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Efficacy and safety of bevacizumab combined with EGFR-TKIs in advanced non-small cell lung cancer: A meta-analysis

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Abstract

Background: The aim of this study was to estimate the efficacy and safety of bevacizumab combined with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in advanced non-small cell lung cancer (NSCLC) patients.

Methods: We searched randomized controlled trials (RCTs) on bevacizumab combined with EGFR TKIs in the NSCLC Cochrane Library, Web of Science, PubMed and Embase. The data were extracted and assessed according to the Cochrane Handbook. We calculated the hazard ratio (HR), risk ratio (RR), and confidence interval (CI), and accomplished this meta-analysis with Stata 14 software.

Results: Of 1301 articles scanned, five articles were involved in this meta-analysis. We determined that compared with using EGFR TKIs alone, combination treatment significantly prolongs progression-free survival (PFS) (HR = 0.61, 95% CI = 0.52–0.70; $p < 0.001$), and increases the objective response rate (ORR) (RR = 1.15, 95% CI: 1.01–1.30, $p = 0.10$). However, there was no significant difference in overall survival (OS) between the two groups (HR = 0.95, 95% CI = 0.78–1.11; $p = <0.001$) and combination treatment increases the risks of serious adverse events (SAEs) (RR = 1.58, 95% CI: 1.21–2.05, $p = 0.002$).

Conclusions: Bevacizumab combined with EGFR-TKI significantly improves PFS and ORR in patients with advanced NSCLC, but there is no substantial difference in OS and increase the risks of serious adverse events.

KEYWORDS
bevacizumab, cancer, EGFR-TKI, meta-analysis, NSCLC

INTRODUCTION

The incidence of lung cancer is the highest in tumors worldwide. The total number of new cancer patients in China was reported to be about 3.94 million in 2015, of which 20% of patients had lung cancer.[1] More than 85% of lung cancer patients in the US have been diagnosed with NSCLC. Over 85% of lung cancer patients in the US have NSCLC. To make matters worse, 60% of patients with NSCLC are initially diagnosed with advanced cancer.[2] We have previously only had systemic cytotoxic chemotherapy for the treatment of cancer. The aim of chemotherapy is to kill cells that are growing or dividing, but unfortunately both malignant and normal cells will be killed during treatment. Improved treatments are

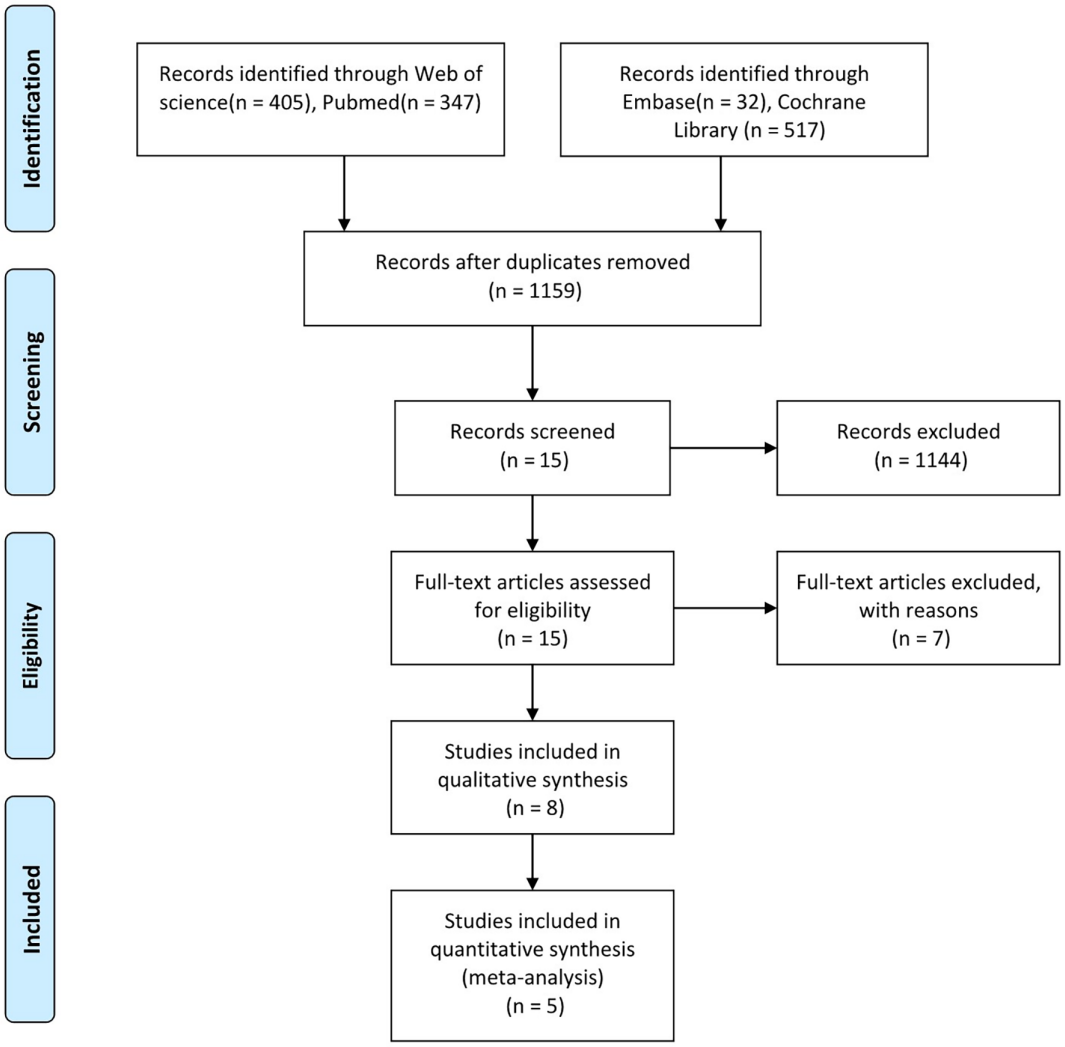

FIGURE 1 Flow diagram of the systematic review of efficacy and safety of bevacizumab combined with EGFR-TKI in advanced non-small cell lung cancer

therefore needed to kill malignant cells, but will also have the potential to identify and avoid destroying normal cells. Patients with NSCLC therefore need appropriate strategies to improve the efficacy with acceptable adverse events.

Research in the molecular pathogenesis of NSCLC have proved that NSCLC is a group of heterogeneous diseases. For specific driver mutations, the application of specific targeted drugs can effectively improve efficacy and reduce the occurrence of side effects. About 15% of patients with NSCLC adenocarcinoma in the United States carry mutations in EGFR tyrosine kinase, especially in non-smokers. The chance of *EGFR* mutations is substantially higher in Asian populations, and up to 30%–50% of Asian populations have *EGFR* mutations.[3] Patients with *EGFR* activating mutations have been confirmed to gain benefit from treatment with EGFR TKIs. Many trials have indicated that EGFR-TKI can prolong progression-free survival (PFS) and improve the objective response rate (ORR).[4]

Vascular endothelial growth factor (VEGF) is a cytokine that can often be created by tumor cells, stroma, and endothelial cells, consistent with autocrine and paracrine modes of action. In many tumors, overexpressed VEGF often indicates poor prognosis and low survival, and many animal and human tumor trials have shown that VEGF blockade may reduce tumor vascular supply and inhibit endothelial cell proliferation, so it has a direct and rapid antivascular effect. Bevacizumab is a humanized antiangiogenic macromolecular monoclonal antibody. Because of the efficacy in advanced colorectal cancer, bevacizumab was approved to be the first angiogenic inhibitor for treatment of cancer in the US. Bevacizumab has also shown outstanding efficacy in clinical trials of other solid tumors. Some studies have shown that combination treatment with bevacizumab can significantly decrease the risk of disease progression in patients with advanced NSCLC, and some combinations can also decrease the risk of death in NSCLC patients.[5] Some RCT trials have shown that compared to treatment with erlotinib alone, bevacizumab added to erlotinib appears to prolong PFS, ORR, and OS.[6] It is therefore interesting and important to analyze the efficacy and safety of combination treatment.

METHODS

Search strategy

The Cochrane Library, Embase, PubMed and Web of Science were searched for randomized controlled trials (RCTs) on bevacizumab combined with first-generation EGFR-TKIs in advanced NSCLC published between June 2010 and March 2021. The search combined keywords: ("Bevacizumab OR Avastin OR EGFR-TKI OR epidermal growth factor receptor tyrosine kinase inhibitors") AND ("RCT OR randomized controlled trial") AND ("PFS OR progression-free OR ORR OR objective response rate OR overall survival OR OS OR SAE OR serious adverse events") AND ("NSCLC OR Non-small-cell Lung Cancer") AND ("cancer OR tumor* OR tumour* OR carcino"), We only searched for articles in English and Chinese.

Inclusion criteria

(i) Population: Patients histologically or cytologically diagnosed with nonsquamous NSCLC, exon 19 deletion or exon 21 Leu858Arg point mutation. (ii) Intervention: bevacizumab combined with EGFR-TKIs. (iii) Comparison: EGFR-TKI alone. (iv) Outcomes: progression-free survival (PFS), objective response rate (ORR), serious adverse events (SAE), overall survival (OS). (v) Study design: RCTs.

Exclusion criteria

(i) Duplication of articles, (ii) did not reflect EGFR status, (iii) no corresponding studies, (iv) other therapies were combined with EGFR-TKI or bevacizumab, and (v) animal or cadaver studies.

Data extraction

According to the selection criteria, two investigators independently extracted data to gain the necessary information: first author, year, number of patients, intervention group and control groups, population, trial phase, *EGFR* mutation points, and outcome.

Assessing risk of bias and grading the quality of evidence

Assessment for risk of bias was performed according to the Cochrane handbook (version 5.1.0). The risk of bias are described as "high risk, low risk, unclear," The grade system are identified as four levels, high: The real results are basically the same as the research results; moderate: The real results may be same as the research results; low: Real results and research results may be significantly different; and very

TABLE 1 Main characteristics of the study

References	Year	Phase	Intervention (I) group	Control (C) group	Participants (I/C)	Median age (year) (I/C)	PFS HR (95% CI)	OS HR (95% CI)	ORR (I/C)	SEA (≥3 grade) (I/C)
Herbst et al.[6]	2011	3	Erlotinib 150 mg/day + bevacizumab 15mg/kg	Erlotinib 150 mg/day	319/317	64.8/65.0	0.62 (0.52-0.75)	0.97 (0.80–1.18)	12.6%/6.2%	66.5%/55.7%
Stinchcombe et al.[9]	2019	2	Erlotinib 150 mg/day + bevacizumab 15mg/kg	Erlotinib 150 mg/day	43/45	65.0/63.0	0.81 (0.50-1.31)	1.41 (0.71–2.81)	81.3%/77.8%	NG
Kato et al.[12]	2014	2	Erlotinib 150 mg/day + bevacizumab 15mg/kg	Erlotinib 150 mg/day	75/77	67.0/67.0	0.52 (0.35-0.76)	0.81 (0.53–1.23)	69.3%/63.6%	90.7%/53.2%
Kawashima et al.[11]	2019	3	Erlotinib 150 mg/day + bevacizumab 15mg/kg	Erlotinib 150 mg/day	112/114	67.0/68.0	0.605 (0.417-0.877)	NG	72.3%/66%	87.5%/46.4%
Kitagawa et al.[13]	2019	2	Gefitinib 250 mg/day + bevacizumab 15 mg/kg	Gefitinib 250 mg/day	6/10	73.5/72.5	NG	NG	50%/44%	NG

Abbreviation: NG, not given.

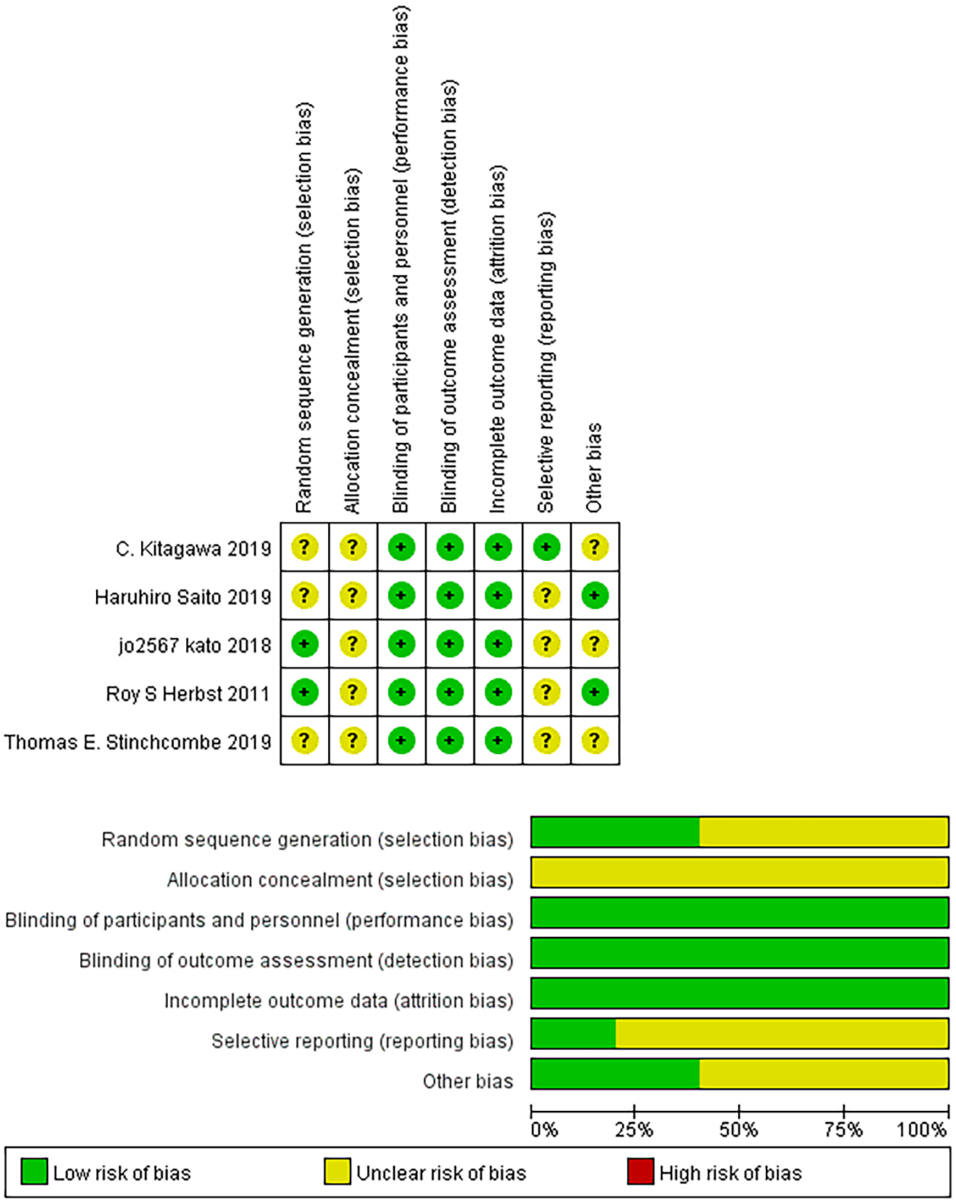

FIGURE 2 The evaluating risk of bias

low: Real results and research results are likely to be significantly different.

Outcome measures

(i) OS (time from randomization to death). (ii) PFS (time from randomization to tumor progression or death). (iii) ORR (patients who complete response and partial response). (iv) SAE (adverse events ≥3 grades).

Statistical analysis

The outcomes of SAE and ORR were estimated by relative risk (RR) with 95% confidence interval (CI). Hazard ratio (HR) was used to estimate time-to-event outcomes with 95% CI. We used I^2 statistic to evaluate the level of heterogeneity. If $I^2 < 50\%$, $p > 0.05$, a fixed-effects model was adopted in the meta-analysis; If $I^2 \geq 50\%$, $p \leq 0.05$, a random effect model was adopted to assess the resource of the heterogeneity. All statistical analyses were calculated using Stata 14.0.

RESULTS

A total of 1301 articles were initially scanned at the first stage of the search and 1119 patients in five studies, of which 555 and 564 were divided into bevacizumab combined with EGFR-TKI and EGFR-TKI alone, were extracted and included in the meta-analysis. Four of these studies

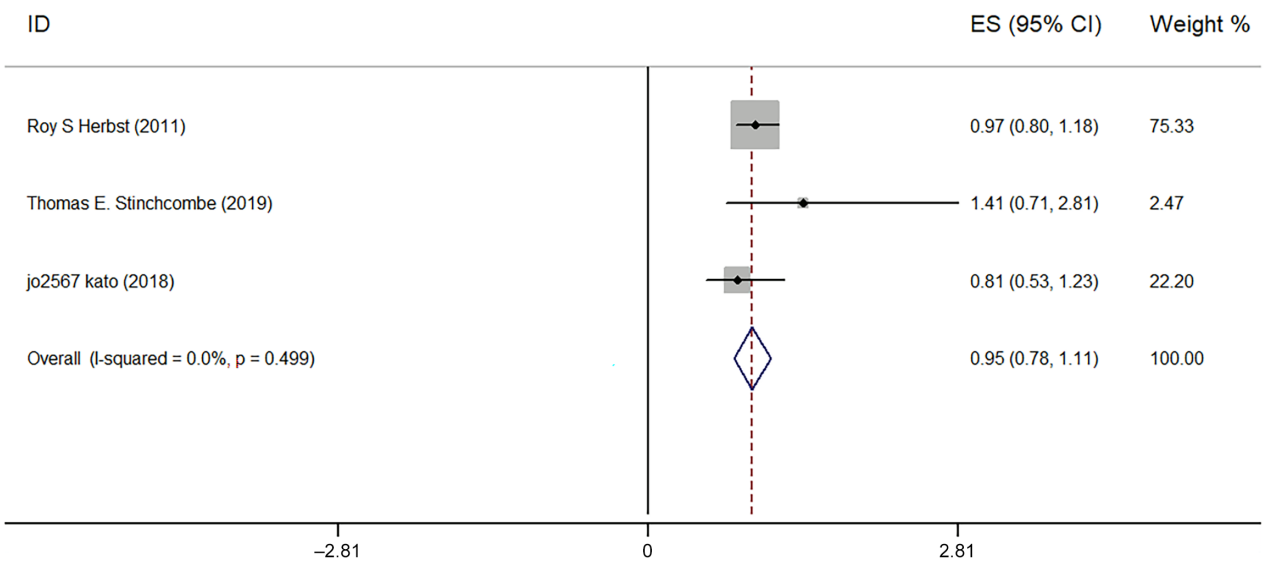

FIGURE 3 Meta-analysis result of OS

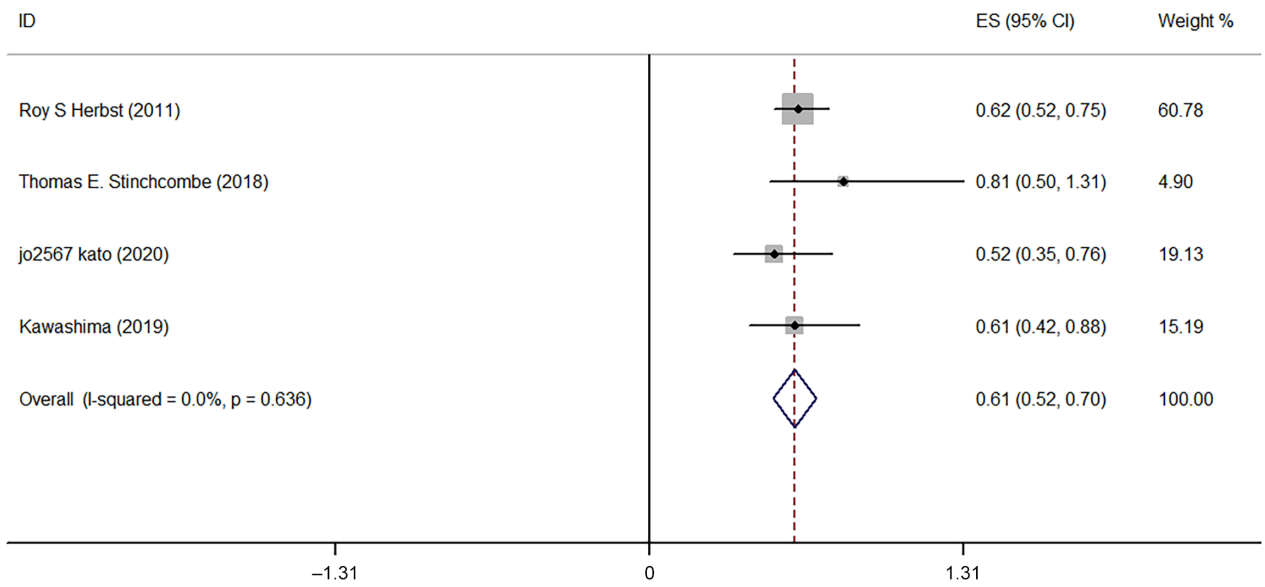

FIGURE 4 Meta-analysis result of PFS

were combined with erlotinib and one combined with gefitinib. All eligible RCTs were published during 2010 to 2021. A flow diagram of the information in the studies is shown in Figure 1. The features of all trials are shown in Table 1. The quality of the evidence grade and evaluation of the risk of bias are shown in Figure 2.

OS (3 studies, 950 patients)

Three studies were selected and the heterogeneity test showed $I^2 = 0\%$ $p = 0.499$. We chose a fixed effects model (HR = 0.95, 95% CI = 0.78–1.11 $p < 0.001$), and HR showed that bevacizumab combined with EGFR-TKIs can increase overall survival, but that the difference is not significant (Figure 3).

PFS (4 studies, 1110 patients)

Four studies were selected and the heterogeneity test showed $I^2 = 0\%$ $p = 0.636$. We chose a fixed effects model (HR = 0.61, 95% CI = 0.52–0.70; $p < 0.001$). HR showed that combined treatment significantly prolongs PFS (Figure 4).

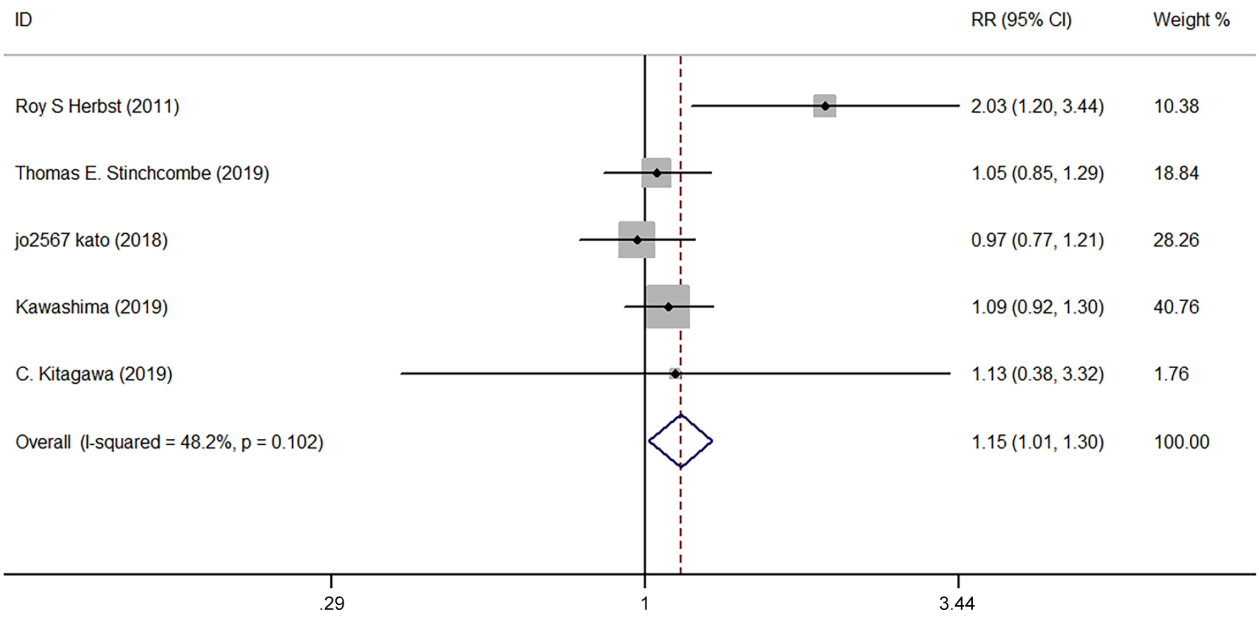

FIGURE 5 Meta-analysis result of ORR

ORR (5 studies, 1086 patients)

Four studies were selected and the heterogeneity test showed $I^2 = 0\%$ $p = 0.636$. We chose a fixed effects model (RR = 1.15, 95% CI: 1.01–1.30, $p = 0.10$). RR showed that combined treatment increases the ORR (Figure 5).

SAE (3 studies, 1004 patients)

Three studies were selected and the heterogeneity test showed $I^2 = 83.8\%$ $p = 0.002$. We chose a random effects model (RR = 1.58, 95% CI: 1.21–2.05, $p = 0.002$), and HR showed that bevacizumab combined with EGFR-TKI can significantly increase SAE (Figure 6).

DISCUSSION

The incidence of lung cancer is the highest in tumors and more than 85% of lung cancers are NSCLC.[2] Many studies have been carried out to find a better therapy for NSCLC. Among them, EGFR-TKI and angiogenesis inhibitors are very important first-line medicine. A study has shown that compared with traditional chemotherapy, combination therapy with bevacizumab can improve ORR by approximately 20%,[7] Some RCT trials have shown that treatment with EGFR-TKI plus bevacizumab significantly extends PFS, ORR and OS with an acceptable safety profile. Others indicate that there is no difference between both groups in ORR and OS.[8] Therefore, the aim of this meta-analysis was to analyze whether combination therapy effectively improves the prognosis of NSCLC patients.

Of 1301 articles scanned, five articles were included in this meta-analysis. The results indicate that combined treatment significantly prolongs PFS, and increases ORR, but that there was no substantial difference in OS between the control and experimental groups. Safety is also a very important part of treatment evaluation, and previously published results show that combination treatment with bevacizumab increases the risks of SAEs.[9–13] Patients with NSCLC are often diagnosed at an advanced stage, and need better treatment choices to effectively improve their prognosis. According to the results, combination therapy can effectively prolong PFS and improve ORR. There is no doubt that this is very good news for NSCLC patients. Although the risk of SAEs is higher, all the trials to date show that most SAEs are not fatal, The SAEs with a high probability of occurrence are bleeding, proteinuria, and high blood pressure, etc.[12] In most cases, patients will not elect to terminate medication early due to these SAEs, so patients are able to obtain the full benefit from combined treatment. Therefore, we believe that combination therapy offers a better choice for patients with *EGFR* mutations in advanced NSCLC treatment.

The strength of this meta-analysis is that the target we aimed at is very common and important in clinical work. Further improvement in the clinical treatment for NSCLC is essential. Better combination therapy is very important in order to improve patient prognosis.

We used the correct measurements to estimate precisely the effect and safety of combination therapy. We also carefully evaluated and verified the trials. They were screened according to strict set standards, and we strived to have high credibility and clinical value for the data used for evaluation.

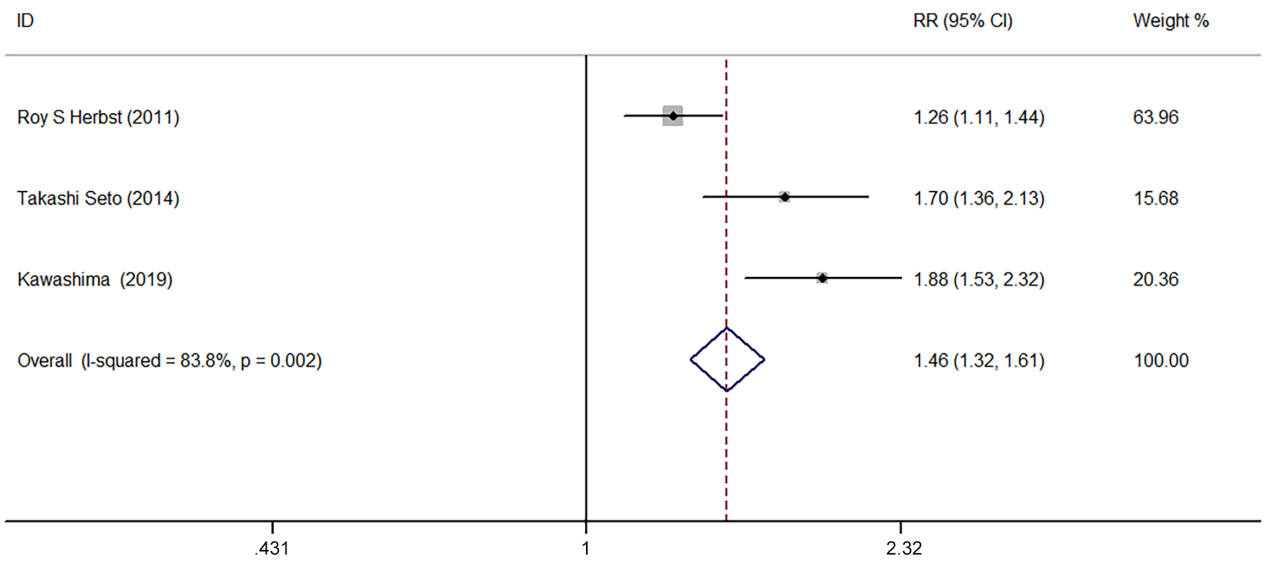

FIGURE 6 Meta-analysis result of SAE

The limitations of this meta-analysis are that only five studies were available to include in the analysis, and the lack of eligible studies may obscure the truth. Because of the lack of studies we were unable to complete the sensitivity analysis. There may also be a publication bias, and we were unable to confirm the heterogeneity of SEA. Further studies are ongoing, and we hope to be able to update this data and follow the latest research to improve this meta-analysis in the future.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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