members, VEGF-A (commonly referred to as VEGF), has been demonstrated to be important in angiogenesis. Among all receptors, vascular endothelial growth factor receptor (VEGFR)-2 is widely thought to be principally linked to the stimuli of angiogenesis in malignancies. Blocking the function of VEGF-A or its receptor VEGFR-2 has been the most important antiangiogenic strategy for cancer therapy.[3]

Bevacizumab and ramucirumab are the most important antiangiogenic monoclonal antibodies, which target VEGF-A and its receptor VEGFR-2, respectively, used in various cancers. Bevacizumab is approved by the Food and Drug Administration (FDA) for the treatment of patients with metastatic colorectal cancer, advanced non-squamous non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma, recurrent glioblastoma, advanced cervical cancer, and platinum-resistant ovarian cancer, and ramucirumab is approved by the FDA for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma, metastatic NSCLC, and advanced colorectal cancer.

Bleeding events are a kind of major adverse events reported in clinical trials of bevacizumab and ramucirumab, which may cause severe outcomes that could be even life threatening.[4] The main mechanism of bleeding is that angiogenesis inhibitors disrupt tumor vasculature through inhibition of VEGF signaling and lead to thrombosis or bleeding.[1,5]

However, the relative risk (RR) of bleeding events in patients with cancer treated with these two antiangiogenic monoclonal antibodies has yet to be defined. Therefore, we conducted an up-to-date meta-analysis of available clinical trials to determine the RR of bleeding in cancer patients treated with antiangiogenic monoclonal antibodies, bevacizumab and ramucirumab.

Materials and methods

Search strategy

This study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[6] (Supplementary material). We searched PubMed, American Society for Clinical Oncology Abstracts, and European Society for Medical Oncology Abstracts for relevant trials till September 2017. Moreover, we also searched the clinical trial registration website (https://www.ClinicalTrials.gov) to obtain information on registered randomized controlled trials (RCTs). Keywords used in the search were "bevacizumab," "avastin," "ramucirumab," "IMC1121B," "LY3009806," and "randomized controlled trials." The search was limited to RCTs published in English.

Selection of trials

Data abstraction and quality assessment were conducted independently by two reviewers. Disagreements were resolved by discussion with an independent expert. The RCTs were eligible for inclusion in our meta-analysis: 1) prospective Phase II and Phase III RCTs in patients with cancer, 2) random assignment of participants to these two antiangiogenic monoclonal antibodies treatment or control groups, 3) available data, including the event or incidence of bleeding and sample size for analysis. Phase I and single-arm phase II trials were excluded because of their lack of control groups.

Data extraction

We extracted details on study characteristics, treatment information, results, and safety profiles from the selected trials. Clinical endpoints were obtained from the safety profile of each clinical trial. All-grade, high-grade bleeding and all-grade, high-grade pulmonary hemorrhage in lung cancers were recorded according to the version of National Cancer Institute-Common Terminology Criteria for Adverse Events used in each trial.

Statistical analysis

Data were calculated by Review Manager version 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). For the outcomes, the RR was calculated for dichotomous data. Statistical heterogeneity in the results of the trials was assessed by the chi-square test, and expressed by the I^2 index.[7] When there was no statistically significant heterogeneity, a pooled effect was calculated with a fixed-effect model. When considerable heterogeneity was found ($p<0.1$, or $I^2>50\%$), a random-effect model was employed. Subgroup analysis was conducted to examine whether the RRs of all-grade and high-grade bleeding varied by drug type, drug dosage, and cancer type.

Results

Search results

We reviewed 2,045 potentially relevant articles from our initial search strategies. A total of 1,906 articles were excluded on screening abstracts and titles for the following reasons: review articles, case reports, basic researches,

Phase I or single-arm Phase II studies, irrelevant topics, and duplicate reports. The remaining 139 articles were retrieved for full evaluation, and 54 articles were excluded for unavailable data for assessment of bleeding or antiangiogenic monoclonal antibodies in both treatment and control arms. Finally, 85 RCTs were included in this meta-analysis.[8–92] The study search process is shown in a flow chart (Figure 1).

Patients

A total of 85 studies and 46,630 patients were included for the analysis. Bevacizumab was investigated in 72 trials[8–79] and ramucirumab was investigated in 13 trials.[80–92] All of the studies included 21 colorectal cancer,[8–26,85,86] 15 breast cancer,[27–39,87,88] 16 lung cancer,[40–52,80–82] three renal cell cancer,[53,54] two pancreatic cancer,[55,56] five ovarian cancer,[57–61] six gastric or gastroesophageal junction adenocarcinoma,[62–65,89–91] three glioblastoma,[66–68] one lymphoma,[69] one lymphocytic leukemia,[70] two melanoma,[71,72] two malignant mesothelioma,[73,74] one prostate cancer,[75] one cervical cancer,[76] one leiomyosarcoma,[77] two urothelial carcinoma,[83,84] two hepatocellular carcinoma,[78,92] and one soft tissue sarcoma.[79] In addition, 35 trials[9,10,12–20,22–26,46,49,52,55,58,62–65,72,78–84,87,88] were treated with low-dose drugs (28 trials for bevacizumab at 2.5 mg/kg/week, seven trials for ramucirumab at 3.3 mg/kg/week) and 46 trials[11,21,27,28,30–39,41,42,44,45,47,48,50,51,53,54,56,57,59–61,66–71,73–77,85,86,89–92] were treated with high-dose drugs (40 trials for bevacizumab at 5 mg/kg/week, six trials for ramucirumab at 4 mg/kg/week). Other 4 three-arm trials[8,29,40,43] were two arms of different dosage levels of bevacizumab and one arm of control. All of these RCTs were judged to be of adequate quality (Jadad score is 3–5). Baseline characteristics of the 85 RCTs are provided in Table 1.

RR of all-grade bleeding

Forty-three RCTs were available to calculate the RR of all-grade bleeding in patients assigned to angiogenesis inhibitors arms versus control arms. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade (RR: 2.38, 95% CI: 2.09–2.71, $p<0.00001$) bleeding compared with control arms. There was statistically significant heterogeneity ($I^2=74\%$) across the trials; we incorporated it into a random-effects model (Figure 2).

RR of high-grade bleeding

The RR of high-grade (≥grade 3) bleeding was determined in 82 RCTs. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade bleeding (RR: 1.71, 95% CI: 1.48–1.97, $p<0.00001$) with a fixed-effects models ($I^2=19\%$) (Figure 3).

RR according to drug type

As an exploratory analysis, patients were stratified according to drug type. We found that bevacizumab significantly increased the risk of all-grade (RR: 2.73, 95% CI: 2.24–3.33, $p<0.00001$) and high-grade bleeding (RR: 1.98, 95% CI: 1.68–2.34, $p<0.00001$), but ramucirumab only increased

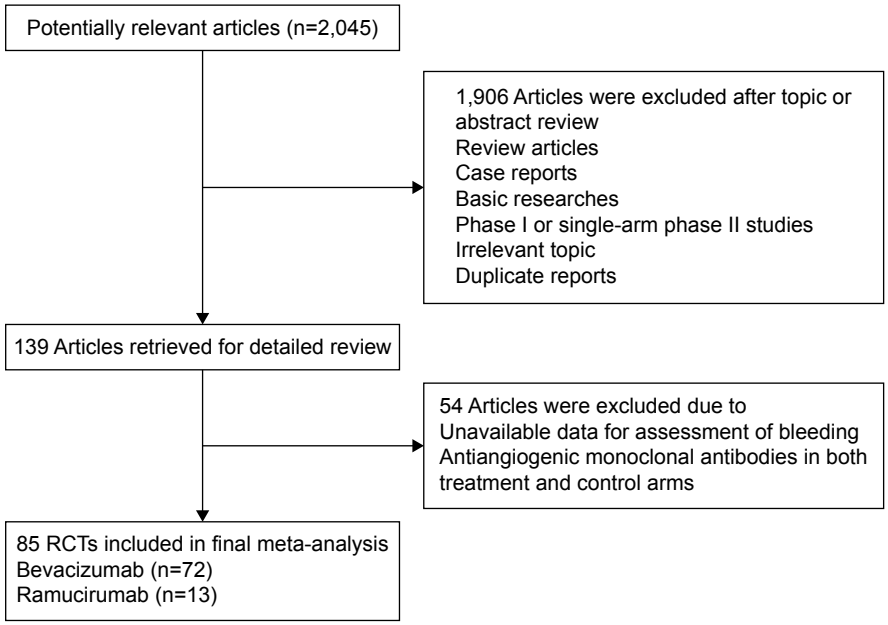

Figure 1 Outline of the search flow diagram.
Abbreviation: RCTs, randomized controlled trials.

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Malignancy	Phase	No. in intervention/control	Concurrent treatment	Dose (mg/kg/week)	No. of bleeding events in intervention/control	
							All grade	Grade ≥3
Bevacizumab								
Kabbinavar et al[8]	2003	CRC	II	67/35	Fluorouracil + leucovorin	2.5 or 5	NR	3/0
Hurwitz et al[9]	2004	CRC	III	393/397	Irinotecan + fluorouracil + leucovorin	2.5	NR	12/10
Kabbinavar et al[10]	2005	CRC	II	100/104	Fluorouracil + leucovorin	2.5	NR	5/3
Giantonio et al[11]	2007	CRC	III	287/285	Oxaliplatin + fluorouracil + leucovorin	5	NR	10/1
Saltz et al[12]	2008	CRC	III	694/675	Capecitabine + oxaliplatin/fluorouracil + folinic acid + oxaliplatin	2.5	NR	13/8
Allegra et al[13]	2009	CRC	III	1,326/1,321	Oxaliplatin + fluorouracil + leucovorin	2.5	NR	25/25
Tebbutt et al[14]	2010	CRC	III	157/156	Capecitabine	2.5	19/19	2/4
Statopoulos et al[15]	2010	CRC	III	114/108	Irinotecan + fluorouracil + leucovorin	2.5	3/0	NR
Guan et al[16]	2011	CRC	III	141/70	Irinotecan + fluorouracil + leucovorin	2.5	NR	1/1
Dotan et al[17]	2012	CRC	II	12/11	Capecitabine + oxaliplatin + cetuximab	2.5	6/4	0/0
De Gramont et al[18]	2012	CRC	III	1,145/1,126	Oxaliplatin + fluorouracil + leucovorin	2.5	NR	14/6
Bennouna et al[19]	2013	CRC	III	401/409	Fluorouracil/capecitabine + oxaliplatin/irinotecan	2.5	NR	8/1
Cunningham et al[20]	2013	CRC	III	134/136	Capecitabine	2.5	34/9	0/1
Cao et al[21]	2015	CRC	II	65/77	Irinotecan + fluorouracil + leucovorin	5	NR	5/0
Hegewisch-Becker et al[22]	2015	CRC	III	156/158	None	2.5	14/11	0/1
Passardi et al[23]	2015	CRC	III	176/194	Irinotecan + fluorouracil + leucovorin/oxaliplatin + fluorouracil + leucovorin	2.5	30/9	NR
Masi et al[24]	2015	CRC	III	91/92	Irinotecan + fluorouracil + leucovorin/oxaliplatin + fluorouracil + leucovorin	2.5	19/2	0/0
Koeberle et al[25]	2015	CRC	III	131/131	None	2.5	5/1	0/0
Snoeren et al[26]	2017	CRC	III	39/36	Capecitabine + oxaliplatin	2.5	NR	0/1
Miller et al[27]	2005	BC	III	229/215	Capecitabine	5	66/24	1/1
Miller et al[28]	2007	BC	III	365/346	Paclitaxel	5	NR	2/0
Miles et al[29]	2010	BC	III	499/231	Docetaxel	2.5 or 5	NR	5/2
Brufsky et al[30]	2011	BC	III	458/221	Capecitabine/taxane/gemcitabine/vinorelbine	5	NR	8/0
Robert et al[31]	2011	BC	III	817/403	Capecitabine/taxane/anthracycline	5	NR	14/1
von Minckwitz et al[32]	2012	BC	III	956/969	Epirubicin/cyclophosphamide/docetaxel	5	NR	4/3
Gianni et al[33]	2013	BC	III	215/206	Docetaxel + trastuzumab	5	NR	3/1
Cameron et al[34]	2013	BC	III	1,288/1,271	Anthracycline/taxane	5	NR	8/2
Coudert et al[35]	2014	BC	II	47/25	Trastuzumab + docetaxel	5	NR	0/0
von Minckwitz et al[36]	2014	BC	III	245/238	Taxane/anthracycline/capecitabine/vinorelbine/gemcitabin/cyclophosphamide	5	33/18	1/4
Sikov et al[37]	2015	BC	II	215/218	Paclitaxel ± carboplatin–doxorubicin + cyclophosphamide	5	NR	7/0
Diéras et al[38]	2015	BC	II	56/57	Trebananib + paclitaxel	5	29/17	0/0
Miles et al[39]	2017	BC	III	238/233	Paclitaxel	5	106/62	2/2
Johnson et al[40]	2004	LC	II	66/32	Carboplatin + paclitaxel	2.5 or 5	NR	6/0

Sandler et al[41]	2006	LC	III	427/440	Paclitaxel + carboplatin	5	NR	19/3
Herbst et al[42]	2007	LC	II	39/42	Docetaxel/pemetrexed	5	NR	3/1
Reck et al[43]	2009	LC	III	659/327	Cisplatin + gemcitabine	2.5 or 5	NR	28/6
Herbst et al[44]	2011	LC	III	313/313	Erlotinib	5	NR	10/7
Niho et al[45]	2012	LC	II	119/58	Carboplatin + paclitaxel	5	94/18	2/0
Boutsikou et al[46]	2013	LC	III	116/113	Docetaxel + carboplatin ± erlotinib	2.5	7/0	3/0
Seto et al[47]	2014	LC	II	75/77	Erlotinib	5	54/22	2/0
Zhou et al[48]	2015	LC	III	140/134	Carboplatin, paclitaxel	5	NR	2/1
Pujol et al[49]	2015	LC	II–III	37/37	Cisplatin + etoposide ± epidoxorubicin + cyclophosphamide	2.5	7/2	0/0
Takeda et al[50]	2016	LC	II	50/50	Docetaxel	5	20/3	0/0
Karayama et al[51]	2016	LC	II	45/35	Pemetrexed	5	NR	0/0
Tiseo et al[52]	2017	LC	III	95/103	Cisplatin + etoposide	2.5	NR	0/0
Escudier et al[53]	2007	RCC	III	337/304	Interferon α	5	112/28	11/1
Rini et al[54]	2010	RCC	III	362/347	Interferon α	5	21/4	4/1
Van Cutsem et al[55]	2009	PC	III	296/287	Gemcitabine + erlotinib	2.5	124/67	22/16
Kindler et al[56]	2010	PC	III	277/263	Gemcitabine	5	NR	5/4
Burger et al[57]	2011	OC	III	608/601	Paclitaxel + carboplatin	5	NR	14/5
Perren et al[58]	2011	OC	III	745/753	Paclitaxel + carboplatin	2.5	295/87	9/2
Pujade-Lauraine et al[59]	2014	OC	III	179/181	PLD/paclitaxel/topotecan	5	NR	2/2
Aghajanian et al[60]	2015	OC	III	247/233	Gemcitabine + carboplatin	5	170/78	15/2
Coleman et al[61]	2017	OC	III	330/327	Paclitaxel + carboplatin	5	140/27	6/3
Ohtsu et al[62]	2011	GC	III	386/381	Cisplatin + capecitabine	2.5	NR	9/9
Okines et al[63]	2013	GC	II/III	99/101	Epirubicin + cisplatin + capecitabine	2.5	NR	1/3
Shen et al[64]	2015	GC, GEJC	III	100/101	Capecitabine + cisplatin	2.5	NR	12/4
Cunningham et al[65]	2017	GEJC	II/III	468/477	Epirubicin + cisplatin + capecitabine	2.5	15/7	2/2
Chinot et al[66]	2014	Glioblastoma	III	461/450	Radiotherapy + temozolomide	5	186/97	15/8
Gilbert et al[67]	2014	Glioblastoma	III	260/233	None	5	NR	4/2
Balana et al[68]	2016	Glioblastoma	II	48/45	Temozolomide	5	NR	5/0
Seymour et al[69]	2014	Lymphoma	III	395/386	Rituximab + doxorubicin + vincristine + cyclophosphamide + prednisone instead of R-CHOP	5	77/31	8/1
Kay et al[70]	2016	Lymphocytic leukemia	II	33/32	Pentostatin + cyclophosphamide + rituximab	5	NR	1/0
Kim et al[71]	2012	Melanoma	II	143/69	Paclitaxel + carboplatin	5	NR	2/5
Corrie et al[72]	2014	Melanoma	III	671/672	None	2.5	153/13	1/1
Kindler et al[73]	2012	MM	II	53/55	Gemcitabine + cisplatin	5	NR	4/1
Zalcman et al[74]	2016	MM	III	222/224	Pemetrexed + cisplatin	5	91/16	2/0
Kelly et al[75]	2012	Prostate cancer	III	504/505	Docetaxel + prednisone	5	NR	35/16
Tewari et al[76]	2014	Cervical cancer	III	220/219	Paclitaxel/topotecan + cisplatin	5	NR	10/2
Hensley et al[77]	2015	uLMS	III	52/51	Gemcitabine + docetaxel	5	1/2	0/1
Pinter et al[78]	2015	HC	II	16/11	TACE	2.5	3/1	3/1
Chisholm et al[79]	2017	STSs	II	71/79	Ifosfamide + vincristine + actinomycin-D + doxorubicin instead of VADO/IVA/cyclophosphamide + vinorelbine	2.5	NR	2/6

(*Continued*)

Table 1 (*Continued*)

Author	Year	Malignancy	Phase	No. in intervention/control	Concurrent treatment	Dose (mg/kg/week)	No. of bleeding events in intervention/control	
							All grade	Grade ≥3
Ramucirumab								
Yoh et al[80]	2016	LC	II	76/81	Docetaxel	3.3	39/23	2/0
Doebele et al[81]	2015	LC	II	67/69	Pemetrexed + cisplatin	3.3	26/13	2/1
Garon et al[82]	2014	LC	III	627/618	Docetaxel	3.3	181/94	15/14
Petrylak et al[83]	2016	UC	II	46/45	Docetaxel	3.3	31/12	2/1
Petrylak et al[84]	2017	UC	III	263/267	Docetaxel	3.3	67/46	8/12
Tabernero et al[85]	2015	CRC	III	529/528	None	4	232/120	13/9
Moore et al[86]	2016	CRC	II	52/49	Oxaliplatin + fluorouracil + leucovorin	4	25/9	NR
Mackey et al[87]	2015	BC	III	752/382	Docetaxel	3.3	361/85	7/7
Yardley et al[88]	2016	BC	II	69/65	Eribulin	3.3	13/3	1/1
Fuchs et al[89]	2014	GC or GEJC	III	236/115	None	4	30/13	8/3
Wilke et al[90]	2014	GC or GEJC	III	327/329	Paclitaxel	4	137/59	14/8
Yoon et al[91]	2016	GC, EC, or GEJC	II	82/80	Oxaliplatin + fluorouracil + leucovorin	4	36/20	5/5
Zhu et al[92]	2015	HC	III	277/276	None	4	90/55	17/21

Abbreviations: CRC, colorectal cancer; BC, breast cancer; LC, lung cancer; RCC, renal cell carcinoma; PC, pancreatic cancer; OC, ovarian cancer; GC, gastric cancer; MM, malignant mesothelioma; uLMS, uterine leiomyosarcoma; UC, urothelial carcinoma; EC, esophagus cancer; GEJC, gastroesophageal junction cancer; HC, hepatocellular carcinoma; STSs, soft tissue sarcomas; NR, not reached; TACE, transarterial chemoembolization.

the risk of all-grade bleeding (RR: 1.94, 95% CI: 1.76–2.13, $p<0.00001$) and no difference was observed for the risk of high-grade bleeding (RR: 1.04, 95% CI: 0.78–1.39, $p=0.79$) compared with the control group. RR of all-grade and high-grade bleeding according to drug type is summarized in Tables 2 and 3, respectively.

In addition, we further assessed the risk of pulmonary hemorrhage of bevacizumab and ramucirumab in all lung cancer patients. The results showed that bevacizumab significantly increased the risk of all-grade (RR: 4.72, 95% CI: 1.99–11.19, $p=0.0004$) and high-grade pulmonary hemorrhage (RR: 3.97, 95% CI: 1.70–9.29, $p=0.001$), but no significant differences in the risk of all-grade (RR: 1.09, 95% CI: 0.76–1.57, $p=0.64$) and high-grade (RR: 1.22, 95% CI: 0.35–4.21, $p=0.75$) pulmonary hemorrhage were observed for ramucirumab. RR of all-grade and high-grade pulmonary hemorrhage is shown in Figures 4 and 5, respectively.

RR according to drug dosage

In the subgroup analysis by dosage, the increased risk of all-grade and high-grade bleeding was observed in both low-dose and high-dose angiogenesis inhibitors.

The risks of all-grade bleeding were comparable between patients with low-dose angiogenesis inhibitors (RR: 2.46, 95% CI: 1.95–3.11) and high-dose angiogenesis inhibitors (RR: 2.34, 95% CI: 2.00–2.73) (Table 2). The risk of high-grade bleeding was more frequently observed in patients with high-dose angiogenesis inhibitors (RR: 2.17, 95% CI: 1.79–2.64) than in those with low-dose angiogenesis inhibitors (RR: 1.31, 95% CI: 1.06–1.60) (Table 3).

RR according to tumor type

Studies were further stratified according to tumor type (colorectal cancer vs non-colorectal tumors). Increased risk of all-grade and high-grade bleeding was observed in both the colorectal cancer arm and non-colorectal tumors arm. The risks of all-grade (RRs for colorectal cancer and non-colorectal tumors were 2.24, 95% CI: 1.58–3.19 and 2.42, 95% CI: 2.09–2.80, respectively) (Table 2) and high-grade bleeding (RRs for colorectal cancer and non-colorectal tumors were 1.52, 95% CI: 1.13–2.03 and 1.77, 95% CI: 1.50–2.09, respectively) (Table 3) were comparable between patients with colorectal cancer and non-colorectal tumors.

Publication bias

To minimize publication bias, we selected papers strictly according to the inclusion criteria. Furthermore, a funnel plot

Study or subgroup	Experimental events	Total	Control events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Aghajanian et al[60]	170	247	78	233	3.8	2.06, 1.68–2.51
Boutsikou et al[46]	7	116	0	113	0.2	14.62, 0.84–252.94
Chinot et al[66]	186	461	97	450	3.8	1.87, 1.52–2.31
Coleman et al[61]	140	330	27	327	3.1	5.14, 3.50–7.53
Corrie et al[72]	153	671	13	672	2.4	11.79, 6.76–20.55
Cunningham et al[20]	34	134	9	136	1.9	3.83, 1.91–7.68
Cunningham et al[65]	15	468	7	477	1.4	2.18, 0.90–5.31
Diéras et al[38]	29	56	17	57	2.7	1.74, 1.08–2.78
Doebele et al[81]	26	67	13	69	2.3	2.06, 1.16–3.66
Dotan et al[17]	6	12	4	11	1.3	1.38, 0.52–3.61
Escudier et al[53]	112	337	28	304	3.1	3.61, 2.46–5.30
Fuchs et al[89]	30	236	13	115	2.2	1.12, 0.61–2.07
Garon et al[82]	181	627	94	618	3.7	1.90, 1.52–2.37
Hegewisch-Becker et al[22]	14	156	11	158	1.7	1.29, 0.60–2.75
Hensley et al[77]	1	52	2	51	0.3	0.49, 0.05–5.24
Koeberle et al[25]	5	131	1	131	0.3	5.00, 0.59–42.21
Mackey et al[87]	361	752	85	382	3.8	2.16, 1.76–2.64
Masi et al[24]	19	91	2	92	0.7	9.60, 2.30–40.05
Miles et al[39]	106	238	62	233	3.6	1.67, 1.30–2.16
Miller et al[27]	66	229	24	215	2.9	2.58, 1.68–3.96
Moore et al[86]	25	52	9	49	2.1	2.62, 1.36–5.04
Niho et al[45]	94	119	18	58	3.0	2.55, 1.72–3.78
Passardi et al[23]	30	176	9	194	1.9	3.67, 1.79–7.52
Perren et al[58]	295	745	87	753	3.8	3.43, 2.76–4.26
Petrylak et al[83]	31	46	12	45	2.5	2.53, 1.50–4.27
Petrylak et al[84]	67	263	46	267	3.3	1.48, 1.06–2.07
Pinter et al[78]	3	16	1	11	0.3	2.06, 0.25–17.34
Pujol et al[49]	7	37	2	37	0.6	3.50, 0.78–15.75
Rini et al[54]	21	362	4	347	1.1	5.03, 1.75–14.51
Seto et al[47]	54	75	22	77	3.1	2.52, 1.72–3.69
Seymour et al[69]	77	395	31	386	3.0	2.43, 1.64–3.59
Statopoulos et al[15]	3	114	0	108	0.2	6.63, 0.35–126.96
Tabernero et al[85]	232	529	120	528	3.9	1.93, 1.60–2.32
Takeda et al[50]	20	50	3	50	1.0	6.67, 2.11–21.02
Tebbutt et al[14]	19	157	19	156	2.2	0.99, 0.55–1.80
Van Cutsem et al[55]	124	296	67	287	3.6	1.79, 1.40–2.30
von Minckwitz et al[36]	33	245	18	238	2.4	1.78, 1.03–3.07
Wilke et al[90]	137	327	59	329	3.6	2.34, 1.79–3.04
Yardley et al[88]	13	69	3	65	0.9	4.08, 1.22–13.67
Yoh et al[80]	39	76	23	81	3.0	1.81, 1.20–2.72
Yoon et al[91]	36	82	20	80	2.8	1.76, 1.12–2.76
Zalcman et al[74]	91	222	16	224	2.6	5.74, 3.49–9.44
Zhu et al[92]	90	277	55	276	3.5	1.63, 1.22–2.18
Total, 95% CI		**10,141**		**9,490**	**100**	**2.38, 2.09–2.71**
Total events	3,202		1,231			

Heterogeneity: τ^2=0.11; χ^2=159.34, df=42 (p<0.00001); I^2=74%
Test for overall effect: Z=12.95 (p<0.00001)

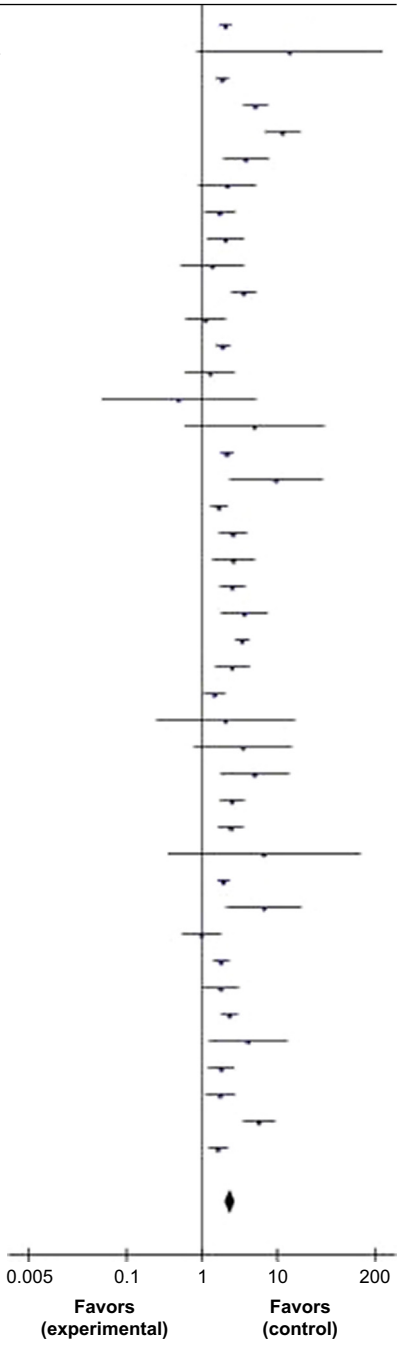

Figure 2 RR of all-grade bleeding.
Abbreviations: M–H, Mantel–Haenszel; RR, relative risk.

was used to detect publication bias and no apparent bias was found according to it for all-grade and high-grade bleeding.

Discussion

To the best of our knowledge, this is the first and the largest meta-analysis to assess the risk of bleeding associated with antiangiogenic monoclonal antibodies bevacizumab and ramucirumab. The results of our meta-analysis showed a significant 2.38-fold increased all-grade bleeding risk and a 1.71-fold increased high-grade bleeding risk with these agents. A similar risk of bleeding is also associated with other VEGF receptor tyrosine kinase inhibitors.[93]

In order to identify potential risk factors, we performed subgroup analysis according to drug types. The results

Study or subgroup	Experimental events	Total	Control events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI
Aghajanian et al[60]	15	247	2	233	0.7	7.07, 1.64–30.60
Allegra et al[13]	25	1,328	25	1,321	8.5	1.00, 0.58–1.73
Balana et al[68]	5	48	0	45	0.2	10.33, 0.59–181.54
Bennouna et al[19]	5	401	1	409	0.3	8.16, 1.06–64.94
Boutsikou et al[46]	3	116	0	113	0.2	6.82, 0.38–130.57
Brufsky et al[30]	8	458	0	221	0.2	8.22, 0.48–141.81
Burger et al[57]	14	500	5	601	1.7	2.77, 1.00–7.64
Cameron et al[34]	8	1,288	2	1,271	0.7	3.06, 0.84–18.55
Cao et al[21]	5	65	0	77	0.2	13.00, 0.73–230.76
Chinot et al[66]	15	451	5	450	2.7	1.83, 0.78–4.27
Chisholm et al[79]	2	71	6	79	1.9	0.37, 0.60–1.78
Coleman et al[61]	6	330	3	327	1.0	1.98, 0.50–7.86
Corrie et al[72]	1	671	1	672	0.3	1.00, 0.06–15.98
Coudert et al[35]	0	47	0	25		Not estimable
Cunningham et al[20]	0	134	1	136	0.5	0.34, 0.01–8.23
Cunningham et al[65]	2	458	2	477	0.7	1.02, 0.14–7.21
De Gramont et al[18]	14	1,145	6	1,126	2.1	2.29, 0.88–5.95
Diéras et al[38]	0	58	0	57		Not estimable
Doebele et al[81]	2	67	1	69	0.3	2.06, 0.19–22.18
Dotan et al[17]	0	12	0	11		Not estimable
Escudier et al[53]	11	337	1	304	0.4	9.32, 1.20–78.41
Fuchs et al[89]	8	236	3	115	1.4	1.30, 0.35–4.81
Garon et al[82]	15	627	14	618	4.8	1.06, 0.51–2.17
Gianni et al[33]	3	215	1	206	0.3	2.47, 0.30–27.41
Giantonio et al[11]	10	287	1	285	0.3	9.93, 1.28–77.07
Gilbert et al[67]	4	250	2	233	0.7	1.79, 0.33–9.70
Guan et al[16]	1	141	1	70	0.3	0.50, 0.00–7.82
Hegewisch-Becker et al[22]	0	156	1	158	0.5	0.34, 0.01–8.22
Hensley et al[77]	0	52	1	51	0.5	0.33, 0.01–7.85
Herbst et al[42]	3	39	1	42	0.3	3.23, 0.35–29.77
Herbst et al[44]	10	313	7	313	2.4	1.43, 0.55–3.71
Hurwitz et al[9]	12	393	10	397	3.4	1.21, 0.53–2.77
Johnson et al[40]	6	65	0	32	0.2	6.40, 0.37–110.26
Kabbinavar et al[8]	3	67	0	35	0.2	3.71, 0.20–69.79
Kabbinavar et al[10]	5	100	3	104	1.0	1.73, 0.43–7.06
Karayama et al[51]	0	46	0	36		Not estimable
Kay et al[70]	1	33	0	22	0.2	2.91, 0.12–04.95
Kelly et al[75]	35	504	16	506	5.4	2.19, 1.23–3.91
Kim et al[71]	2	143	5	69	2.3	0.19, 0.04–0.97
Kindler et al[56]	5	277	4	263	1.4	1.39, 0.32–4.37
Kindler et al[73]	4	53	1	55	0.3	4.15, 0.48–35.05
Koeberle et al[25]	0	131	0	131		Not estimable
Mackey et al[87]	7	752	7	382	3.2	0.51, 0.10–1.44
Masi et al[24]	0	91	0	92		Not estimable
Miles et al[29]	5	499	2	231	0.9	1.15, 0.23–5.92
Miles et al[39]	2	238	2	233	0.7	0.98, 0.14–6.89
Miller et al[27]	1	229	1	215	0.4	0.94, 0.06–14.92
Miller et al[28]	2	355	0	346	0.2	4.74, 0.23–98.32
Niho et al[45]	2	119	0	68	0.2	2.46, 0.12–50.39
Ohtsu et al[62]	9	346	8	201	3.1	0.99, 0.40–2.46
Okines et al[63]	1	90	3	101	1.0	0.34, 0.04–3.25
Perren et al[58]	9	746	2	753	0.7	4.56, 0.99–20.96
Petrylak et al[83]	2	46	1	45	0.3	1.96, 0.18–20.53
Petrylak et al[84]	8	263	12	267	4.0	0.66, 0.28–1.63
Pinter et al[78]	3	16	1	11	0.4	2.06, 0.25–17.34
Pujade-Lauraine et al[59]	2	179	2	181	0.7	1.01, 0.14–7.10
Pujol et al[49]	0	37	0	37		Not estimable
Reck et al[43]	28	650	5	327	2.7	2.32, 0.97–5.54
Rini et al[54]	4	352	1	347	0.3	3.83, 0.43–34.14
Robert et al[31]	14	617	1	400	0.5	6.91, 0.91–52.33
Saltz et al[12]	13	694	8	675	2.4	1.56, 0.66–3.79
Sandler et al[41]	19	427	3	440	1.0	6.53, 1.95–25.89
Seto et al[47]	2	75	0	77	0.2	0.13, 0.25–105.14
Seymour et al[69]	5	395	1	388	0.3	7.02, 0.01–62.21
Shen et al[64]	12	100	4	101	1.4	3.03, 1.01–0.08
Sikov et al[37]	7	215	0	218	0.2	15.21, 0.07–254.64
Snoeren et al[26]	0	39	1	36	0.5	0.31, 0.01–7.34
Tabernero et al[85]	13	529	9	528	3.1	1.44, 0.62–3.34
Takeda et al[50]	0	50	0	60		Not estimable
Tebbutt et al[14]	2	157	4	158	1.4	0.50, 0.09–2.67
Tewari et al[76]	10	220	2	219	0.7	4.98, 1.10–22.45
Tiseo et al[52]	0	96	0	103		Not estimable
Van Cutsem et al[55]	22	296	16	287	5.5	1.33, 0.71–2.49
von Minckwitz et al[32]	4	958	3	289	1.0	1.35, 0.30–0.02
von Minckwitz et al[36]	1	246	4	238	1.4	0.24, 0.03–2.16
Wilke et al[90]	14	327	8	329	2.7	1.76, 0.76–4.14
Yardley et al[88]	1	59	1	65	0.3	0.94, 0.06–14.75
Yoh et al[80]	2	76	0	81	0.2	5.32, 0.26–109.15
Yoon et al[91]	5	82	5	80	1.7	0.98, 0.29–3.24
Zalcman et al[74]	2	222	0	224	0.2	5.04, 0.24–104.49
Zhou et al[48]	2	140	1	134	0.3	1.91, 0.18–20.87
Zhu et al[92]	17	277	21	276	7.1	0.81, 0.44–1.50
Total, 95% CI		**24,062**		**21,855**	**100**	**1.71, 1.48–1.97**
Total events	626		276			

Heterogeneity: χ^2=90.19, *df*=72 (*p*=0.07); I^2=20%
Test for overall effect: *Z*=7.38 (*p*<0.00001)

Figure 3 RR of high-grade bleeding.
Abbreviations: M–H, Mantel–Haenszel; RR, relative risk.

showed that ramucirumab differed from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients. The mechanisms underlying these differences remained unclear. A possible explanation was that bevacizumab, as an anti-VEGF-A agent, specified both VEGFR-1 and VEGFR-2, whereas ramucirumab was only specified for VEGFR-2. VEGFR-2 was the major mediator

Table 2 RR of all-grade bleeding associated with angiogenesis inhibitors in the subgroup analysis

Bleeding	No. of trials	No. of events/total (%)		RR, 95% CI
		Treatment	Control	
Type of drug				
Bevacizumab	30	1,934/6,738 (28.7)	679/6,586 (10.3)	2.73, 2.24–3.33
Ramucirumab	13	1,268/3,403 (37.3)	552/2,904 (19.0)	1.94, 1.76–2.13
Drug dosage				
Low dose	22	1,452/5,220 (27.8)	508/4,863 (10.4)	2.46, 1.95–3.11
High dose	21	1,750/4,921 (35.6)	723/4,627 (15.6)	2.34, 2.00–2.73
Tumor types				
Colorectal cancer	10	387/1,552 (24.9)	184/1,563 (11.8)	2.24, 1.58–3.19
Non-colorectal cancer	33	2,815/8,589 (32.8)	1,047/7,927 (13.2)	2.42, 2.09–2.80

Abbreviation: RR, relative risk.

of VEGF-driven responses in endothelial cells. The precise function of VEGFR-1 was not entirely established and some studies showed that VEGFR-1 could also regulate proliferation and survival of endothelial cells.[94–97] Increased level of tumor VEGFR-1 expression has been shown to be associated with high tumor angiogenesis.[96] VEGF/VEGFR-1 signaling-mediated tumor cell monocyte chemoattractant protein-1 expression could represent a mechanism responsible for the tumor angiogenic switch.[97] Therefore, bevacizumab increased the risk of bleeding by inhibiting both VEGFR-1 and VEGFR-2. Squamous cell tumors are more frequently centrally located and have a greater tendency to cavitate as compared to adenocarcinoma, which is the main risk factor of pulmonary hemorrhage.[98] The difference in the risk of pulmonary hemorrhage caused bevacizumab to be used only for non-squamous NSCLC and ramucirumab to be used for any tumor histology of NSCLC.

Our study also demonstrated that both low-dose and high-dose angiogenesis inhibitors increased the risk of bleeding. The risk of high-grade bleeding was more frequently observed in patients with high-dose angiogenesis inhibitors, suggesting that the risk may be dose-dependent and close supervision and careful management should be emphasized especially in patients with high dosage.

In a meta-analysis of bevacizumab, patients with colorectal cancer were found to have the highest risk of bleeding compared to other tumors.[99] For colorectal cancer patients, high-grade bleeding such as perforation was commonly fatal and life threatening.[100] Therefore, we performed a subgroup analysis according to colorectal cancer and non-colorectal tumors in order to identify the potential risk factors. Results showed that the risk of all-grade and high-grade bleeding was comparable between patients with colorectal cancer and non-colorectal tumors, suggesting that the increased risk of bleeding is associated with many tumor types.

Limitations

There are several limitations in this meta-analysis. First, we performed stratification analysis only for colorectal cancer and non-colorectal tumor types because too many tumor types were included in the analysis and assessment was difficult. Second, we did not evaluate the risk of pulmonary hemorrhage between bevacizumab and ramucirumab in

Table 3 RR of high-grade bleeding associated with angiogenesis inhibitors in the subgroup analysis

Bleeding	No. of trials	No. of events/total (%)		RR, 95% CI
		Treatment	Control	
Type of drug				
Bevacizumab	70	432/20,731 (2.1)	194/19,000 (1.0)	1.98, 1.68–2.34
Ramucirumab	12	94/3,351 (2.8)	82/2,855 (2.9)	1.04, 0.78–1.39
Drug dosage				
Low dose	37	203/10,569 (1.9)	149/10,089 (1.5)	1.31, 1.06–1.60
High dose	49	323/13,513 (2.4)	135/12,391 (1.1)	2.17, 1.79–2.64
Tumor types				
Colorectal cancer	18	111/5,868 (1.9)	71/5,747 (1.2)	1.52, 1.13–2.03
Non-colorectal cancer	64	415/18,214 (2.3)	205/16,108 (1.3)	1.77, 1.50–2.09

Abbreviation: RR, relative risk.

Study or subgroup	Experimental events	Total	Control events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI
Bevacizumab						
Boutsikou et al[46]	7	116	0	113	0.9	14.62, 0.84–252.94
Karayama et al[51]	1	45	1	35	1.9	0.78, 0.05–12.00
Niho et al[45]	26	119	3	58	6.9	4.22, 1.33–13.38
Seto et al[47]	6	75	1	77	1.7	6.16, 0.76–49.95
Subtotal, 95% CI		**355**		**283**	**11.3**	**4.72, 1.99–11.19**
Total events	40		5			
Heterogeneity: χ^2=2.37, *df*=3 (*p*=0.50); I^2=0%						
Test for overall effect: *Z*=3.52 (*p*=0.0004)						
Ramucirumab						
Garon et al[82]	49	627	46	618	78.8	1.05, 0.71–1.55
Yoh et al[80]	8	76	6	81	9.9	1.42, 0.52–3.91
Subtotal, 95% CI		**703**		**699**	**88.7**	**1.09, 0.76–1.57**
Total events	57		52			
Heterogeneity: χ^2=0.30, *df*=1 (*p*=0.58); I^2=0%						
Test for overall effect: *Z*=0.47 (*p*=0.64)						
Total, 95% CI		**1,058**		**982**	**100**	**1.50, 1.09–2.07**
Total events	97		57			
Heterogeneity: χ^2=10.81, *df*=5 (*p*=0.06); I^2=54%						
Test for overall effect: *Z*=2.47 (*p*=0.01)						
Test for subgroup differences: χ^2=9.42, *df*=1 (*p*=0.002); I^2=89.4%						

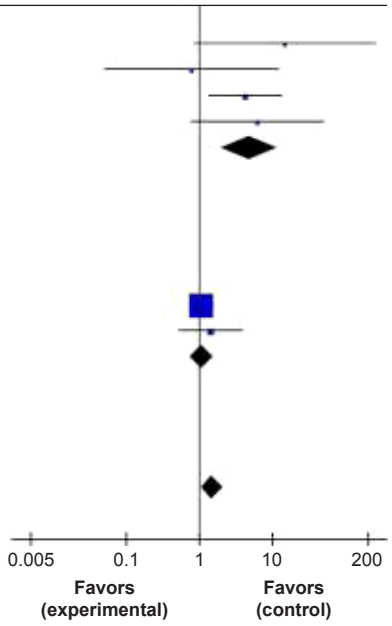

Figure 4 RR of all-grade pulmonary hemorrhage.
Abbreviations: M–H, Mantel–Haenszel; RR, relative risk.

Study or subgroup	Experimental events	Total	Control events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI
Bevacizumab						
Boutsikou et al[46]	3	116	0	113	4.4	6.82, 0.36–130.57
Herbst et al[42]	2	39	0	42	4.2	5.38, 0.27–108.58
Herbst et al[44]	3	313	1	313	8.7	3.00, 0.31–28.68
Johnson et al[40]	6	66	0	32	5.8	6.40, 0.37–110.26
Karayama et al[51]	0	45	0	35		Not estimable
Niho et al[45]	1	119	0	58	5.8	1.48, 0.06–35.66
Pujol et al[49]	0	37	0	37		Not estimable
Reck et al[43]	8	659	2	327	23.2	1.98, 0.42–9.29
Sandler et al[41]	8	427	1	440	8.6	8.24, 1.04–65.63
Seto et al[47]	0	75	0	77		Not estimable
Takeda et al[50]	0	50	0	50		Not estimable
Tiseo et al[52]	0	95	0	103		Not estimable
Zhou et al[48]	0	140	0	134		Not estimable
Subtotal, 95% CI		**2,181**		**1,761**	**60.8**	**3.97, 1.70–9.29**
Total events	31		4			
Heterogeneity: χ^2=1.96, *df*=6 (*p*=0.92); I^2=0%						
Test for overall effect: *Z*=3.18 (*p*=0.001)						
Ramucirumab						
Garon et al[82]	4	627	4	618	35.0	0.99, 0.25–3.92
Yoh et al[80]	1	76	0	81	4.2	3.19, 0.13–77.25
Subtotal, 95% CI		**703**		**699**	**39.2**	**1.22, 0.35–4.21**
Total events	5		4			
Heterogeneity: χ^2=0.44, *df*=1 (*p*=0.51); I^2=0%						
Test for overall effect: *Z*=0.32 (*p*=0.75)						
Total, 95% CI		**2,884**		**2,460**	**100**	**2.89, 1.46–5.72**
Total events	36		8			
Heterogeneity: χ^2=4.50, *df*=8 (*p*=0.81); I^2=0%						
Test for overall effect: *Z*=3.05 (*p*=0.002)						
Test for subgroub differences: χ^2=2.37, *df*=1 (*p*=0.12); I^2=57.7%						

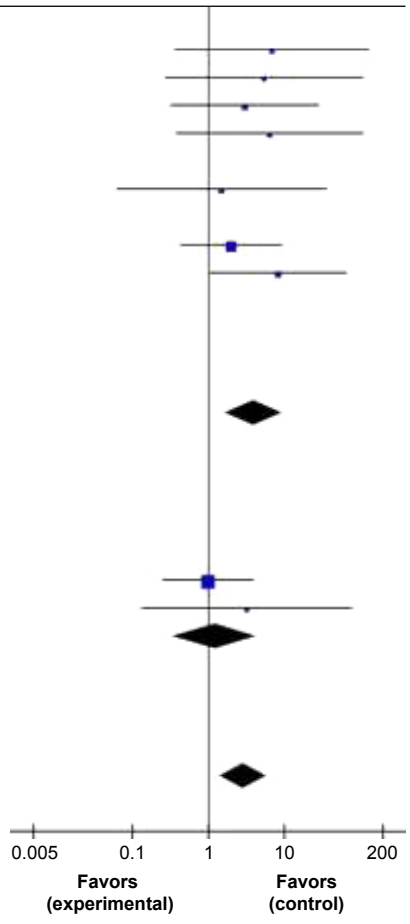

Figure 5 RR of high-grade pulmonary hemorrhage.
Abbreviations: M–H, Mantel–Haenszel; RR, relative risk.

lung squamous cell carcinoma patients due to the small sample size or absence of original data. Finally, our literature search was limited to articles published in English leading to some selection bias.

Conclusion

Despite the limitations of our meta-analysis, we conclude that antiangiogenic monoclonal antibodies are associated with a significant increase in the risk of all-grade and high-grade bleeding. Ramucirumab may be different from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients. Clinicians should be aware of this adverse effect and ensure close monitoring, especially in patients at high risk.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7,8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	7,8

(*Continued*)

PRISMA 2009 Checklist (*Continued*)

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	7,8
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	11

Notes: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. For more information, visit: www.prisma-statement.org.