Systematic Review and Meta-Analysis

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Efficacy and safety of erlotinib combined with bevacizumab in the treatment of non-small cell lung cancer

A systematic review and meta-analysis

Kenan Zhou, MS[a], Shishun Zhao, PhD[a], Wenlai Guo, PhD[b], Lei Ding, MD[c,*]

Abstract

Background: Non-small cell lung cancer (NSCLC) has a poor prognosis despite conventional treatments of surgery, radiotherapy, and chemotherapy. Small-molecule tyrosine kinase inhibitors acting on epidermal growth factor receptor (EGFR) have shown high efficacy and low toxicity for NSCLC. In particular, combining erlotinib with the VEGF antibody bevacizumab has therapeutic value in NSCLC, but the drugs' separate effects as monotherapy and any adverse outcomes of combination therapy remain unclear.

Objectives: To determine the efficacy and safety of erlotinib and bevacizumab for NSCLC, we conducted a meta-analysis and systematic review of randomized controlled trials.

Data sources: PubMed, Embase, Web of Science, and Cochrane databases were searched using keywords and manual review.

Study eligibility criteria, participants, and interventions: We reviewed randomized controlled trials on the use of erlotinib combined with bevacizumab in adult patients with NSCLC, including data on outcome measures of overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events.

Study appraisal and synthesis methods: After quality assessment, datasets were evaluated for heterogeneity. In the event of significant heterogeneity, a random-effects model was used to assess the overall outcome measures as a result of treatments. Subgroup analysis was conducted to evaluate the source of heterogeneity on PFS.

Results: Compared with erlotinib or bevacizumab alone, the combined treatment did not significantly prolong OS (95% confidence interval [CI] = 0.84–1.11; $P = .62$) or increase the ORR (95% CI = 0.91–1.20; $P = .52$), but significantly improved PFS (95% CI = 0.58–0.73; $P < .001$). This improvement was especially notable in patients with the following characteristics: Eastern Cooperative Oncology Group Performance Status score of 0 or 1, female, no smoking history, adenocarcinoma, and EGFR Exon19 deletion or Exon21 Leu858Arg mutation. Combination therapy significantly increased incidence of grade 1–2 hypertension (20.3% vs 6.3%, 95% CI 1.73–5.88; $P < .01$) and severe diarrhea (10% vs 3.2%, 95% CI 1.36–6.60; $P = .01$).

Limitations: The low number of available randomized controlled trials could influence interpretation.

Conclusions: Compared with erlotinib or bevacizumab monotherapy, their combination effectively prolongs PFS but increases incidence of adverse events in NSCLC patients.

Abbreviations: CI = confidence interval, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = non-small cell lung cancer, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, RCT = randomized controlled trial, RR = risk ratio.

Keywords: bevacizumab, erlotinib, metaanalysis, non-small cell lung cancer, systematic review

1. Introduction

With a poor overall prognosis, lung cancer is the leading cause of cancer-related deaths worldwide,[1,2] and less than 15% of patients survive for 5 years.[3] Non-small cell lung cancer (NSCLC) accounts for over 85% of all lung cancer cases, and approximately 75% of NSCLCs are diagnosed at a terminal stage (unresectable or metastatic).[4] Current NSCLC treatments mainly include surgery and chemotherapy,[5,6] although targeted drugs are preferred if traditional treatment is ineffective.

The targeted drug bevacizumab is reported to significantly extend progression-free survival (PFS) and overall survival (OS) in patients with NSCLC; thus, it has been approved for treating advanced NSCLC without hemoptysis.[7,8] The drug is an antibody specific to vascular endothelial growth factor (VEGF), a key signaling molecule for promoting angiogenesis, critical to endothelial cell survival and neovascularization. Additionally, the targeted drug erlotinib is a small-molecule inhibitor of

Editor: Jianxun Ding.

The authors report no conflicts of interest.

[a] College of Mathematics, Jilin University, [b] Department of Hand Surgery, The Second Hospital of Jilin University, [c] Department of Radiology, China-Japan Union Hospital of Jilin University, Changchun, China.

[*] Correspondence: Lei Ding, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China (e-mail: leiding197@163.com).

How to cite this article: Zhou K, Zhao S, Guo W, Ding L. Efficacy and safety of erlotinib combined with bevacizumab in the treatment of non-small cell lung cancer: A systematic review and meta-analysis. Medicine 2020;99:3(e18771).

Received: 13 October 2019 / Received in final form: 27 November 2019 / Accepted: 11 December 2019

http://dx.doi.org/10.1097/MD.0000000000018771

epidermal growth factor receptor (EGFR). Used to treat patients with advanced or metastatic NSCLC who are not responding to chemotherapy regimens,[9–11] erlotinib is particularly effective in improving survival rate of patients without prior treatment.[12]

Although current treatment regimens typically involve single targeted drugs as monotherapy, combination therapy may have improved effects on patients with advanced or metastatic disease.[13] However, 1 study showed that patients with advanced NSCLC had no significant response to combination therapy, leading to controversy on its advantages.[14] In addition, targeted drugs are associated with a high risk of adverse events such as hypertension, rash, paronychia, diarrhea, neutropenia, and fatigue.[15] Therefore, substantial attention has been paid to potential increases in incidence of adverse side-effects when applying a combined therapy.

The extensive research on these targeted drugs for NSCLC[16,17] have not thus far made a distinction between first-line and second-line treatment. Moreover, little research is available on adverse events associated with combining erlotinib and bevacizumab. To resolve these issues, we conducted a meta-analysis and systematic review of randomized control trials (RCTs). We compared the effects of erlotinib+bevacizumab combination therapy with the respective monotherapies, specifically examining OS, PFS, objective response rate (ORR), as well as incidence and severity of adverse events. We also conducted subgroup analyses on the specific clinical and demographic factors affecting PFS and adverse events.

2. Materials and methods

All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

2.1. Study selection

Two researchers independently conducted a literature screen, assessed the quality of retrieved studies, then extracted and cross-checked data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18] Disagreement between the 2 researchers was resolved through consulting a third researcher.

2.2. Search strategy

On June 2, 2019, 2 researchers independently retrieved articles published before June 2019 from the PubMed, Embase, Web of Science, and Cochrane databases for all RCTs on the combined use of erlotinib and bevacizumab to treat NSCLC. Keywords were "Non-Small Cell Lung Cancer" [MeSH], "Carcinoma, Non-Small Cell Lung," "Lung Carcinoma, Non-Small-Cell," "Erlotinib" [MeSH], "Hydrochloride, Erlotinib," "Gefitinib"

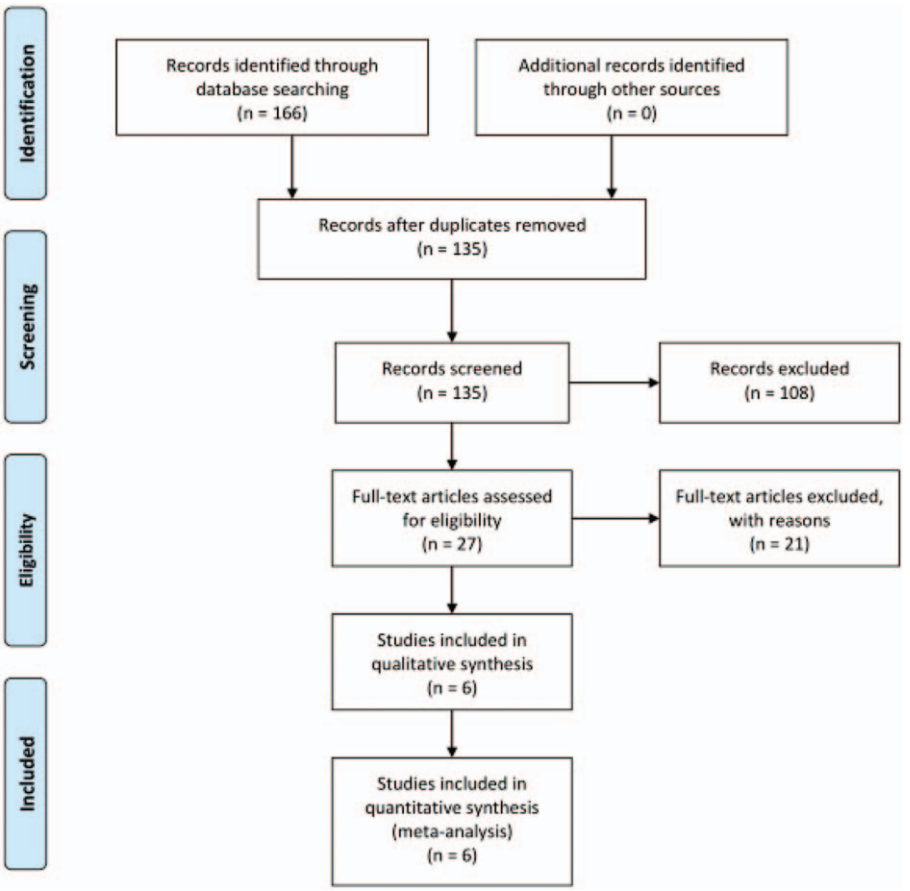


Figure 1. Flowchart of literature retrieval and selection.

[MeSH], and "Iressa." All references in the relevant articles were manually reviewed for appropriate studies.

2.3. Inclusion and exclusion criteria

Inclusion criteria for literature retrieval included:

1. patients aged 18 years or older;
2. histologically or cytologically confirmed NSCLC;
3. assessment of erlotinib vs erlotinib combined with bevacizumab, or bevacizumab vs erlotinib combined with bevacizumab;
4. RCTs; (5) data on OS, PFS, or ORR, and incidence of adverse events.

Exclusion criteria included:

1. animal or cadaver studies;
2. studies without extractable or valid data;
3. comments and conference papers without full text;
4. systematic reviews, meta-analyses, case reports, and retrospective studies.

2.4. Data extraction

Two researchers independently extracted baseline data from RCTs that met the inclusion criteria, including: study date, number of patients, sex ratio, ethnicity, smoking history, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score, histology, clinical stage, regional therapy, lines of therapy, and outcome measures. Any discrepancies were resolved through discussions with a third researcher. Researchers requested original data or relevant information from study authors via email if data were unavailable in the paper.

2.5. Quality assessment

Risks of bias among the included studies were assessed using the Cochrane Intervention System Review Manual,[19] including random sequence generation, allocation concealment, double blinding of researchers and participants, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each study was qualified as high, low, or unclear risk of bias.[20]

2.6. Outcome measures

Primary outcome variables were

1. OS (time from randomization to death, considered as the best therapeutic endpoint in cancer clinical trials),
2. PFS (time from randomization to tumor progression or death),
3. ORR (proportion of patients whose symptoms were relieved to a predetermined value within the minimum time limit), and
4. PFS in patient subgroups.

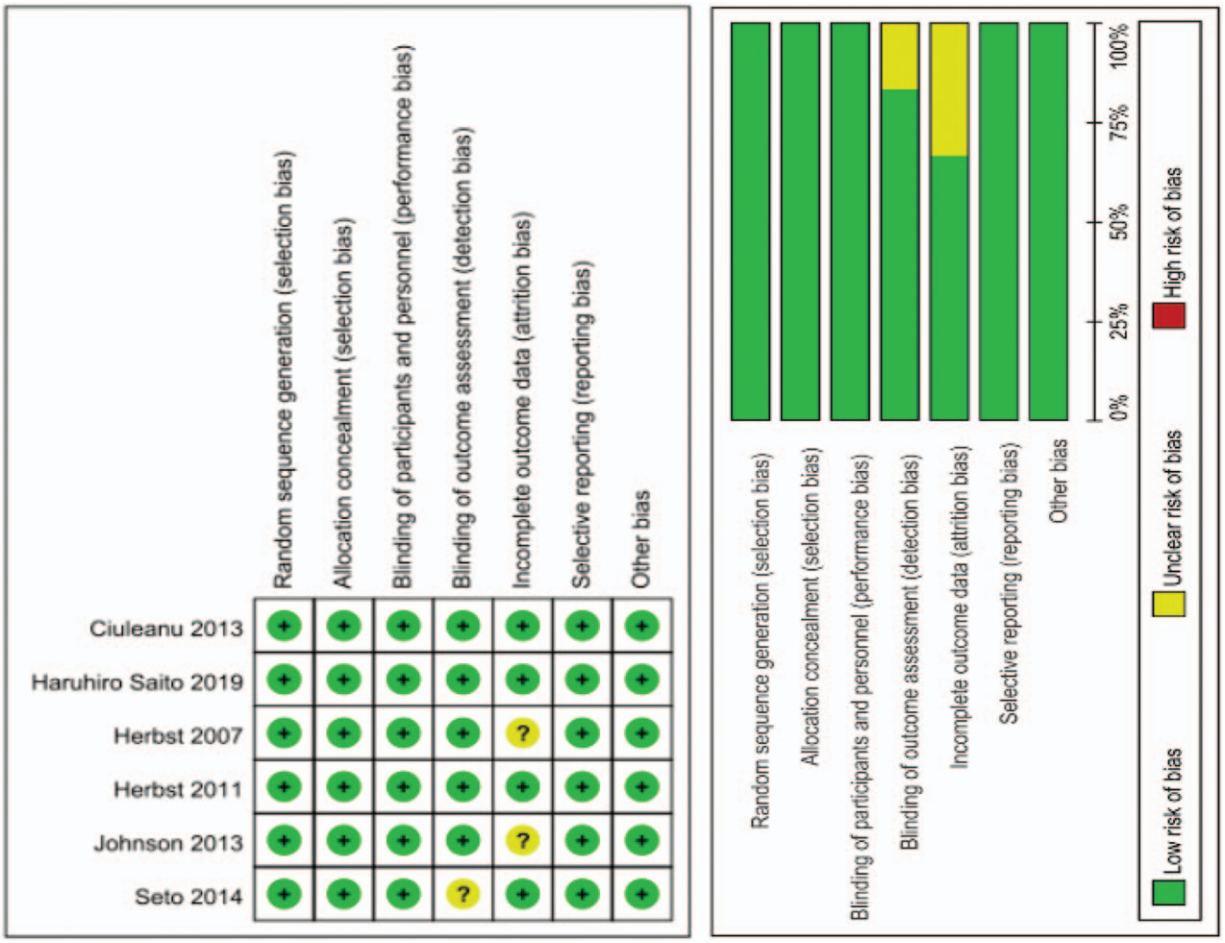


Figure 2. Methodological quality of studies included in meta-analysis.

Table 1

Summary of studies included in the final meta-analysis.

Author	Year	Group	Number	Male/ Female	Race (White/ Asian or Pacific Island/Other)	Smoking history (Never/previous/ current)	ECOGPS (0/1/2)	Histology (large-cell carcinoma/ adeno-carcinoma/ squamous/other)	Clinical stage (IIIB/IV/Other)	Region	Line of treatment
Herbst et al[26]	2007	B+E	39	17/22	29/3/7	NR	19/20/0	0/32/0/7	NR	USA	Second
		B+chemo	40	23/17	34/2/4	NR	19/21/0	9/30/0/1	NR		
Herbst et al[21]	2011	B+E	319	171/148	264/23/32	34/237/48	129/166/23	23/242/11/43/38	NR	USA	Second
		E+placebo	317	170/147	257/18/42	33/212/72	121/176/20	25/235/14/40	NR		
Ciuleanu et al[25]	2013	B+E	63	37/26	NR	21/20/11	28/35/0	NR	NR	Romania	First
		B+gem	61	36/25	NR	23/14/24	20/41/0	NR	NR		
Johnson et al[22]	2013	B+E	370	193/177	293/43/34	61/180/129	180/190/0	30/301/11/28	32/317/21	USA	Second
		B+placebo	373	196/177	290/45/38	66/178/129	173/198/1	26/309/6/32	37/310/25		
Seto et al[23]	2014	B+E	75	30/45	NR	42/9/24	43/32/0	0/74/1/0	1/60/14	Japan	First
		E	77	26/51	NR	45/6/26	41/36/0	1/76/0/0	0/62/15		
Saito et al[24]	2019	B+E	112	41/71	NR	65/6/41	64/48/0	1/110/0/1	8/82/22	Japan	First
		E	112	39/73	NR	64/7/41	68/42/2	0/112/0/0	8/84/20		

B = bevacizumab; chemo = chemotherapy; E = erlotinib; gem = gemcitabine; NR = not reported.

Analyses aimed to determine whether combination therapy increased these variables compared with monotherapy. Specifically, subgroup analyses were performed to determine the effects of age (>65 or ≤65 years),[21–24] disease stage (IIIB, IV, and other stages),[22–24] ethnicity (Caucasian, Asian, or Pacific Islanders),[21,22] ECOG-PS score (PS0, PS1, or PS2),[21–24] sex (male or female),[21–24] smoking history (none, currently smoking, or former smokers),[21–24] medical history, pathological classification (large cell carcinoma, adenocarcinoma, squamous cell carcinoma, and other diseases),[21–23] and EGFR mutation (Exon19 deletion, Exon21 Leu858Arg mutation, EGFR FISH-positive, EGFR-FISH negative, and EGFR wild type),[21,23–25] and adverse events (rash, diarrhea, hypertension, and bleeding) on PFS. Adverse events were rated as levels 1–2 and levels 3–5 (serious) according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events (version 3.0).[26]

2.7. Statistical analysis

Statistical analysis was performed in Stata Version 11.0 and Review Manager (Revman) Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was assessed by the Chi-Squared test.[27] If significant heterogeneity was detected ($I^2 > 50\%$ or $P < .1$),[28] a random-effects model was used; otherwise, a fixed-effect model was used. Significance was set at $P < .05$. Time-event variables, including OS and PFS, were assessed according to the hazard ratio (HR). Dichotomous variables, including ORR and incidence of adverse events, were assessed as risk ratios (RR) with 95% confidence interval (CI) estimates. Hypothetical test results for each variable were listed in a forest map. For outcome indicators with significant heterogeneity, a sensitivity analysis was performed, eliminating the included studies 1 at a time to determine the source of heterogeneity. Subgroup analyses were performed on factors that could influence PFS, i.e., age, ethnicity, sex, ECOG, and smoking history. If outcome measures of >10 primary documents, the funnel figure shall be used for publication bias test. And the publication bias test was performed using Egger test, when outcome measures of >20 primary documents.

3. Results

3.1. Literature retrieval

We retrieved 166 studies from the 4 databases that fit our initial inclusion criteria, then excluded 31 duplicate studies and 108 ineligible studies. Of the remaining 27 articles, reviews, meta-

Table 2

Number of patients with different epidermal growth factor receptor mutation status.

			EGFR mutation status				EGFR FISH status		EGFR IHC status	
Study	Year	Grouping	Mutant	Wild type	Exon 19 deletion	Exon21 Leu858Arg mutation	Positive	Negative	Positive	Negative
Herbst et al	2007	B+E	1	8						
		B or E	0	13						
Herbst et al	2011	B+E	12	173			33	69	135	49
		B or E	18	152			43	59	119	42
Ciuleanu et al	2013	B+E	2	19			12	7	15	4
		B or E	0	11			6	5	5	5
Seto et al	2014	B+E			40	35				
		B or E			40	37				
Saito et al	2019	B+E			28	24				
		B or E			32	33				

B = bevacizumab; E = erlotinib; EGFR = epidermal growth factor receptor; FISH = fluorescent in situ hybridization; IHC = immunohistochemistry.

Table 3

Incidence of level 1–2 adverse events in 2 studies.

Year	Seto et al 2014		Saito et al 2019	
N	75	77	112	112
Group	B+E	E	B+E	E
Rash	55	61	75	75
Diarrhea	60	59	47	45
Hemorrhage	52	22	27	2
Paronychia	55	47	15	15
Hypertension	12	2	26	10
Fatigue	9	3		

B = bevacizumab; E = erlotinib.

analysis, and topic-independent studies were excluded. The final meta-analysis thus used 6 studies (Fig. 1). Evaluation of the quality of the reports is shown in Figure 2.

3.2. Study characteristics

The 6 included studies[21–26] involved 1960 participants and were published from October 2007 to April 2019 (Table 1). Four studies[21,23,24,26] compared erlotinib with combination therapy, and 2 studies[22,25] compared bevacizumab with combination therapy. Three studies[23–25] explored the role of erlotinib +bevacizumab as first-line therapy, while others[21,22,26] focused on second-line therapy. Three studies[22–24] provided data on disease stage (IIIB, IV, and other stages). Five studies[21,23–26] described EGFR status, and 2[28,29] elaborated on the specific EGFR mutation detected (Exon19 deletion or Exon21 Leu858Arg mutation) (Table 2). Tables 3 to 5 summarizes the different levels of adverse events.

3.3. Outcome measures

3.3.1. OS. Four studies[21,22,25,26] reported OS. We selected the fixed-effects model because heterogeneity was low ($I^2 = 0\%$). Combination therapy as either first-line or second-line treatment did not significantly improve OS (HR = 1.24, 95% CI = 0.75–2.05, $P = .40$; HR = 0.94, 95% CI = 0.81–1.10, $P = .44$) (Fig. 3A).

3.3.2. PFS. All 6 studies reported PFS. The study by Ciuleanu et al[22] resulted in significant heterogeneity ($I^2 = 64.1\%$) and was removed after sensitivity analysis. Removal reduced I^2 to 0%, allowing the use of a fixed-effects model. Compared with erlotinib or bevacizumab alone, first-line and second-line combination therapy prolonged PFS (HR = 0.62, 95% CI = 0.46–0.85, $P < .01$; HR = 0.65, 95% CI = 0.58–0.74, $P < .01$) (Fig. 3B).

Table 4

Incidence of serious adverse events in all studies.

Year	Herbst 2007		Herbst 2011		Ciuleanu 2013		Johnson 2013		Seto 2014		Saito 2019	
N	39	40	319	317	63	61	370	373	75	77	112	112
Group	B+E	B	B+E	E	B+E	B	B+E	B	B+E	E	B+E	E
Rash	1	0	19	49	31	6	25	2	19	15	23	24
Hypertension	1	2	4	15	9	7	23	22	45	8	26	1
Diarrhea	3	0			20	12	36	7	1	1	6	2
Hemorrhage			7	8					2	0	2	1
Paronychia					6	1			2	3	2	3
Neutropenia	2	8			0	21						
Fatigue	3	5			5	9			1	0		
Nausea	2	2			10	31						
Vomiting	0	2			5	18						
Dyspnea	2	4			9	6						

B = bevacizumab; E = erlotinib.

Table 5

Incidence of overall adverse events in four studies.

Year	Herbst et al 2007		Johnson et al 2013		Seto et al 2014		Saito et al 2019	
No.	39	40	370	373	75	77	112	112
Group	B+E	B	B+E	B	B+E	E	B+E	E
Rash	26	5	231	82	74	76	98	99
Diarrhea	29	17	190	73	61	60	53	47
Hypertension	8	6	88	85	57	10	52	11
Hemorrhage			60	60	54	22	2	0
Paronychia					57	50		
Fatigue	25	26						
Nausea	18	15						
Vomiting	8	10						

B = bevacizumab; E = erlotinib.

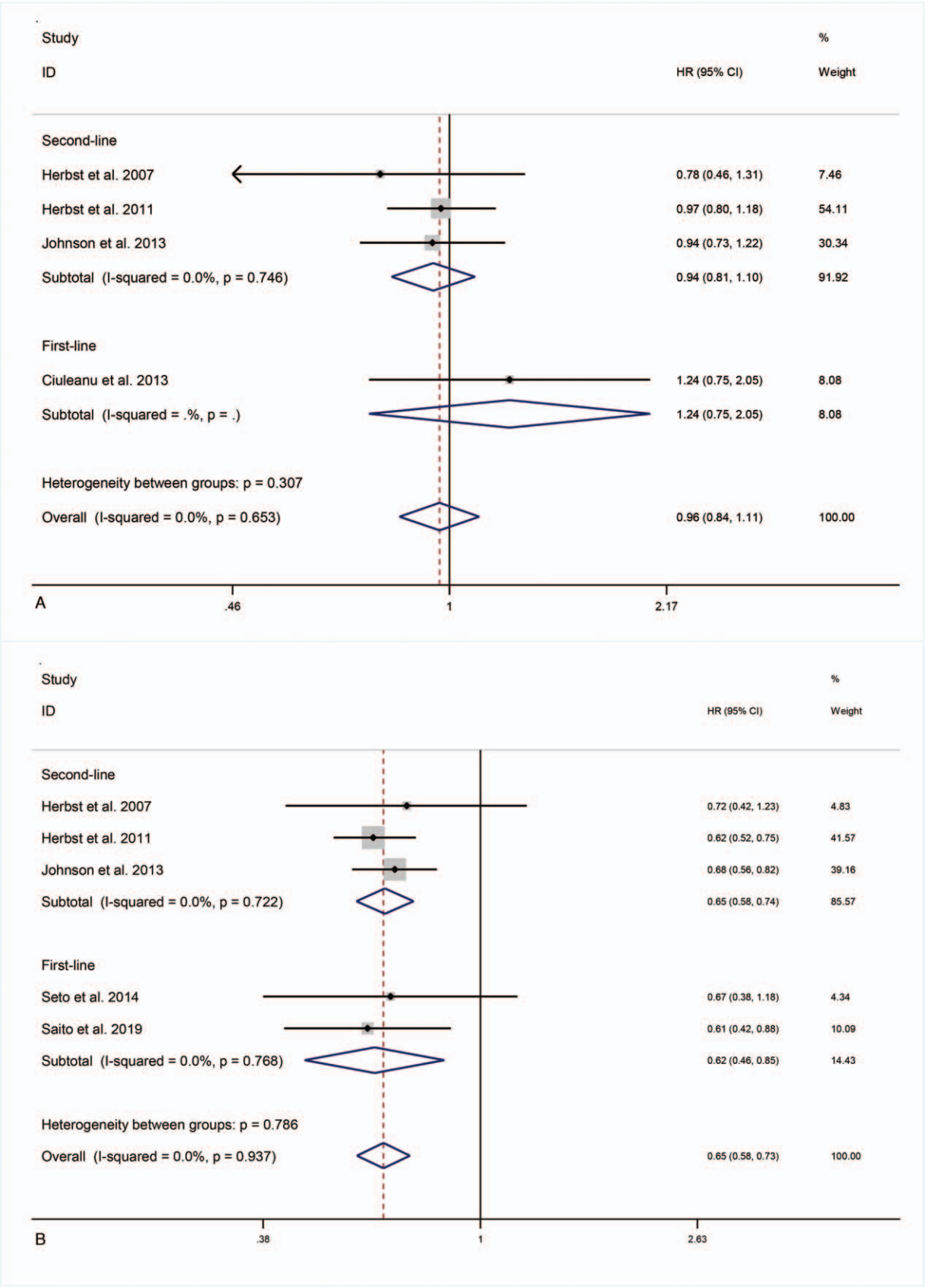


Figure 3. OS, PFS or ORR for combination therapy of bevacizumab plus erlotinib with bevacizumab or erlotinib alone.

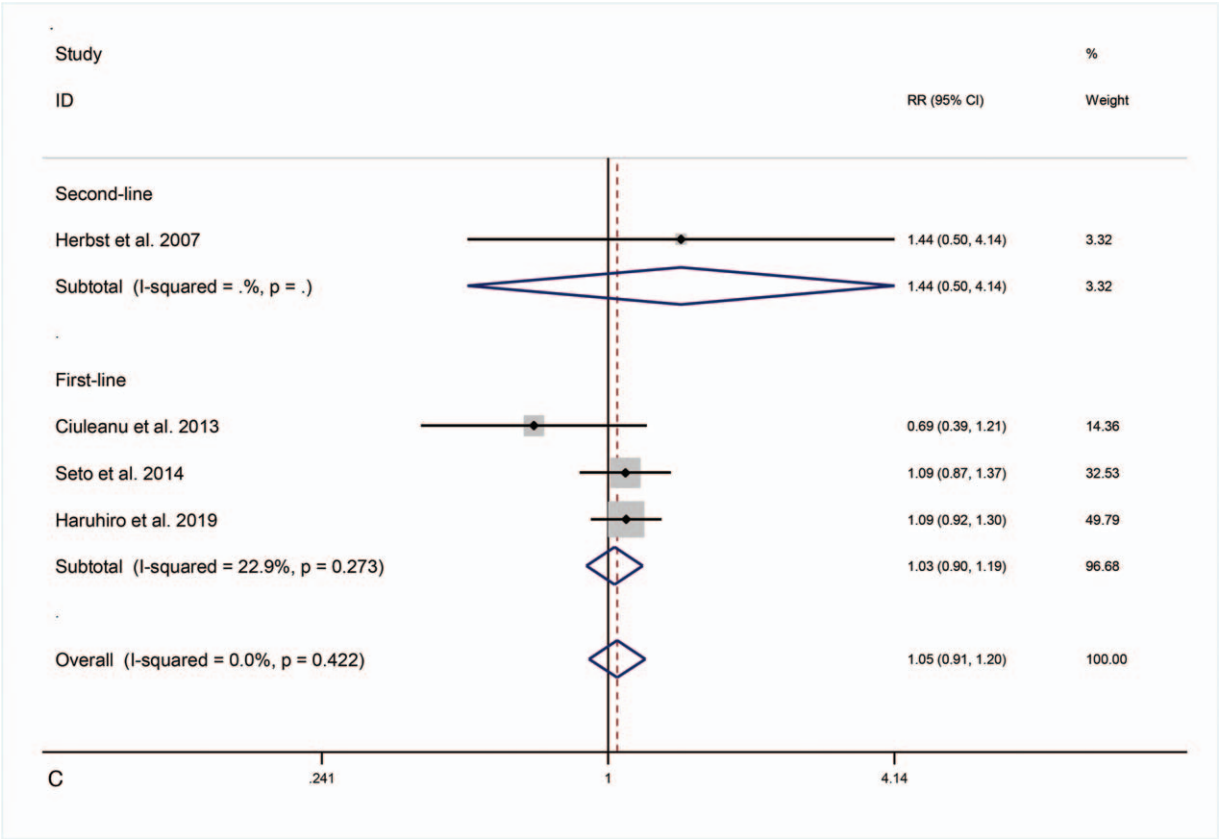


Figure 3. (continued).

3.3.3. ORR. Five studies[21,23–26] reported ORR. The study by Herbst et al[21] led to $I^2=72\%$ and was removed after sensitivity analysis, reducing I^2 to 0%. The fixed-effects model revealed that compared with erlotinib or bevacizumab alone, first-line and second-line combination therapy did not elevate ORR (RR = 1.03, 95% CI = 0.90–1.19, $P=.65$; RR = 1.44, 95% CI = 0.50–4.14, $P=.50$) (Fig. 3C).

3.3.4. PFS in subgroup analyses. Three studies[22–24] reported subgroup data for disease staging. Compared with monotherapy, combination therapy significantly prolonged PFS in patients with stage IIIB disease (HR = 0.59, 95% CI = 0.42–0.84; $P<.01$), stage IV disease (HR = 0.69, 95% CI = 0.58–0.81; $P<.001$), and at other stages (HR = 0.47, 95% CI = 0.26–0.83; $P=.01$) (Fig. 4A).

Four studies[21–24] reported subgroup data for age. Combination therapy extended PFS in patients <65 and ≥65 years old (HR = 0.73, 95% CI = 0.62–0.85, $P<.001$; HR = 0.79, 95% CI = 0.66–0.95, $P=.01$) (Fig. 4B).

Two studies[21,22] reported subgroup data for ethnicity. Combination therapy did not significantly prolong PFS in Caucasian or Asian and Pacific Islander patients (HR = 0.70, 95% CI = 0.25–1.99, $P=.51$; HR = 0.41, 95% CI = 0.10–1.63, $P=.21$) (Fig. 4C).

Four studies[21–24] reported subgroup data for ECOG-PS. Combination therapy significantly improved PFS in patients with ECOG-PS0 (HR = 0.75, 95% CI = 0.61–0.91; $P<.01$) and ECOG-PS1 (HR = 0.78, 95% CI = 0.67–0.91; $P<.01$), but had no significant effect on patients with ECOG-PS2 (HR = 0.92, 95% CI = 0.45–1.87; $P=.82$) (Fig. 4D).

Four studies[21–24] reported subgroup data for sex. Combination therapy did not significantly prolong PFS in male patients but did in female patients (HR = 0.76, 95% CI = 0.54–1.06, $P=.10$; HR = 0.69, 95% CI = 0.49–0.96, $P=.03$) (Fig. 4E).

Four studies[21–24] reported subgroup data for smoking. Combination therapy significantly prolonged PFS in patients with no smoking history (HR = 0.50, 95% CI = 0.38–0.66, $P<.001$), but not in those currently smoking or former smokers (HR = 0.72, 95% CI = 0.49–1.06, $P=.19$; HR = 0.87, 95% CI = 0.66–1.15, $P=.33$) (Fig. 4F).

Three studies[21–23] reported subgroup data for pathological typing. Combination therapy did not significantly prolong PFS in patients with large cell carcinoma (HR = 0.70, 95% CI = 0.43–1.13; $P=.15$), squamous cell carcinoma (HR = 1.01, 95% CI = 0.48–2.12; $P=.98$), or other diseases (HR = 0.88, 95% CI = 0.58–1.33; $P=.54$), but significantly prolonged PFS in patients with adenocarcinoma (HR = 0.78, 95%CI = 0.67–0.90; $P<.01$) (Fig. 4G).

Four studies[21,23–25] reported subgroup data for EGFR mutations. Combination therapy significantly prolonged PFS in patients with EGFR Exon19 deletion and Exon21 Leu858Arg mutation (HR = 0.54, 95% CI = 0.32–0.89, $P=.02$; HR = 0.62,

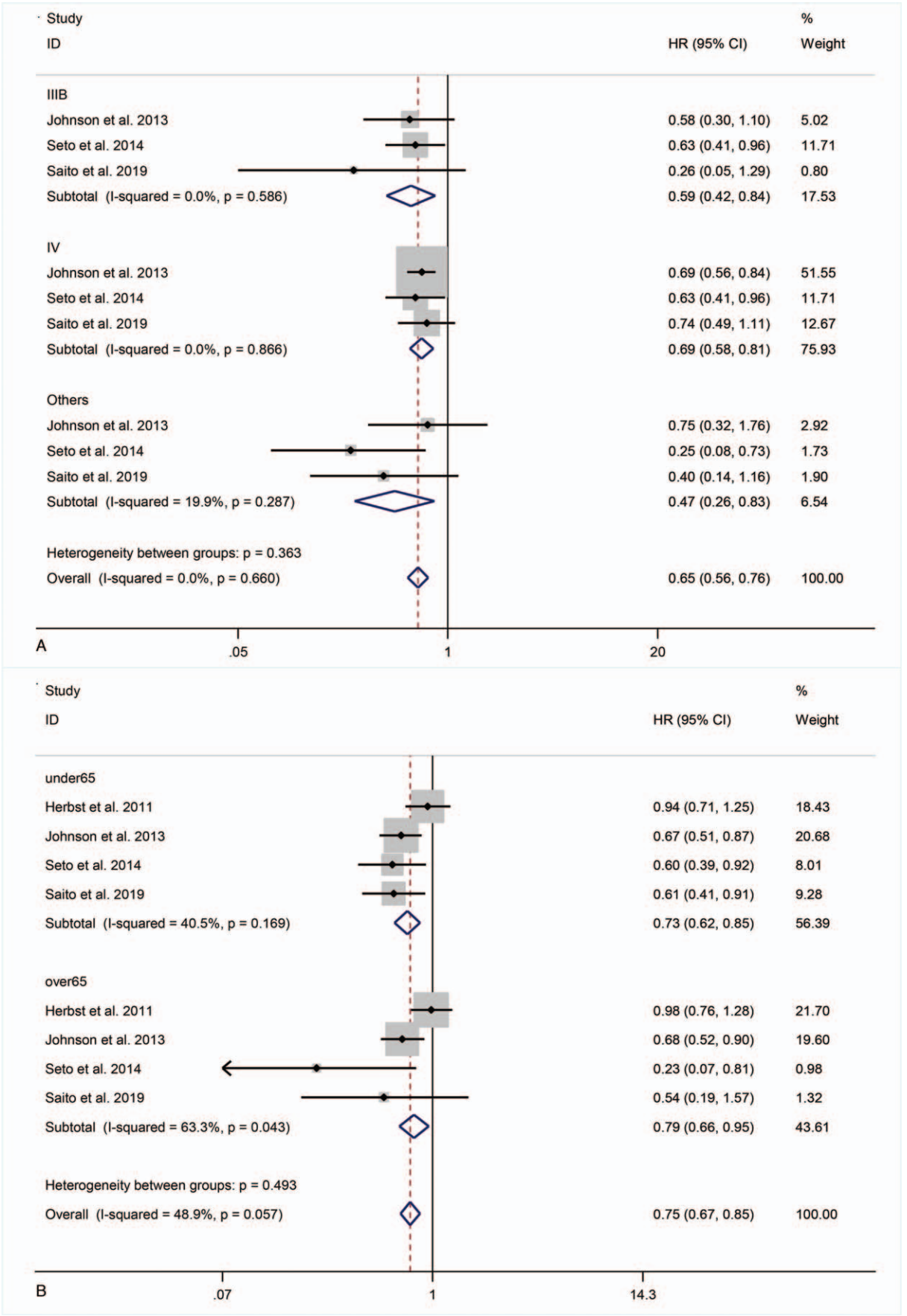
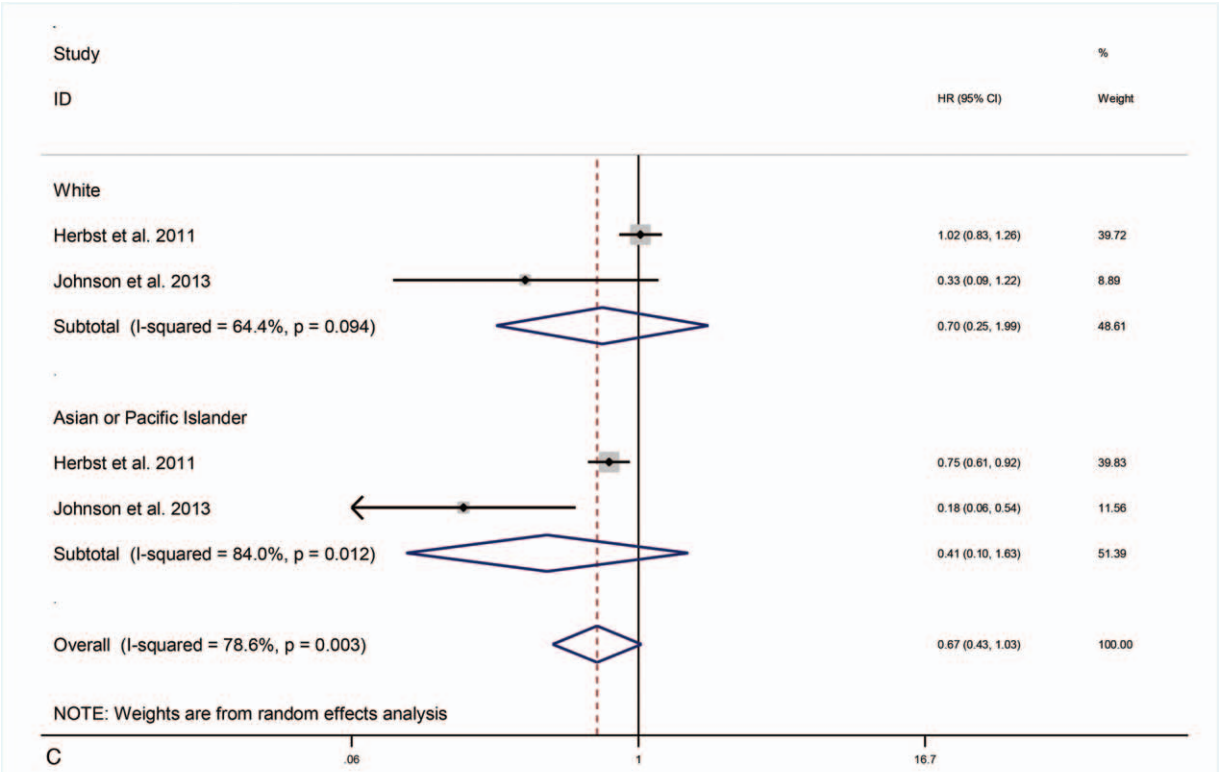
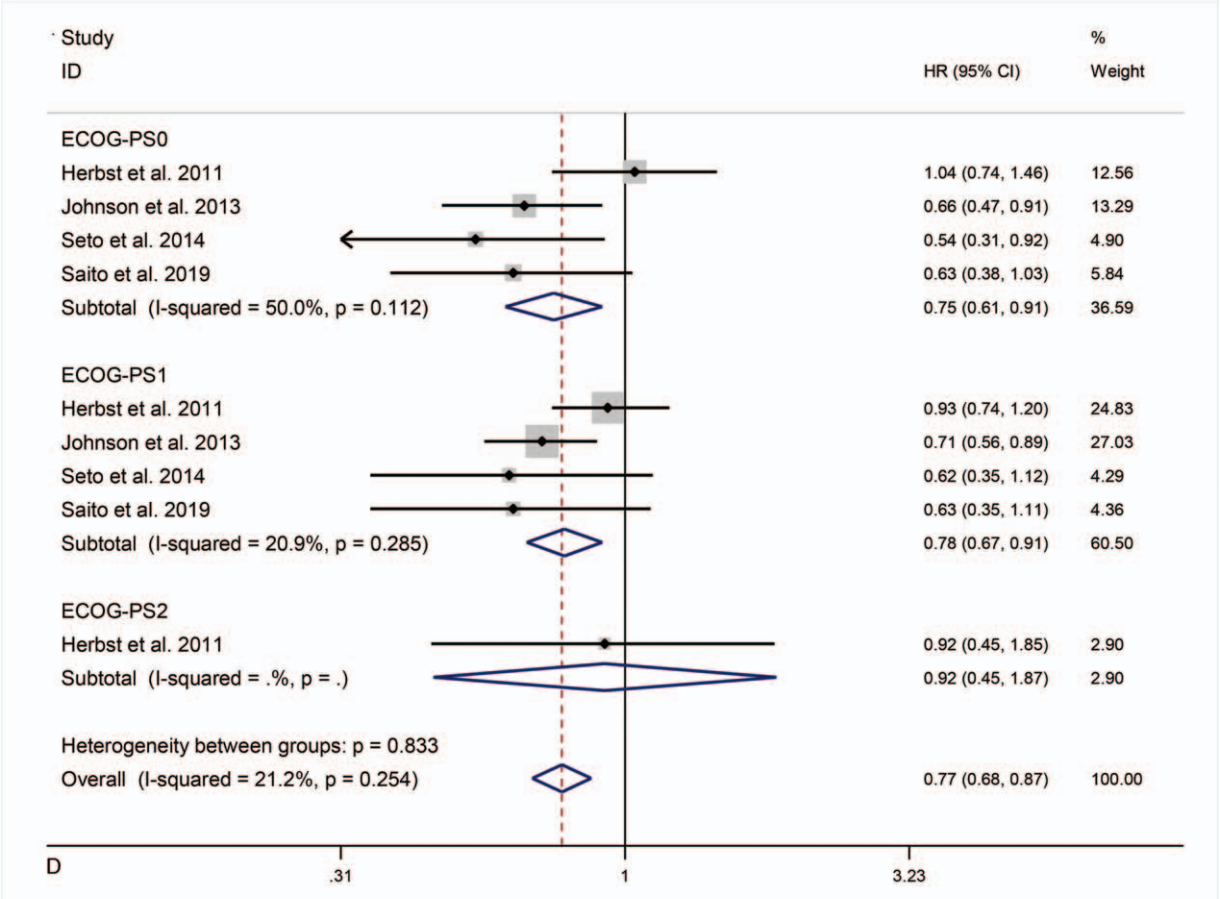


Figure 4. PFS in subgroup analyses.





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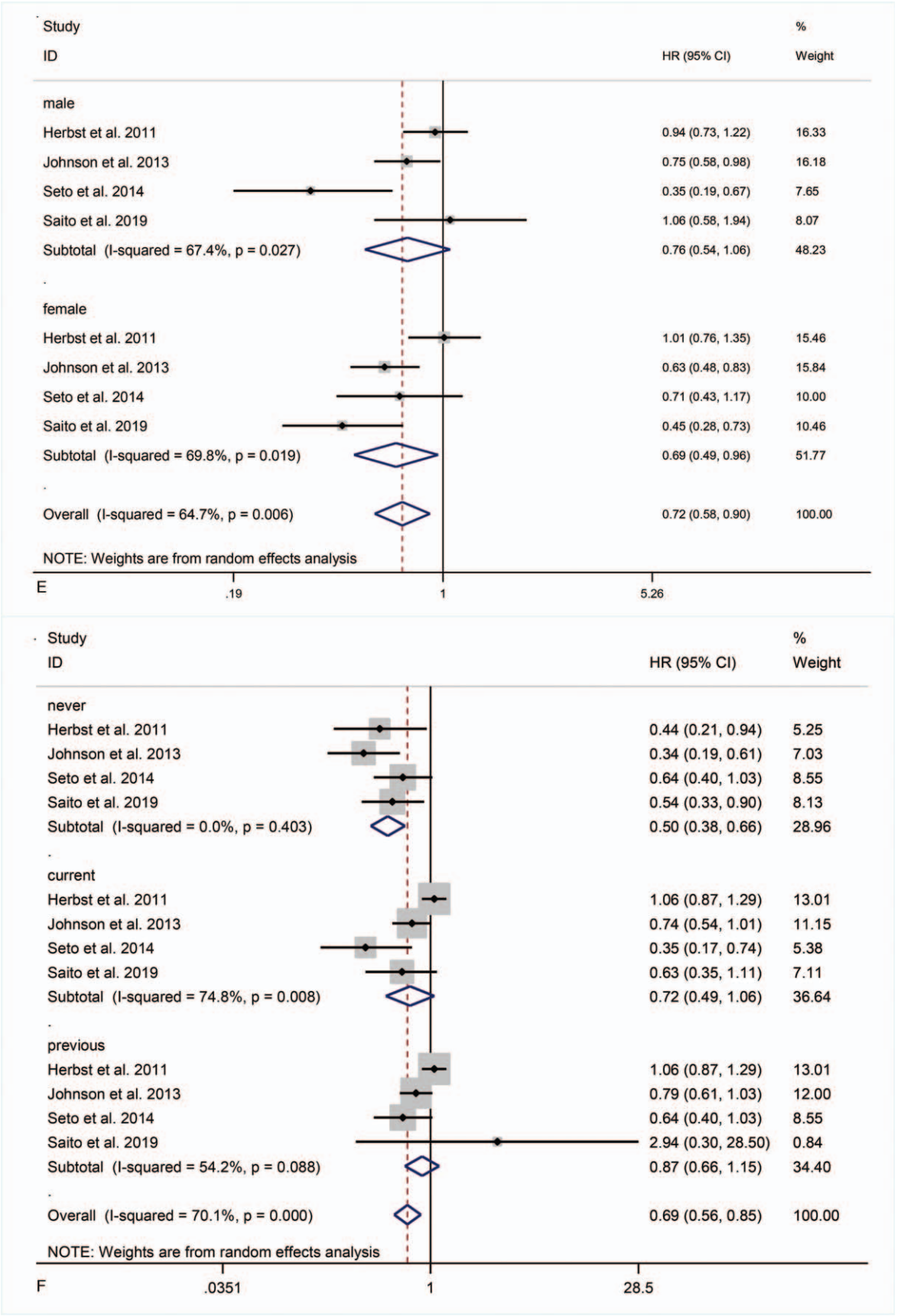

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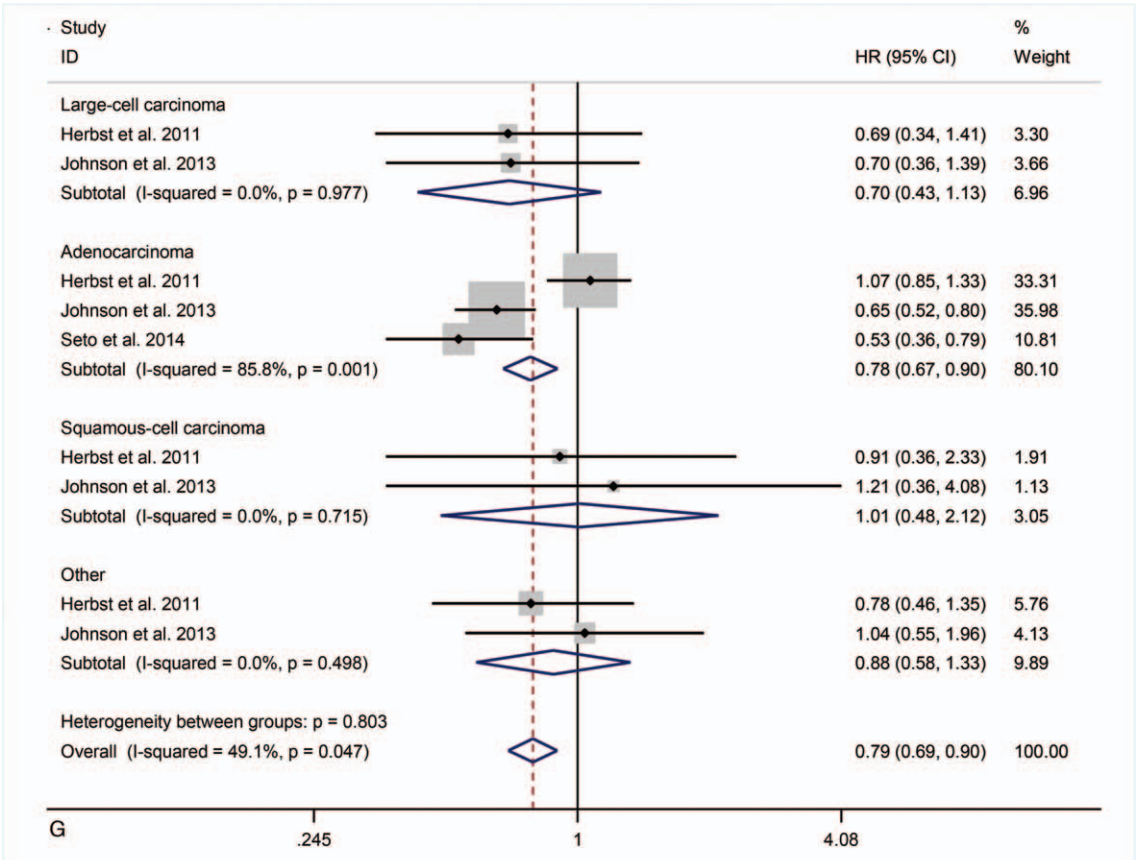

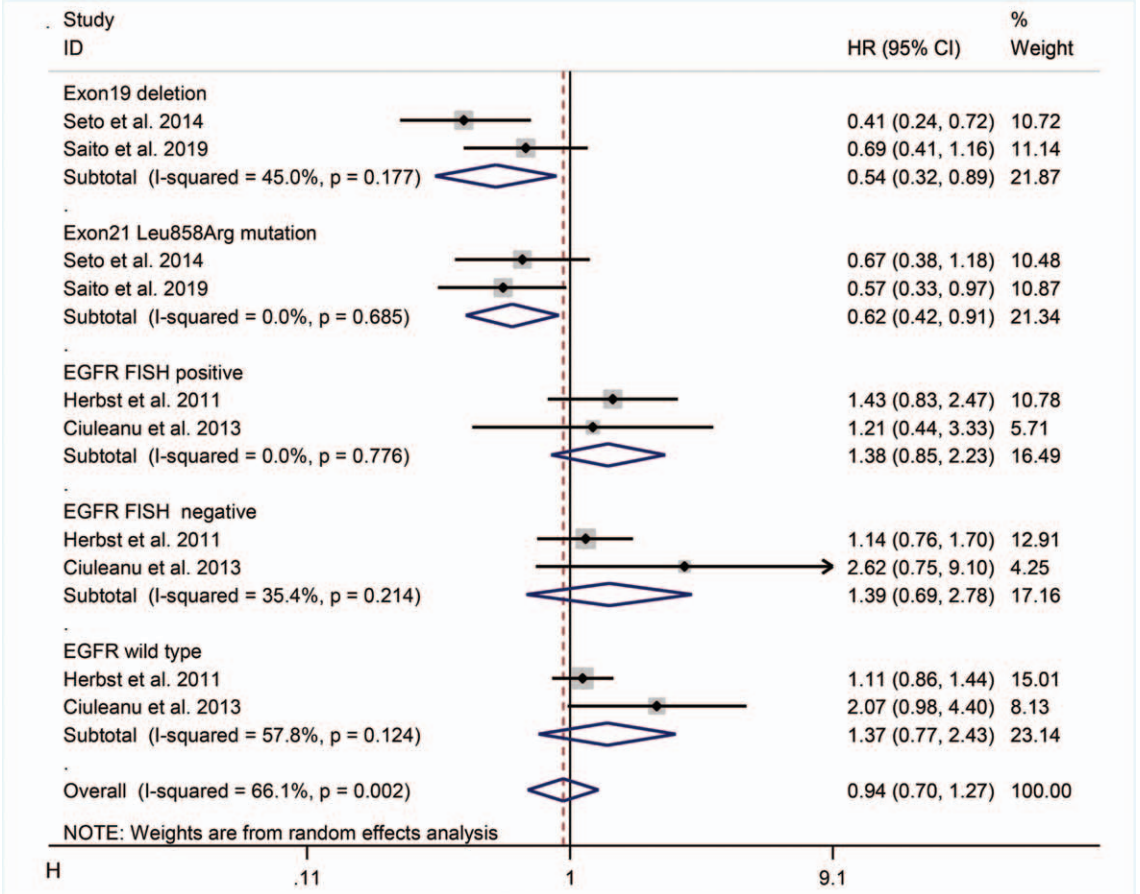

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95% CI=0.42–0.91, *P*=.02), but did not do so in patients with EGFR FISH-positive (HR=1.38, 95% CI=0.85–2.23; *P*=.20), EGFR FISH-negative (HR=1.39, 95% CI=0.69–2.78; *P*=.35), or EGFR wild-type (HR=1.37, 95% CI=0.77–2.43; *P*=.29) tumors (Fig. 4H).

3.3.5. Adverse events. Patients who received monotherapy vs combined bevacizumab+erlotinib did not significantly differ in incidence of rash (72% vs 43.5%, 95% CI=1.51–1.82; *P*=.21), diarrhea (55.9% vs 32.7%, 95% CI=0.88–2.63; *P*=.13), hypertension (34.4% vs 18.6%, 95% CI=0.90–6.98; *P*=.08), or hemorrhage (20.8% vs 14.6%, 95% CI=0.73–4.01; *P*=.21) (Fig. 5A).

Monotherapy and combined therapy groups did not differ significantly in levels 1–2 adverse events of rash (69.5% vs 72%, 95% CI=0.85–1.09; *P*=.54), diarrhea (57.2% vs 55%, 95% CI=0.90–1.21, *P*=.13), hemorrhage (42.2% vs 12.7%, 95% CI=0.81–32.39, *P*=.08), or paronychia (37.4% vs 32.8%, 95% CI=0.95–1.46, *P*=.13), but differed significantly in hypertension incidence (20.3% vs 6.3%, 95% CI=1.73–5.88, *P*=.001) (Fig. 5B). For severe adverse events, the 2 groups differed significantly in diarrhea incidence (10% vs 3.2%, 95% CI=1.36–6.60; *P*=.01), but not in incidence of rash (12.1% vs 9.8%, 95% CI=0.70–4.57; *P*=.22), hypertension (11% vs 5.6%, 95% CI=0.55–4.94; *P*=.37), fatigue (5.1% vs 7.9%, 95% CI=0.28–1.40; *P*=.25), paronychia (4% vs 1.6%, 95% CI=0.48–9.93; *P*=.31), or hemorrhage (2.2% vs 1.6%, 95% CI=0.45–3.89; *P*=.61) (Fig. 5C).

4. Discussion

4.1. Findings and interpretations

Our meta-analysis indicates that compared with monotherapy, erlotinib+bevacizumab combination therapy prolongs PFS of patients with NSCLC, but cannot extend OS or elevate ORR. Prolongation of PFS was not associated with disease stage, age, or ethnicity. However, female patients and those with ECOG-PS0 or

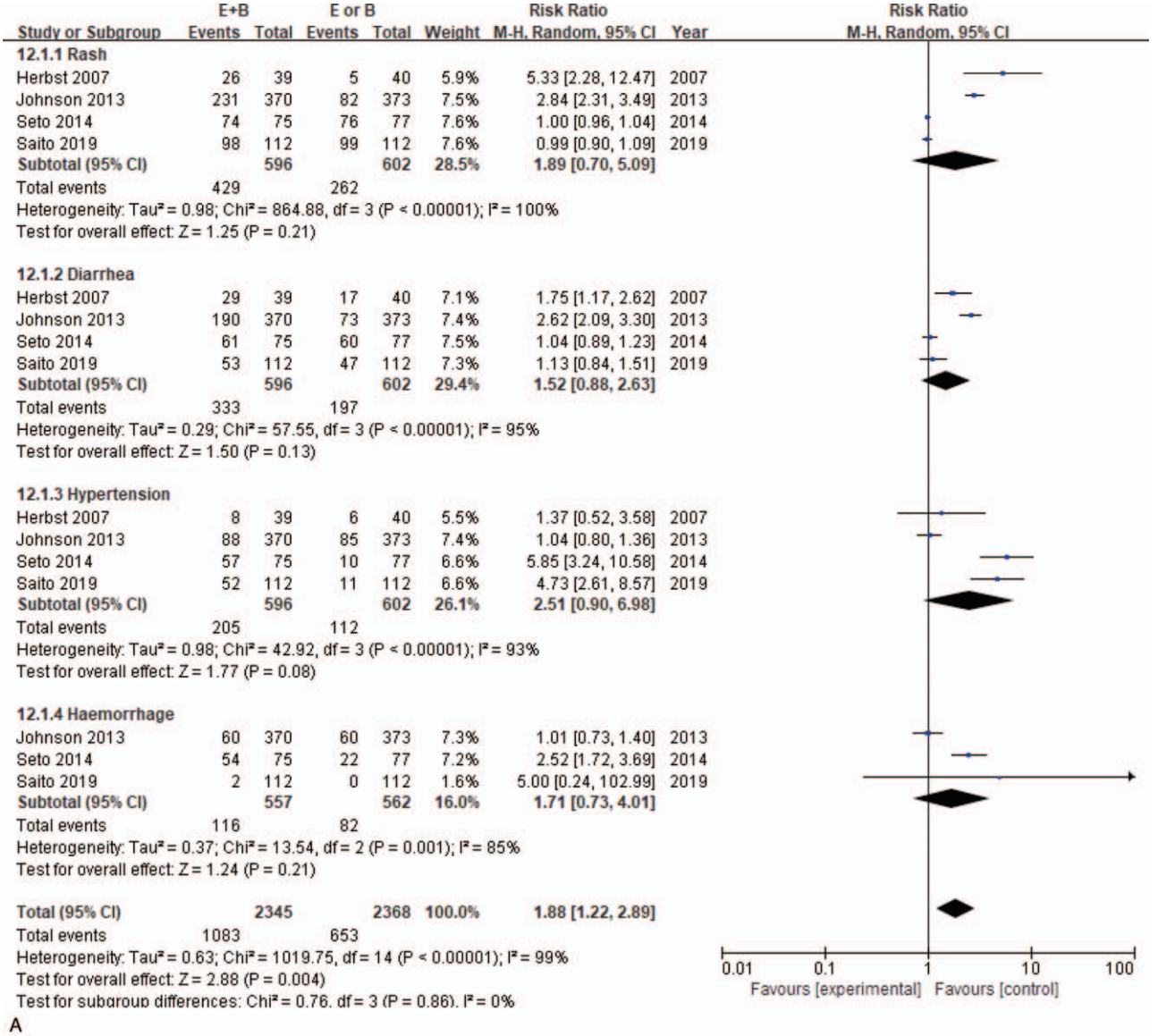

Figure 5. Adverse events for combination therapy of bevacizumab plus erlotinib with bevacizumab or erlotinib alone.

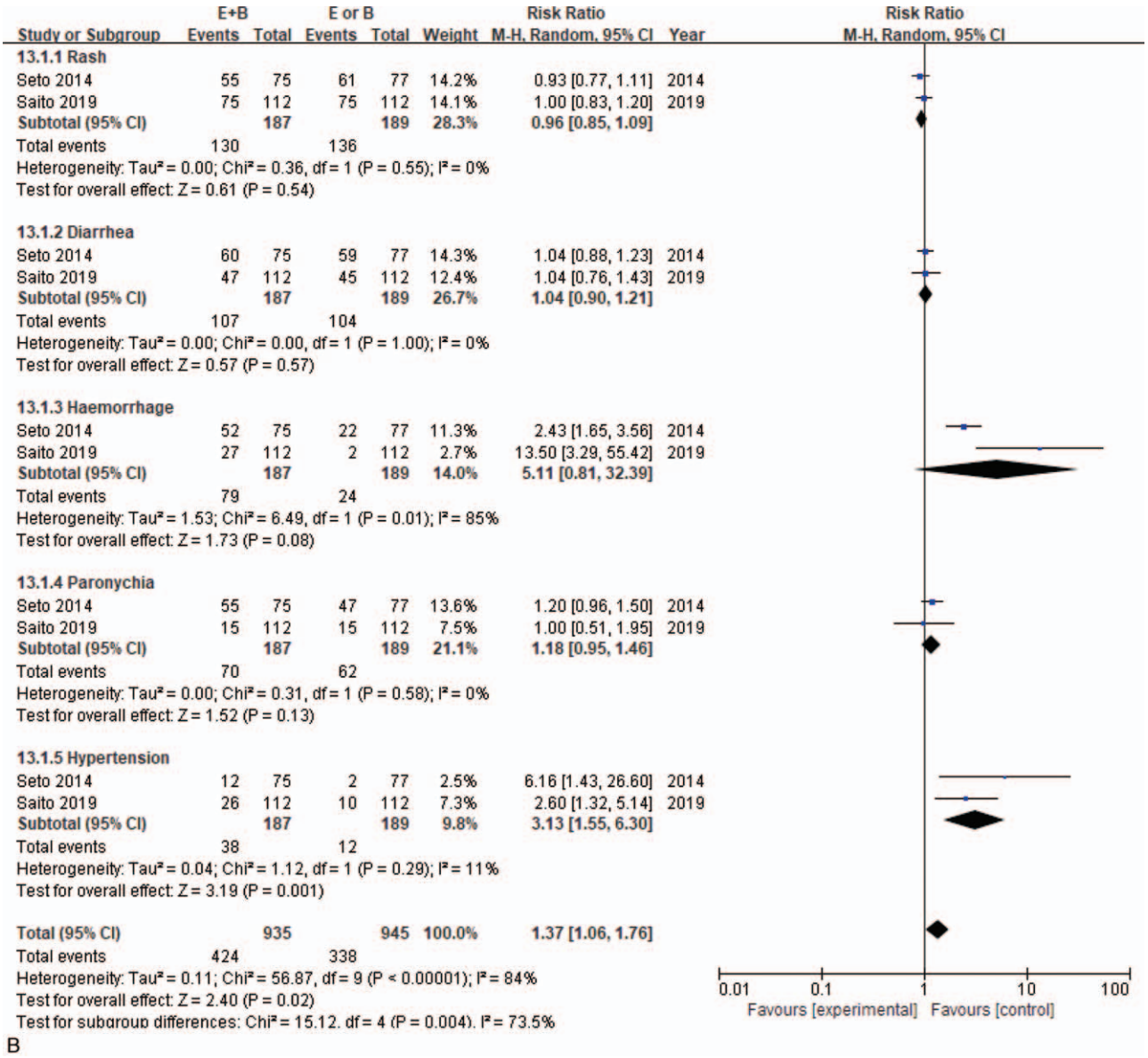

Figure 5. (continued).

ECOG-PS1, no smoking history, adenocarcinoma, EGFR Exon19 deletion, or Exon21 Leu858Arg mutation all experienced prolonged PFS under combination therapy. Moreover, combination therapy increased incidence of common complications, such as rash, diarrhea, hypertension, hemorrhage, and severe diarrhea in levels 1–2 adverse events.

This study provides new insight to help resolve existing controversies surrounding the combined use of erlotinib and bevacizumab for NSCLC treatment. Although we clearly demonstrated a benefit for PFS, the lack of an effect on OS requires further investigation. Our finding is similar to a previous meta-analysis, where the authors suggested that a low number of studies and small sample size resulted in limited statistical power to detect effects on OS.[17] However, although we increased sample size and merged data, we still found that combination therapy failed to prolong OS, indicating that sample size is not the issue. Moreover, combination therapy could not improve ORR, consistent with previous studies.[29–31] Heterogeneity was high in studies on ORR, largely due to the report by Herbst et al[21] Therefore, combination therapy might improve ORR with the use of a prespecified fixed sequence test.

We also detected high heterogeneity (stemming from Ciuleanu et al[25]) among studies evaluating PFS. The randomized follow-up design of Ciuleanu et al did not allow for effective evaluation in some patients. Previous studies have found that kinase plays an important role in normal and malignant biology,[32,33] chemotherapy can affect the therapeutic effects of EGFR and tyrosine kinase inhibitors,[34–37] resulting in a lower response rate.[38] Therefore, we also compared first- and second-line treatments, but neither influenced the beneficial effect of combination therapy on prolonging PFS.

Our stratification analysis indicated that combination therapy differentially affected certain patient subgroups but not others. Specifically, erlotinib+bevacizumab prolonged PFS regardless of disease stage, age, or ethnicity. Additionally, while combination

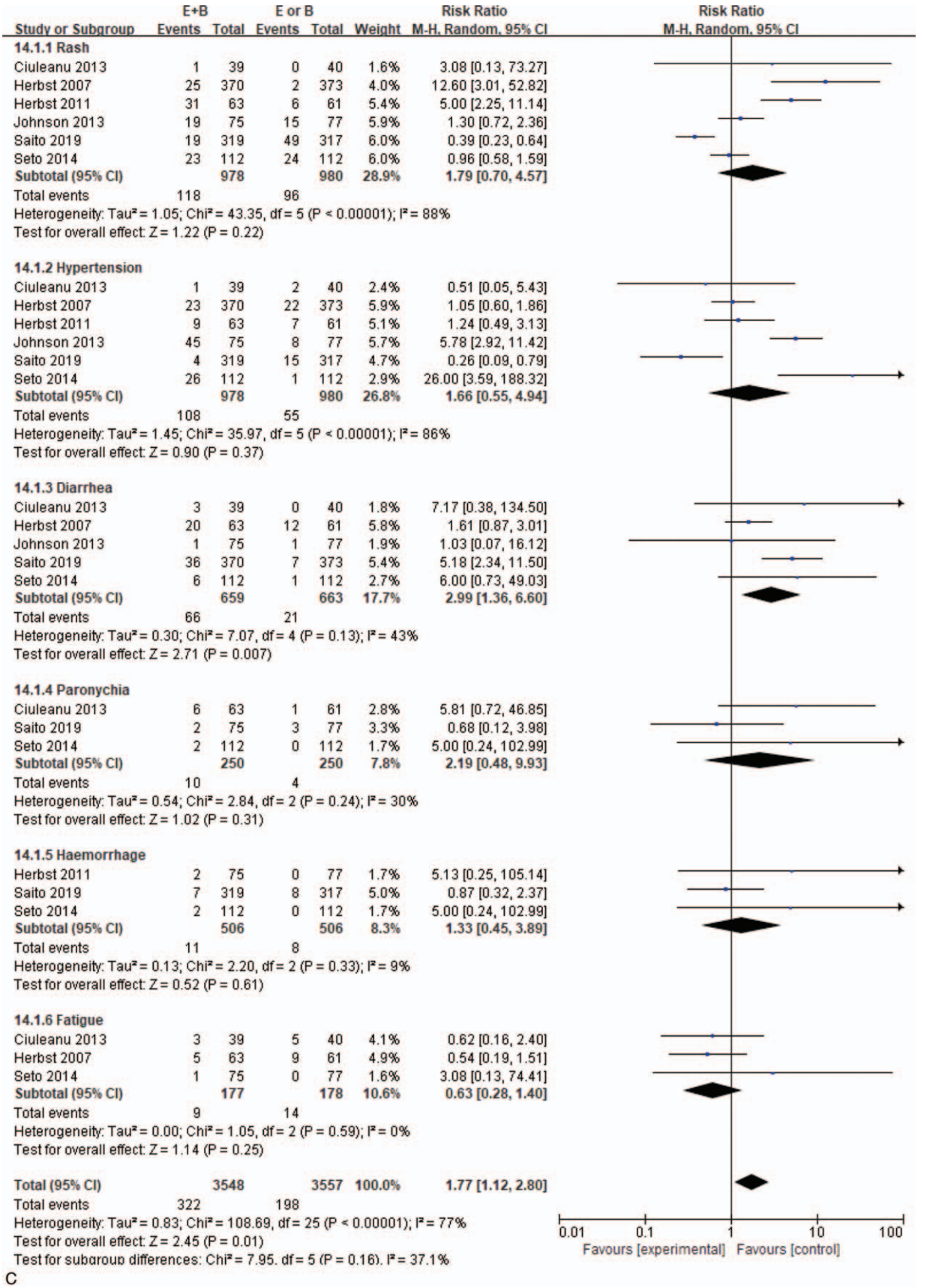

Figure 5. (continued).

therapy extended PFS in patients with ECOG-PS0 and ECOG-PS1, patients with ECOG-PS2 did not see such benefits. However, this result requires further verification because only one study reported patients with ECOG-PS2.[21] Combination therapy also improved PFS in female patients but not in male patients. Furthermore, patients who currently or formerly smoked did not see the same benefits from combination therapy as non-smokers. Patients would thus benefit from quitting smoking to increase the likelihood of a positive response to treatment. Combination therapy also appears to be appropriate for patients experiencing pathological NSCLC, as the outcomes were either beneficial or neutral; individuals with adenocarcinoma had significantly longer PFS under combination therapy than patients with other pathological NSCLC types. Previous studies[39–41] found that erlotinib was more effective in patients with the Exon19 deletion than in those with the Exon21 Leu858Arg mutation, similar to our results here. Combination therapy extended PFS in patients with EGFR gene mutations, but was not effective for patients with other mutations. Therefore, pre-therapy genetic testing is necessary to avoid unnecessary treatment while targeting those most likely to receive benefits.

Previous studies have suggested unsatisfactory outcomes after combination therapy, pointing to increased incidence of adverse events such as rash, diarrhea, hypertension, hemorrhage, paronychia, and fatigue.[15] In this study, combination therapy increased incidence of rash, diarrhea, hypertension, and bleeding. When we examined subgroups based on severity of adverse events, we found that combination therapy did not significantly increase level 1–2 rash, diarrhea, hemorrhage, and paronychia incidence, but significantly increased level 1–2 hypertension. Additionally, severe hypertension, rash, and paronychia were not significantly elevated, while severe diarrhea was. These outcomes suggest that combination therapy only increases minor adverse events that can be treated with proper control of patient blood pressure and administration of antidiarrheal drugs. However, we note the importance of considering differences in individual responses to combined drugs. We should also consider the costs of combination therapy vs monotherapy when assessing treatment appropriateness, with the aim of minimizing medical waste.

4.2. Strengths and limitations

The main strengths of this study are that we performed a comprehensive database and literature search, including recent studies that had not been considered in previous meta-analyses. Moreover, we performed a detailed stratification analysis of subgroups and adverse events, allowing a detailed examination of factors contributing to variation in patient responses under combination therapy for NSCLC.

Nevertheless, our study has one major limitation: is a low number of available RCTs, resulting in an insufficient sample to evaluate different outcome measures. Therefore, high-quality RCTs with large sample sizes are necessary to verify our conclusions and to further explore the efficacy and adverse events of erlotinib+bevacizumab combination therapy.

5. Conclusions

Combining erlotinib and bevacizumab did not improve OS and ORR of patients with NSCLC but did prolong PFS. Subgroup analysis confirmed that combination therapy prolonged PFS without causing severe incurable complications in female patients, as well as those with ECOG-PS0 or ECOG-PS1, no smoking history, adenocarcinoma, and an EGFR Exon19 deletion or Exon21 Leu858Arg mutation. Therefore, we particularly recommend combination therapy for these patients. Our findings can help resolve existing controversies surrounding the benefits of erlotinib+bevacizumab therapy, thus further improving and personalizing patient selection for this treatment.

Author contributions

KZ searched the literatures, drew charts and wrote the article. SZ searched the literatures and drew charts. WG searched the literatures and revised the article. LD designed the experiment and provided guidance.

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