ORIGINAL RESEARCH

Prognostic value of *EGFR* and *KRAS* in resected non-small cell lung cancer: a systematic review and meta-analysis

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Background: The prognostic value of *EGFR* and *KRAS* mutations in resected non-small cell lung cancer (NSCLC) has been reported. However, conflicting results were reported in these studies. The effect of mutations in these two genes in resected NSCLC remains controversial.
Methods: We searched Internet databases for studies reporting disease-free survival (DFS) and overall survival (OS) in resected NSCLC patients with *EGFR* or *KRAS* mutations. A meta-analysis calculating the pooled hazard ratio (HR) for DFS and OS was used to measure the association of *EGFR* or *KRAS* mutations with the prognosis of patients after surgery.
Results: A total of 9,635 patients from 32 studies were included in this analysis. The combined HR for *EGFR* mutations on DFS was 0.77 (95% CI 0.66–0.90, *p*=0.001) and on OS was 0.72 (95% CI 0.66–0.80, *p*<0.00001). In addition, the combined HR for *KRAS* mutations on DFS was 1.5 (95% CI 1.15–1.96, *p*=0.002) and on OS was 1.49 (95% CI 1.28–1.73, *p*<0.00001). Sensitivity analysis, subgroup analysis, and bias analysis proved the stability of the results.
Conclusion: The analysis showed that *EGFR* mutations were significantly associated with DFS and OS. These findings indicated that surgically treated NSCLC patients with *EGFR* mutations were inclined to exhibit a prolonged DFS and OS. In addition, the results indicated that *KRAS* mutations predicted worse DFS and OS in patients with resected NSCLC.
Keywords: *EGFR* mutations, *KRAS* mutations, meta-analysis, non-small cell lung cancer, prognosis, resected

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Introduction

Lung cancer is one of the most common malignancies in the world and the main cause of cancer-related death.[1] Lung cancer is generally classified into small cell lung cancer and non-small cell lung cancer (NSCLC) according to its pathology and treatment, and NSCLC accounts for more than 80% of all lung cancer cases.[2] Although the treatment for NSCLC has made great strides, the 5-year survival rate is only approximately 15%.[1] The principal treatments for NSCLC are surgery, chemotherapy, radiotherapy, and targeted drug therapy. Among these treatments, surgery is recognized as the most efficient treatment, but relapse after surgical treatment occurs in 20–50% of all cases, and the prognosis remains elusive.[3–6]

Numerous studies have reported prognostic factors that could predict survival and recurrence of NSCLC. Lee et al[7] discovered that gene mutations can sensibly predict postoperative recurrence. Many mutant genes in NSCLC have been identified, including *KRAS*, *EGFR*, HER2, and FGFR1.[8] Among them, the most well-studied mutant genes are *EGFR* and *KRAS*.

EGFR is a stimulatory factor and driving gene in NSCLC. *EGFR* mutations lead to abnormal activation of receptors and downstream molecules in the absence of ligands. *EGFR* mutations promote tumorigenesis by increasing cell proliferation and reducing cell apoptosis, angiogenesis, and metastasis.[9] The discovery of *EGFR* has led to a completely new phase of systemic treatment of NSCLC. Identification of mutations in NSCLC molecular pathways and the continuous improvement in genetic testing methods in clinical research have prompted the individualized treatment trend in NSCLC. *EGFR* mutations are the predicting factor for *EGFR*-TKI.[10] However, the predictive value of *EGFR* mutations on postoperative survival and recurrence of resected NSCLC remains unclear. The results of studies about the prognostic impact of *EGFR* mutations in resected NSCLC are inconsistent. Kim et al[11] suggested that *EGFR* is not a prognostic factor for resected NSCLC, whereas Ma et al[12] suggested that *EGFR* mutations seem to be more likely a predictive marker for *EGFR*-TKI treatment than a prognostic marker for overall survival (OS). However, the study by Izar et al[13] demonstrated that *EGFR* mutations are positive prognostic markers in completely resected stage I NSCLC.

KRAS is involved in several solid tumors, including colorectal cancer and NSCLC. *KRAS* is a signal transducer downstream of tyrosine kinase receptors including *EGFR*, which is a complex signaling cascade involved in the development of cancer. Mutated *KRAS* can activate this pathway automatically and initiate transduction of downstream signals in the absence of *EGFR* signaling to allow NSCLC to further develop. Mutated *KRAS* also renders the *EGFR*-targeted drug in upstream of tyrosine kinase receptors ineffective.[14] It is generally believed that *KRAS* mutations are contraindications to the use of anti-*EGFR* antibody therapy in colorectal cancer,[15] but the effect of these mutations in NSCLC is unclear. The prognostic value of *KRAS* mutations in NSCLC in each study is inconsistent, and the considerable heterogeneity is noted among studies. Kadota et al[16] studied the effect of *KRAS* mutations on the prognosis of 129 NSCLC patients undergoing surgical resection. The results showed that the 5-year OS of *KRAS*-mutated NSCLC patients was significantly reduced compared with that of wild-type *KRAS* patients, and the relapse rate of patients with *KRAS* mutations increased. However, in a retrospective study[17] assessing *KRAS* mutations in postoperative NSCLC, the results revealed no significant difference between recurrence-free survival (RFS) and OS in patients with *KRAS* mutations and wild-type *KRAS*. Some studies suggest that *KRAS* mutations are prognostic factors of NSCLC, whereas other studies demonstrate no relationship between

KRAS mutations and NSCLC patient survival. In addition, a meta-analysis assessing *KRAS* mutations in the surgical treatment of NSCLC has not been reported to date. Although *EGFR* and *KRAS* are hotspot studies on NSCLC, their real prognostic value in resected NSCLC remains unknown. To elucidate the prognostic significance, we performed meta-analysis to explain the prognostic value of *EGFR* and *KRAS* mutations in resected NSCLC patients.

Methods
Search strategy and selection criteria
We searched PubMed, the Cochrane Library, and Web of Science as well as the references of included studies. The literature search was completed in July 2017. The articles must meet the following criteria for inclusion in our study: 1) all patients were pathologically confirmed to have NSCLC; 2) all patients underwent complete excision operations; 3) all patients harbored EFGR or *KRAS* mutations; and 4) the hazard ratio (HR) of disease-free survival (DFS) and OS is reported in the article or can be calculated from the relevant parameters. If the same researcher reported the results of the same patient population, we used most recent study or the study for which the data were most complete.

Quality assessment of articles
We used the European Lung Cancer Working Group (ELCWP) Quality Scale used by Steels et al[18] to ensure the quality of the included studies. There were scientific design, laboratory methods, reproducibility, and result analysis in the list, and also there were some specific items in each category. Maximum of 2 points awarded in each item. One point was given for an incomplete or unclear description, and an item that was not defined was given 0 point. Then, we employed SPSS (www.spss.com) analysis to ensure the accuracy of the score.

Data extraction and summary effect analysis
The main data we extracted from the literature included the following: first author, year of publication, source of patients, number of patients, stage, *EGFR* mutation rate, *KRAS* mutation rate, *KRAS* mutation state, *EGFR* mutation state, detection method, and HR. We set DFS as the first end point and OS served as the second end point. A $p<0.05$ indicated that the result was statistically significant. The analysis utilized Review Manager 5.3 (http://community.cochrane.org/help/tools-and-software/revman-5) and stata12 (https://www.stata.com/). The results were combined with p-values for HR. The fixed-effect model ($I^2<50\%$) and the random-effect model

($I^2 \geq 50\%$) were chosen based on heterogeneity. We used sensitivity analysis to identify studies that caused heterogeneity. Subgroup analysis was used to further explore the source of heterogeneity. The grouping was based on statistical methods of the study, NSCLC stages of patients, the detection methods of gene mutations, and the population origin of samples. We used Begg's test and Egger's test to explore publication bias among the items that included more than 10 studies.

Results
Selection of studies

A total of 2,501 potential studies were defined, and 2,463 studies were excluded after screening. Moreover, the full texts of 38 articles were intensively scrutinized and five studies were excluded due to incomplete data. Finally, 33 studies[11,13,16,17,19–47] fulfilling all of the inclusion criteria were eligible for meta-analysis. Figure 1 shows the flowchart of the search results.
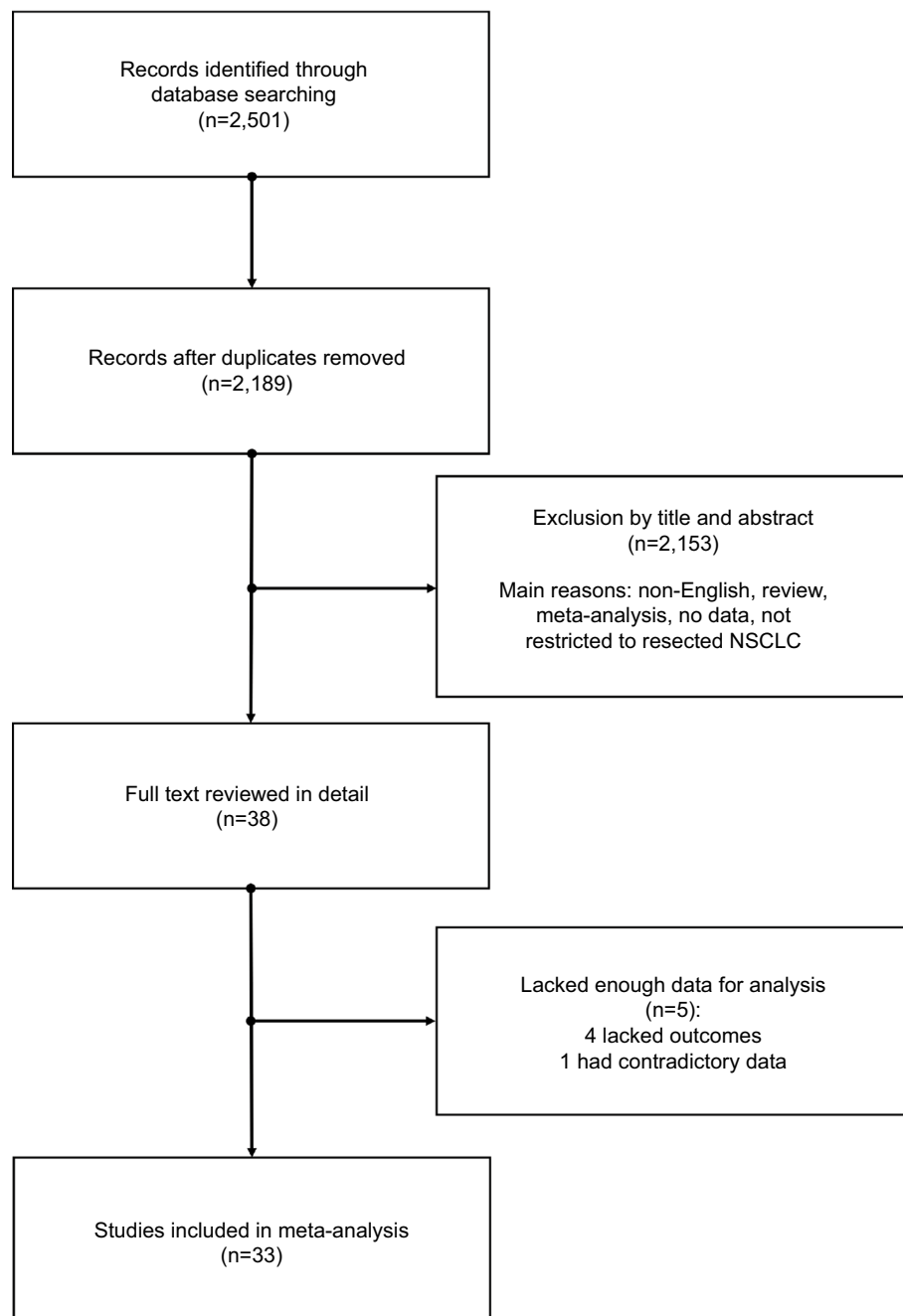

Figure 1 Flowchart of publication search and selection.
Abbreviation: NSCLC, non-small cell lung cancer.

Study description and quality assessment

The total number of NSCLC patients was 10,869, including 3,651 harboring *EGFR* mutations and 1,687 harboring *KRAS* mutations. The *EGFR* mutation rate was 9.6–82.2%, and the *KRAS* mutation rate was 3.5–75.2%. We concluded that the average mutation frequency of *EGFR* in Asian populations (43.5%) was higher than that in other races (37.9%), whereas the average frequency of *KRAS* mutations in Asian populations (12.7%) was much lower than that in other races (46.1%). The main mutation site of *EGFR* involves exons 18–21, and the main mutation site of *KRAS* is exon 2. Among these studies, three studies[28,36,45] mentioned other *KRAS* mutation sites (exons 3 and 6). Table 1 presents the primary characteristics of these included studies.

The results of our quality assessment are presented in Table S1. We removed some items that were not suitable for our study. Studies with 20 or more points out of 38 points qualified for inclusion. The overall score of 31 studies was between 21 and 30, and the median score was 27 points. No significant difference ($p=0.605>0.05$) was noted between Asian and non-Asian studies, which is revealed in Table 2. The scores of studies that exclusively focused on *EGFR* or *KRAS* did not differ significantly from studies that researched both *EGFR* and *KRAS* ($p=0.78>0.05$). The included the studies because the scores indicated that the quality of those studies met our standards.

Predictive value of *EGFR* mutations

DFS

Seventeen studies with 5,261 patients assessed the relationship between *EGFR* mutations and DFS,[11,13,22,25,29,31,32,34–38,42–44,46,47] and six studies demonstrated that *EGFR* mutations positively influenced the DFS of resected NSCLC patients.[13,25,35,42,43,47] Significant heterogeneity was observed between these studies ($I^2=72\%$, $p<0.00001$; Figure S1). We used sensitivity analysis to explore the sources of heterogeneity (Figure 2A). We identified four studies that may lead to heterogeneity.[11,35,36,43] No obvious heterogeneity was noted among the studies after excluding four studies ($I^2=32\%$, $p=0.13$). The remaining 13 studies were subject to meta-analysis using fixed-effect model, and the combined HR was 0.77 (95% CI 0.66–0.90, $p=0.001$; Figure 2B). The results suggest that the effect of *EGFR* mutations on DFS is statistically significant and that *EGFR* mutations are prognostic factors for relapse in resected NSCLC patients.

Subgroup analysis was used to further explore heterogeneity. We considered the heterogeneity of stage, statistical methods, and source of study based on the four studies previ-

ously identified (Figure S2A–C). In the subgroup analysis, heterogeneity remained relatively large, and the value of I^2 ranged from 53% to 75%. Among the subgroups, we found that the univariate analysis subgroup which included five studies that exhibited no significant heterogeneity revealed negative influence of *EGFR* mutations on DFS (HR 1.18, 95% CI 1.03–1.34, $p=0.03$; Figure 2C). In contrast, the multivariate analysis subgroup revealed an opposite result (HR 0.68, 95% CI 0.52–0.88, $p=0.004$; Figure S1B). Moreover, many studies[11,25,30,31,37] have shown that the clinical impact of *EGFR*-TKIs cannot be ignored in *EGFR*-mutant patients. The data from the studies were divided into the *EGFR*-TKI subgroup and the no *EGFR*-TKI subgroup to verify the effects. The results revealed that significant heterogeneity remained in the *EGFR*-TKI group (*EGFR*-TKI: $I^2=72\%$, $p=0.01$; no *EGFR*-TKI: $I^2=65\%$, $p=0.0007$; Figure S2D). Moreover, we conducted bias analysis using funnel plot (Figure 2D), Begg's test ($p=0.537$), and Egger's test ($p=0.116$; Figure S3). No significant publication bias was observed in the studies.

OS

The relationship between *EGFR* mutations and OS was evaluated based on 26 studies,[11,13,16,19–23,25,27–31,33–40,42–44,47] with 8,100 patients, and seven studies[11,13,28,33,35,42,47] indicated that *EGFR* mutations were a favorable prognostic factor for OS in resected NSCLC patients. Some heterogeneity was noted between the studies ($I^2=42\%$, $p=0.008$; Figure S4A). We conducted a sensitivity analysis to identify the source of heterogeneity (Figure 3A). We identified that two studies[16,35] that may cause heterogeneity; however, no significant heterogeneity was noted among the studies after excluding these two studies ($I^2=24\%$, $p=0.13$, HR 0.72, 95% CI 0.66–0.80, $p<0.00001$; Figure 3B). The pooled analysis indicated a better OS for NSCLC patients with *EGFR* mutations.

We used subgroup analysis to continue to explore heterogeneity. We divided the study into different subgroups based on detection method, statistical analysis method, research source, pathological stage, and *EGFR*-TKIs (Figure S4B–F). Among them, the real-time polymerase chain reaction subgroup of the detection method group ($I^2=8\%$, $p=0.35$, HR 0.46, 95% CI 0.31–0.67, $p<0.0001$), the other subgroup of the research source group ($I^2=23$, $p=0.26$, HR 0.86, 95% CI 0.74–0.99, $p=0.03$), the other subgroup of the stage group ($I^2=22$, $p=0.17$, HR 0.71, 95% CI 0.62–0.81, $p<0.00001$), and the *EGFR*-TKI subgroup ($I^2=26\%$, $p=0.23$, HR 0.73, 95% CI 0.64–0.84, $p<0.00001$) exhibited no significant heterogeneity (Figure 3C–F). The results of these groups indicated that the *EGFR* mutation is a benign prognostic factor for OS. Sig-

Table I Characteristics of the included studies

Reference	Year	Source	Patients (N)	Stage	Mutation number (%)	Mutation type (locus/exon)	Gene testing method	Statistical methods
Na et al[19]	2007	Korea	133	I–III	EGFR 32 (24)	EGFR (18–21)	SEQ	Univariate
Suehisa et al[20]	2007	Japan	187	I–IIIA	EGFR 79 (43)	EGFR (19, 21)	PCR, SEQ	Multivariate
Marks et al[21]	2008	USA	296	I–III	EGFR 40 (13.6), KRAS 50 (17)	EGFR (18–21), KRAS (2)	PCR, SEQ	Multivariate
Kobayashi et al[22]	2008	Japan	127	I	EGFR 64 (50.4)	EGFR (19, 21)	Mutant-enriched PCR	Multivariate
Woo et al[24]	2009	Japan	190	I	KRAS 24 (12.6)	KRAS (2)	PCR	Multivariate
Hosokawa et al[23]	2009	Japan	93	I–III	EGFR 37 (40)	EGFR (18–21)	PCR, SEQ	Univariate
Lee et al[25]	2009	Korea	117	I–IIIA	EGFR 48 (41.8)	EGFR (18–21)	Nested PCR	Univariate
Galleges Ruiz et al[26]	2009	The Netherlands	178	I–III	KRAS 25 (14)	No data	Nested PCR	Multivariate
Kosaka et al[27]	2009	Japan	397	I–IV	EGFR 196 (49), KRAS 142 (38)	EGFR (18–21), KRAS (2)	PCR, SEQ	Multivariate
Liu et al[28]	2010	Taiwan (China)	164	I–IIIA	EGFR 52 (31.7), KRAS 7 (4.3)	EGFR (18–21), KRAS (2, 3)	SEQ	Multivariate
Tsao et al[29]	2011	Canada	436	IB–II	EGFR 27 (12.2)	EGFR (19, 21)	ARMS	Multivariate
D'Angelo et al[30]	2012	USA	1,118	I–III	EGFR 896 (80.1), KRAS 841 (75.2)	EGFR (19, 21), KRAS (2)	PCR, SEQ	Multivariate
Kim et al[31]	2012	Korea	229	I–IV	EGFR 110 (48), KRAS 8 (3.5)	EGFR (18–21), KRAS (2)	Nested PCR	Multivariate
Scoccianti et al[32]	2012	Europe (multinational)	152	I–IV	EGFR 18 (11.8)	EGFR (18–21)	PCR, SEQ	Multivariate
			249	I–IV	KRAS 46 (18.5)	KRAS (2)	Mutant-enriched PCR, SEQ	Multivariate
Sonobe et al[33]	2012	Japan	180	I–III	EGFR 148 (82.2)	EGFR (18–21)	RT-PCR	Multivariate
Izar et al[13]	2013	USA	307	I	EGFR 62 (19.9), KRAS 127 (40.7)	EGFR (18–21), KRAS (2)	SEQ, multiplex PCR	Multivariate
Sun et al[35]	2013	China	150	IIIA	EGFR 43 (28.7)	EGFR (19, 21)	RT-PCR	Multivariate
Maki et al[34]	2013	Japan	105	IA	EGFR 51 (49)	No data	PCR, SEQ	Univariate
Kim et al[11]	2013	Korea	863	IB–IIA	EGFR 354 (41)	EGFR (18–21)	PCR, SEQ	Univariate
Ragusa et al[36]	2014	Italy	230	I–III	EGFR 22 (9.6), KRAS 39 (16.9)	EGFR (18–21), KRAS (2, 3)	Nested PCR	Univariate
Ohba et al[37]	2014	Japan	354	I	EGFR 122 (34.4)	EGFR (19, 21)	PCR, SEQ (EGFR)/RFLP (KRAS)	Univariate
Liu et al[38]	2014	China	131	I–IIIA	EGFR 58 (44.3)	EGFR (18–21)	Nested PCR	Multivariate
Ayyoub et al[39]	2014	Spain	216	I–III	EGFR 21 (9.7), KRAS 29 (3.4)	EGFR (18–21), KRAS (2)	RT-PCR	Univariate
Kudo et al[40]	2015	Japan	198	I–III	EGFR 57 (28.7)	EGFR (18, 19, 21)	PCR, SEQ	Univariate
Nadal et al[41]	2015	USA	179	I–IV	KRAS 85 (47.5)	KRAS (2)	PCR, SEQ	Multivariate
Nishii et al[42]	2017	Japan	388	I	EGFR 185 (47.7)	EGFR (19–21)	PCR	Univariate
Kadota et al[16]	2016	USA	378	I	EGFR 85 (22.5)	EGFR (18–21)	Sequenom	Multivariate
			482	I–II	KRAS 129 (27)	KRAS (2)	PCR	Multivariate
Isaka et al[43]	2016	Japan	202	II–IIIA	EGFR 100 (49.5)	EGFR (19, 21)	PCR	Multivariate
Zheng et al[17]	2016	China	1,368	I–IV	KRAS 118 (8.26)	KRAS (2)	RT-PCR, SEQ	Multivariate
Kaseda et al[44]	2017	Japan	162	I	EGFR 81 (50), KRAS 17 (10.5)	EGFR (19, 21), KRAS (2)	PCR	Univariate
Sullivan et al[45]	2017	USA	131	IA–IIB	No data	KRAS (6)	RT-PCR	Multivariate
Takamochi et al[47]	2017	Japan	939	I–IV	EGFR 418 (44.5)	EGFR (18, 19, 21)	PCR	Multivariate
Yotsukura et al[46]	2017	Japan	369	I–II	EGFR 160 (46.9)	EGFR (19, 21)	PCR	Multivariate

Abbreviations: ARMS, amplification refractory mutation system; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT, reverse transcription; SEQ, sequencing.

nificant heterogeneity was noted in the early subgroup of the pathological stage group (I^2=66%, p=0.02). Minimal heterogeneity existed in the sequencing subgroup of the detection method group (I^2=38%, p=0.02), the analysis method group (multivariate: I^2=38%, p=0.04, univariate: I^2=49%, p=0.04), and the Asian subgroup of the source group (I^2=38%, p=0.03). The multivariate analysis subgroup demonstrated that *EGFR* mutations had a positive effect on the OS, and the univariate analysis subgroup revealed no significant association between *EGFR* mutations and OS (Figure S4C). The Asian subgroup results indicated that *EGFR* mutations were benign factors of OS, and the other subgroup revealed that *EGFR* mutations did not significantly influence OS (Figure S4D). The results of

the *EGFR*-TKI group revealed no significant heterogeneity in the *EGFR*-TKI subgroup (I^2=26%, p=0.23), but heterogeneity was noted in the *EGFR*-TKI subgroup (I^2=47%, p=0.006; Figure S4F). When the prognostic value of *EGFR* mutations is estimated, different analysis methods and different ethnic groups may influence the outcome of the study. No significant publication bias was observed in the funnel plot (Figure 3G), Begg's test (p=0.175), and Egger's test (p=0.595; Figure S5).

Predictive value of *KRAS* mutations
DFS

Nine studies with 3,045 patients were used to explain the relationship between *EGFR* mutations and DFS.[13,17,24,31,32,36,41,44,45] Four studies demonstrated that *KRAS* mutations were not beneficial for recurrence of resected NSCLC patients.[13,24,41,45] Significant heterogeneity was noted between the studies (I^2=57%, p=0.02; Figure S6A). We found that one article[13] was a source of heterogeneity based on sensitivity analysis (Figure 4A). Heterogeneity was significantly reduced after removing this article (I^2=36%, p=0.14; Figure 4B). The merged HR was 1.5 (95% CI 1.15–1.96, p=0.002) based on fixed-effect model. The result indicated that *KRAS* mutations were a negative factor for DFS.

Table 2 Statistical characteristics of quality assessment score

	Number of studies	Median score	Average score	Difference test (*p*-value)
All studies	33	26	26.1	–
Asian	22	26	25.95	0.605
Non-Asian	11	27	26.5	
Only[a]	22	26.5	26.3	0.78
Both[b]	11	26	26.4	

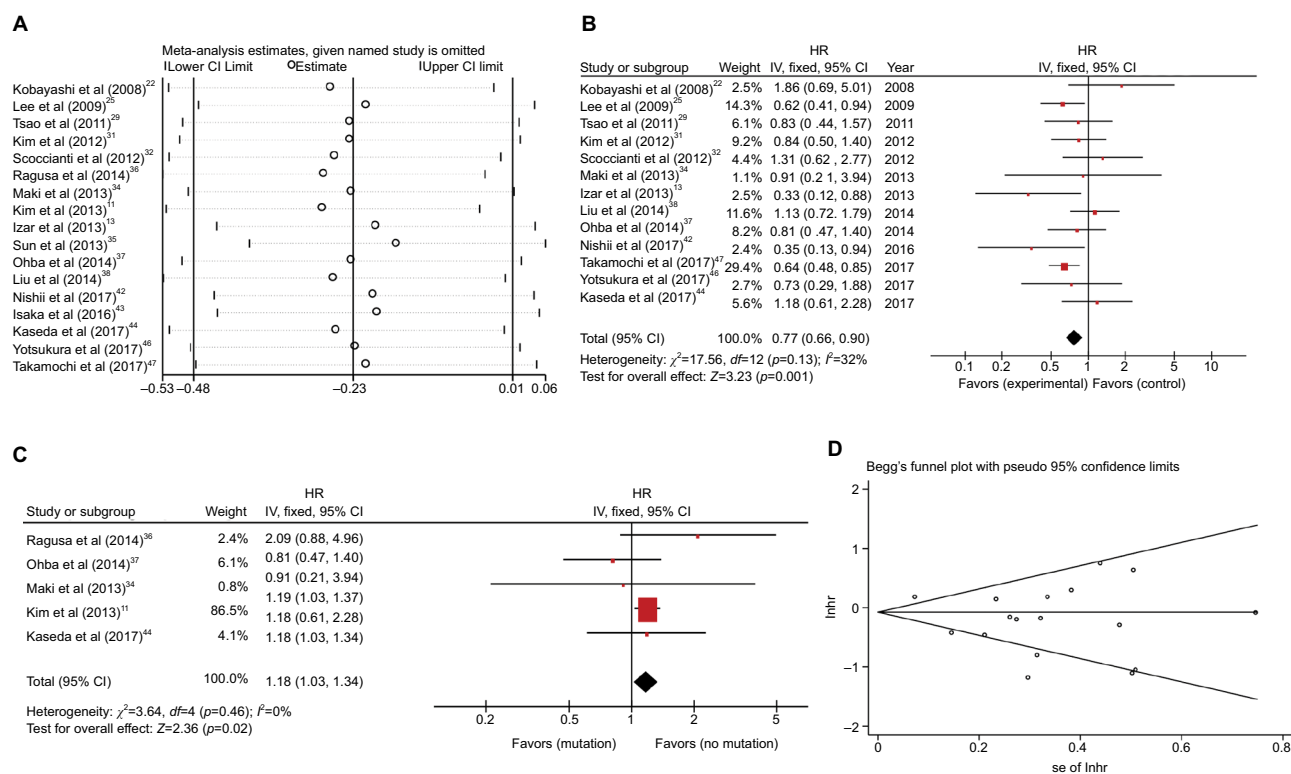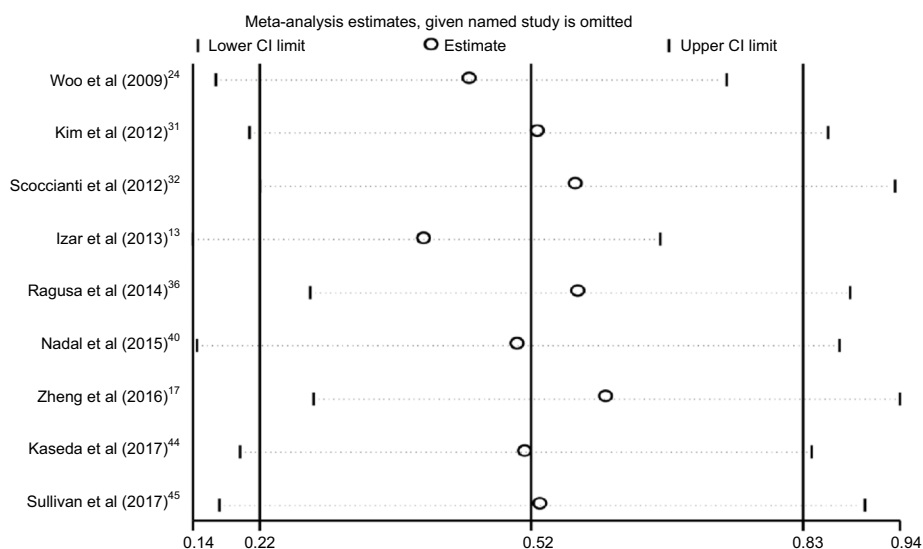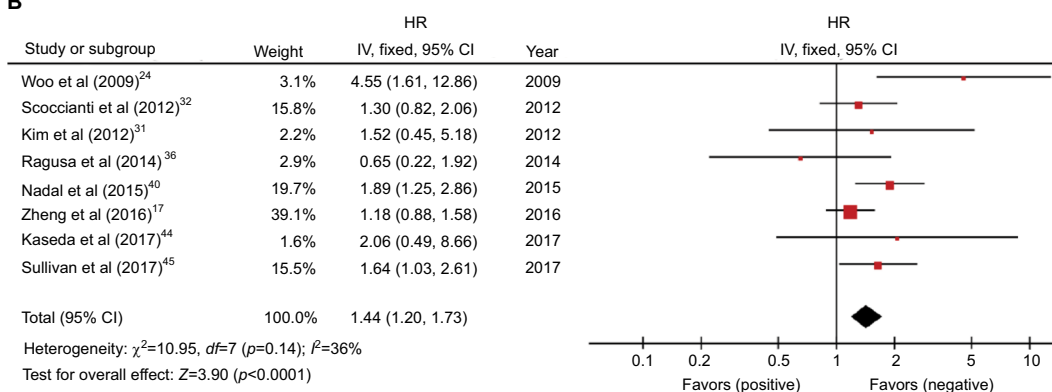**Notes:** [a]Studies of *EGFR* or *KRAS*. [b]Studies of both *EGFR* and *KRAS*.

Figure 2 (**A**) Sensitivity analysis for combined HR of *EGFR* on DFS. (**B**) Fixed-effect model forest plot of DFS of *EGFR* mutations after removing the studies that caused the heterogeneity. (**C**) Fixed-effect model forest plot of DFS in univariate analysis subgroup according to *EGFR* mutation. (**D**) Begg's funnel plot of enrolled studies for DFS of *EGFR*.
Abbreviations: DFS, disease-free survival; HR, hazard ratio; lnhr, logarithm of HR; IV, inverse variance; se, standard error.
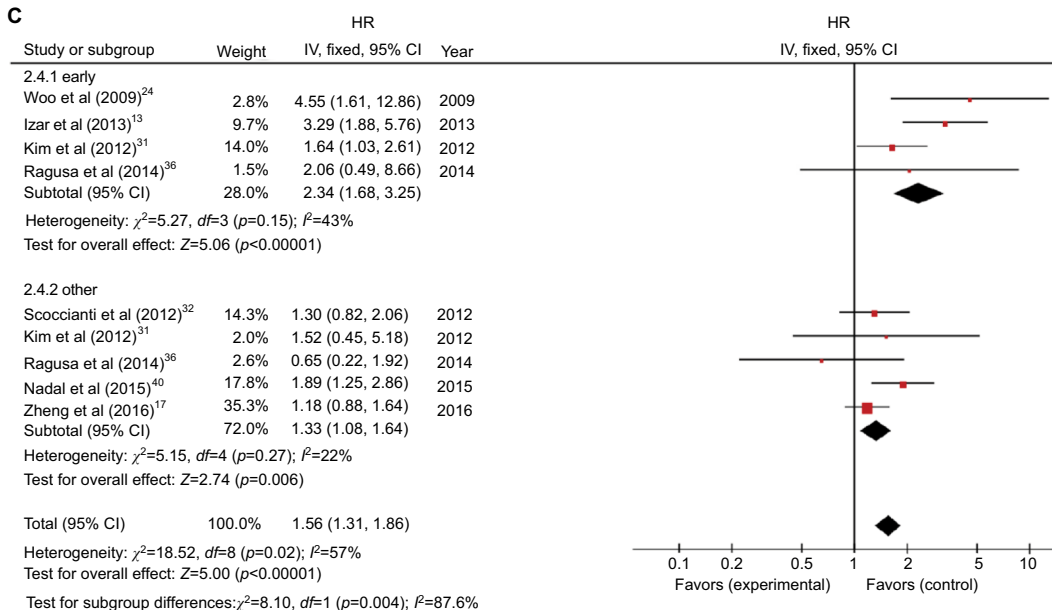
Figure 3 (**A**) Sensitivity analysis for combined HR of *EGFR* on OS. [a]All patients; [b]five patients with no data at the EGFR mutation variable, and 18 patients who had received TKI treatment for tumor recurrence were not included; [c]mutation site: L858R; [d]mutation site: 19 Del; [e]mutation site: others. (**B**) Fixed-effect model forest plot of OS of *EGFR* mutations after removing two studies that caused the heterogeneity. (**C**) Fixed-effect model forest plot of OS of *EGFR* mutations in RT-PCR subgroup (detection methods group). (**D**) Fixed-effect model forest plot of OS of *EGFR* mutations in other subgroups (research sources group). (**E**) Fixed-effect model forest plot of OS of *EGFR* mutations in other subgroups (stage group). (**F**) Fixed-effect model forest plot of OS of *EGFR* mutations in the *EGFR*-TKIs subgroup. (**G**) Begg's funnel plot of enrolled studies for OS of *EGFR*.
Abbreviations: HR, hazard ratio; IV, inverse variance; lnhr, logarithm of HR; OS, overall survival; PCR, polymerase chain reaction; RT, reverse transcription; se, standard error.

We grouped the studies based on pathological stage, research sources, and statistical methods to further explore the sources of heterogeneity (Figures 4C and S6B and C). No significant heterogeneity was noted in the early subgroup and other subgroups of the stage group in the subgroup analysis (Figure 4C). This finding indicated that data from patients with different pathological stages may generate heterogeneity.

Figure 4 (**A**) Sensitivity analysis for combined HR of *KRAS* on DFS. (**B**) Fixed-effect model forest plot of DFS of *KRAS* mutations after removing the study that caused the heterogeneity. (**C**) Random-effect model forest plot of DFS of *KRAS* mutations in stage subgroup analysis according to the patient's pathological staging.
Abbreviations: DFS, disease-free survival; HR, hazard ratio; IV, inverse variance.

OS

Thirteen studies with 5,326 patients were based on the connection between *KRAS* mutations and OS of resected NSCLC.[13,16,17,21,26–28,30,31,36,39,41,44] Four of these studies indicated that *KRAS* mutations represented a risk factor for resected NSCLC.[13,16,26,41] Significant heterogeneity was not noted in the studies ($I^2=30\%$, $p=0.14$). The overall HR was 1.49 (95% CI 1.28–1.73, $p<0.00001$; Figure 5A). The outcome indicated that patients with *KRAS* mutations exhibited shorter OS. No significant publication bias was observed in the funnel plot (Figure 5B), Begg's test ($p=1$), and Egger's test ($p=0.74$; Figure S7).

Discussion

Surgery is an effective method to treat patients with NSCLC. Both *EGFR* and *KRAS* are driver genes of NSCLC.[8] Most studies suggest that *EGFR* and *KRAS* mutations are often mutually exclusive.[48–51] Some clinical studies have reported that *KRAS* mutations can appear in patients with *EGFR* mutations, but the incidence of double mutations is <1%.[52] Therefore, the simultaneous detection of *EGFR* and *KRAS* mutations is significant in guiding the individualized treatment of NSCLC patients. We assessed the prognostic significance of *EGFR* and *KRAS* mutations in postoperative NSCLC patients using meta-analysis that collect large amounts of data. Our meta-analysis reviewed thoroughly and released the latest data. Low heterogeneity was noted in this study, and no publication bias was found.

The results indicated that *EGFR* mutations not only extend the DFS of resected NSCLC but also contribute to the OS of patients. Zhang et al[53] reported opposite conclusion demonstrating that the *EGFR* mutations were unrelated to the OS (HR 0.84, 95% CI 0.34–2.06, $p=0.12$) and DFS

(HR 0.96, 95% CI 0.79–1.16, $p=0.65$). The cause involves deviations from the included studies or the differences in HRs from the survival curves. In this study, the meta results of *EGFR* DFS became statistically significant after excluding the four studies that caused heterogeneity. On the one hand, the great heterogeneity among studies may cause the results to be inaccurate. On the other hand, the excluded data also caused the results to change. Significant heterogeneity was discovered in the DFS studies. We identified four studies as the sources, but the heterogeneity was not resolved after subgroup analysis based on these studies. It is likely that we cannot accurately group based on some elements, such as gender and smoking. Moreover, the outcome of the multivariate subgroup was in complete opposition to the univariate subgroup. This finding suggests that different statistical approaches may affect the judgment of *EGFR* mutations in DFS. Therefore, we should carefully consider this point in subsequent research. The heterogeneity between OS study groups has not been accurately resolved. Subgroup analysis of OS revealed the difference between Asian and non-Asian studies. Heterogeneous results may be attributed to the fact that *EGFR* mutations play a different role in different races, so we need to consider this difference in the development of comprehensive treatment strategies. In addition, the statistical method group revealed that different statistical methods may affect the influence of *EGFR* mutations on OS. The results of the two subgroups of the stage group are also different, but this difference is likely caused by the great heterogeneity of the early subgroup. Moreover, we cannot consider the *EGFR*-TKIs as a source of heterogeneity of both DFS and OS according to the subgroup analysis of *EGFR*-TKIs. The reason may be that our existing data are not sufficiently comprehensive; we cannot completely separate patients who
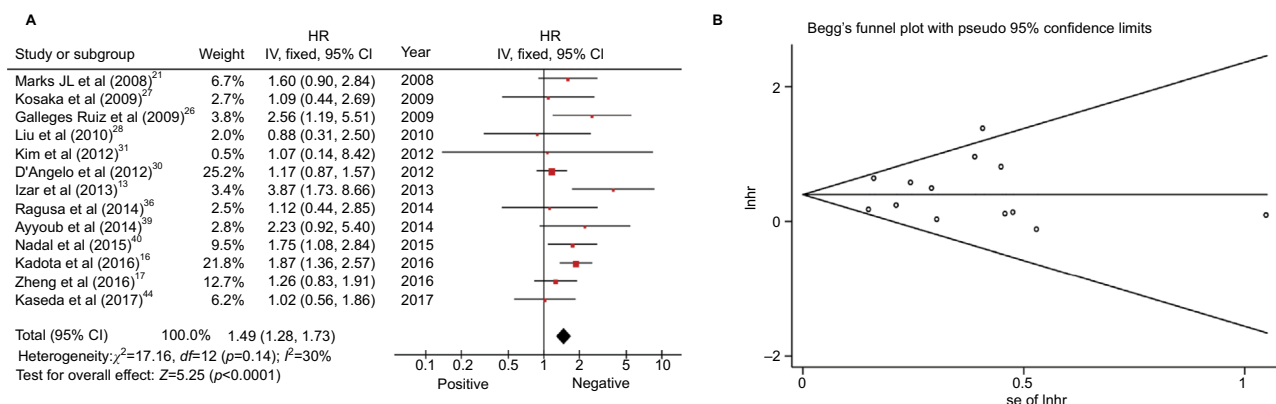

Figure 5 (**A**) Random-effect model forest plot of OS of *KRAS* mutations. (**B**) Begg's funnel plot of enrolled studies for OS of *KRAS*.
Abbreviations: HR, hazard ratio; IV, inverse variance; lnhr, logarithm of HR; OS, overall survival; se, standard error.

receive *EGFR*-TKI therapy from all patients. We are unable to conduct more rigorous analysis.

KRAS mutations are a negative factor of DFS and OS in patients with postoperative NSCLC. The meta-analysis revealed that the resected NSCLC patients with *KRAS* mutations exhibited reduced DFS and OS. This finding indicates that *KRAS* is an important indicator of the prognosis of patients with NSCLC. The DFS subgroup analysis expresses a difference of DFS between patients from different sources. This difference is likely because non-Asian patients are more affected by *KRAS* mutations than Asian patients. In addition, in the subgroup analysis of DFS, both the research sources group and the statistical methods group exhibited significant heterogeneity. On the one hand, this finding may indicate that neither of these two factors represent the source of DFS heterogeneity. On the other hand, given the relatively limited number of DFS studies, data from one study will lead to significant fluctuation of heterogeneity.

Despite all our efforts to provide accurate and comprehensive analysis, the meta-analysis still has some limitations. First, we did not conduct subgroup analyses due to insufficient data on age, gender, and smoking status to provide additional results. Second, we did not distinguish between patients who only underwent surgery or were subject to other treatments after surgical resection, which could result in bias. Moreover, additional and more complex studies based on different *EGFR* and *KRAS* mutation sites were not included. In future studies, these studies can be included in the analysis to provide more data available.

Despite these limitations, the meta-analysis revealed that *EGFR* mutations were associated with better OS and DFS in resected NSCLC patients. Patients with *EGFR* mutations who undergo surgical treatment exhibit an improved long-term prognosis for DFS and OS. *KRAS* mutations in NSCLC patients who undergo surgery predict worse DFS and OS.

Conclusion

Our meta-analysis found that *EGFR* mutations were associated with better DFS and OS, and *EGFR* mutations were a benign prognostic factor for DFS and OS of resected NSCLC. In addition, *KRAS* mutations indicate worse DFS and OS in resected NSCLC. The *KRAS* mutation is a poor prognostic factor for DFS and OS in patients with NSCLC after surgery.

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Disclosure

The authors report no conflicts of interest in this work.

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