Original Article

The impact of epidermal growth factor receptor mutations on the prognosis of resected non-small cell lung cancer: a meta-analysis of literatures

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Background: Epidermal growth factor receptor (EGFR) mutation represents a good response to EGFR-tyrosine kinase inhibitor and an advantageous prognostic factor in advanced-stage non-small cell lung cancer (NSCLC). However, the predictive value of EGFR mutation for prognosis in NSCLC patients after complete surgery, which more reflective of natural process, remains controversial. We sought to examine the predictive value of EGFR mutation in NSCLC. Several studies with small sample sizes have been reported but small studies bring bias especially in a postoperative setting. Therefore, we sought to pool all current evidence to show the true effects.

Methods: Electronic databases were used to search the relevant articles. Disease-free survival (DFS), which will be less effected by subsequent treatments after recurrence, was the primary endpoint. The DFS between EGFR mutated and wild-type patients were compared focus on stage I patients who are rarely received adjuvant therapy. Besides, the DFS of patients with 19 exon deletion (19del) and 21 exon L858R mutation (L858R) were compared. A random effects model was used.

Results: A total of 19 relevant studies which involved 4,872 cases were enrolled and 2,086 patients were EGFR-mutated. The majority of studies used PCR-based methods to detect EGFR mutations. Through meta-analysis, we observed the DFS of EGFR-mutated patients were similar to wild type patients in overall population (HR 0.93, 95% CI: 0.74 to 1.17). Similar results were observed in stage I subgroup (HR 0.82, 95% CI: 0.50 to 1.33). DFS of 19 del patients were potentially inferior to L858R patients but the difference was not significant (HR 1.38, 95% CI: 0.76 to 2.52).

Conclusions: There was no significant difference in postoperative DFS between EGFR-mutant patients and wild-type with resected NSCLC. In addition, there is still insufficient evidence to support different postoperative treatment strategies (especially for stage I) for both mutated and wild-type patients. However, 19 del may be a negative factor, which may require more strict management. Thus, we strongly encourage

reporting specific prognostic impacts of different mutation types.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor mutation (EGFR mutation); disease-free survival (DFS); meta-analysis

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Introduction

Primary lung cancer has become the leading cause of cancer-related death in both male and female populations in most part of the world (1). Non-small cell lung cancer (NSCLC) which predominantly consists of adenocarcinoma, squamous cell carcinoma and large cell carcinoma, accounts for 80–85% of all lung cancer cases (2). Complete surgical resection is the gold standard treatment of early-stage NSCLC. However, even patients with completely resected stage IA NSCLC have a 5-year mortality rate of approximately 30% (3). A meta-analysis which was composed of 52 randomized clinical trials and included 9,387 cancer patients concluded that adjuvant chemotherapy only reduced 13% of the risk mortality in the first year and suggested a considerable number of patients do not benefit from adjuvant chemotherapy (4). It is important to identify high-risk patients for poor outcome with adjuvant chemotherapy and find other adjuvant therapies that can improve survival in this population. Previous studies regarding the prognostic factor of lung cancer focus on the clinical features and gene expression (5-7). In recent years, the discovery of oncogenic driver mutations have led to the emergence of a new therapeutic strategy in lung cancer. Furthermore, different oncogenic driver mutations have exhibited a tendency to correlate with different biological behaviors which suggests that some clinical findings need to be reconsidered. Epidermal growth factor receptor (EGFR) is a crucial mutation that the frequency of which ranges from 15% to 44% in East Asian patients with adenosquamous lung carcinoma.

EGFR, a 170-kDa receptor tyrosine kinase (TK), plays a critical role in promoting cell division, migration, angiogenesis and inhibits apoptosis (8). The exon 19 deletion and exon 21 L858R mutations are the most common EGFR mutations which account for 85–90% of all EGFR mutation cases (9,10). EGFR mutation is associated with advantageous clinical outcomes in patients with advanced NSCLC, predominantly as a result of its favorable response to EGFR-tyrosine kinase inhibitors (11,12). In addition to their important role in the planning of treatment strategies for advanced or recurrent NSCLC, EGFR mutations have intrinsic impact on the prognosis (13). However, its impact on the prognosis of resectable NSCLC after complete surgery remains controversial. To elucidate the prognostic value of EGFR mutation status, we attempted to conduct a meta-analysis of all available evidence to assess the correlation between EGFR mutations and prognosis in surgically resected lung cancer.

Methods

Literature search

Relevant studies were retrieved by searching PubMed, Embase and the Central Registry of Controlled Trials of the Cochrane Library, using the following terms: "EGFR mutation" AND "disease-free survival" AND Resected OR resectable OR Prognosis. The last research time was May 6, 2017. Language was restricted to Chinese and English. In addition, a manual search through reference lists of relevant reviews and included studies were conducted. The search was carried out independently by two authors.

Inclusion criteria and Exclusion criteria

The following criteria was used to select publications: (I) studies assessed the correlation between disease-free survival (DFS) and EGFR status in resectable NSCLC after complete surgery; (II) all patients had never been treated with EGFR-TKI; (III) the available tumor tissue samples instead of circulating free DNA in serum were used to analyze the EGFR mutations; (IV) studies needs to be in English or Chinese in spite of publication time. Studies that fail to meet all above criteria were excluded from analyses.

Data collection

The primary outcome of our study was progression-free

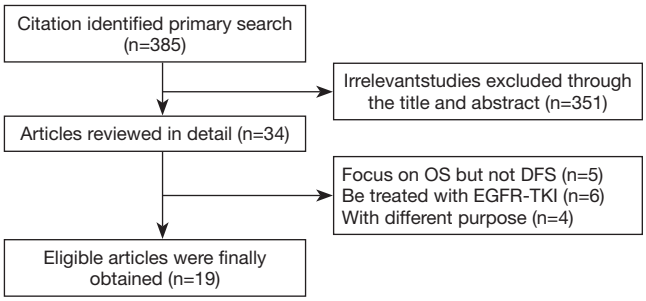

Figure 1 Profile summarizing the trial flow.

survival (PFS). Publication characteristics details such as first author's name, publication year, tumor type, sample size, EGFR status, stage, evaluation method of EGFR mutation status was extracted by two independent investigators. Any disagreement was discussed amongst investigators to reach consensus. Only univariate analysis results were used when both univariate and multivariate analysis results were supplied in a study as the most of included studies were univariate analysis. We used the data directly when the included studies provided precise HR (95% CI). In the case of the studies only provided Kaplan-Meier survival curves, Engage Digitizer version 2.11 software was used to extract relevant numerical value from survival curves and calculate the HR (95% CI) (14,15).

Statistical analysis

The heterogeneity of the individual HR was calculated using Cochran's Q-statistic test and I^2 test. I^2<25% was considered as no heterogeneity, I^2=25–50% and I^2>50% were considered as moderate heterogeneity and strong heterogeneity respectively (16,17). P value less than 0.05 was considered to be statistical significance. In order to avoid any potential heterogeneity, a random-effects model was used in this meta-analysis. When available, subgroup and sensitivity analysis were stratified for predisposed factors. To assess the strength of the findings, sensitivity analyses were conducted by excluding one study at a time. Egger's test was used to investigate publication bias. All statistical analyses were performed using STATA 11.0 software.

Results

Eligible studies

We identified 385 potentially relevant records through the search strategy. And 351 studies were excluded after checking the title and abstract, for it was very clear that their research contents didn't meet our inclusion criteria. Then the full texts of 34 articles were carefully screened, and a total of 19 studies (18-36) were eligible for the final analysis. *Figure 1* summarized the flow chart.

Our meta-analysis was composed of 19 studies to include a total of 4,872 cancer patients with no history of EGFR-TKI as adjuvant or neoadjuvant therapy. The period of included studies ranged from 2007 to 2016. The DFS between EGFR mutated and wild-type patients were compared in 18 studies (18-35); 7 of them reported specific data on stage I patients. DFS of patients with 19 exon deletion (19del) and 21 exon L858R mutation (L858R) were compared in 4 studies. *Table 1* summarized the characteristics of all involved studies.

Meta-analysis

According to all literatures with available data, 18 studies consisting of 4,353 patients reported the results on the DFS between EGFR mutated and wild-type patients. As shown in *Figure 2*, the DFS of EGFR-mutated patients were similar to wild type patients in overall population (HR 0.93, 95% CI: 0.74 to 1.17; heterogeneity, P=0.000, I^2=66.8%). We conducted subgroup analysis based on information provided by 7 studies (18,21-23,26,33,34). We found that EGFR status had no significant effect on DFS in stage I patients, with the HR of 0.82 (95% CI: 0.50 to 1.33), and obvious heterogeneity existed among them (I^2=45.4%, P=0.089; *Figure 3*). There was also no significant difference between patients with EGFR mutation and patients with wide type on DFS in stage II–III patients (HR 0.73, 95% CI: 0.43 to 1.24; heterogeneity, P=0.002, I^2=79.7%; *Figure 4*). To avoid the selection bias of the EGFR status, we performed retrospective test subgroup and retrospective review subgroup. And no significant difference was observed in retrospective test subgroup (HR 0.86, 95% CI: 0.65 to 1.15; P=0.316; heterogeneity, P=0.005, I^2=59%; *Figure 5*) and retrospective review subgroup (HR 1.09, 95% CI: 0.81 to 1.48; heterogeneity, P=0.002, I^2=79.7%; *Figure 6*). Additionally, we pooled the results of 19del patients and L858R patients. Four studies composed of 1,471 patients reported this data (19,21,22,36). However, no differences between 19del and L858R groups were observed (HR 1.38, 95% CI: 0.76 to 2.52; heterogeneity: P=0.062, I^2=59.1%; *Figure 7*). Additional subgroup analysis was performed since significant heterogeneity was observed

Table 1 Characteristic of the included studies

First author	Year	Tumor type	No. of patients	Mt	Region	Stage	Evaluation
Dong	2013	Adenocarcinoma	301	158	China	Ia–IIIa	Real-time quantitative PCR + DNA sequencing technology
Isaka	2016	Adenocarcinoma	202	100	USA	I–III	Cycleave polymerase chain reaction or loop-hybrid mobility shift assays
Zhi	2016	Adenosquamous	106	29	China	Ia–IIIa	–
Nishii	2017	Adenosquamous	388	185	Japan	I	–
Liu	2014	Adenosquamous	131	58	China	Ia–IIIa	Nested PCR amplification
Izar	2013	NSCLC	317	62	USA	I	Direct sequencing and SNaPshot
Lin	2014	Adenosquamous	163	97	Taiwan	I	PCR
Ragusa	2014	NSCLC	230	22	Italy	Ia–IIIa	DNA Sequencing
Kobayashi	2008	Adenosquamous	127	64	Japan	Ia	PCR
Lim	2007	Adenosquamous	27	15	Taiwan	Ia–IIIa	PCR
Nose	2009	Adenosquamous	393	147	Japan	Ia–IIIa	PCR
Sun	2013	NSCLC	150	43	China	IIIa	PCR
Lee	2009	Adenosquamous	117	53	Korea	Ia–IIIa	Nested PCR ampliWcation
Hayasaka	2017	Adenosquamous	519	519	–	Ia–IIIa	–
Koh	2010	NSCLC	130	–	Korea	I–III	PCR
Tsao	2011	NSCLC	436	393	Canada	Ib–II	PCR
Maki	2013	Adenosquamous	28	7	Japan	Ia	Mutant non-enriched PCR
Ohba	2014	Adenosquamous	242	122	Japan	I	PCR
Kim	2013	NSCLC	865	354	Korea	I–III	Nested PCR

NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

in the overall analysis. After stratification by tumor type, no significant difference was observed in adenocarcinoma studies (HR 0.92, 95% CI: 0.77 to 1.11; heterogeneity, P=0.328, I^2=12.2%; *Figure 8*) and NSCLC studies (HR 0.90, 95% CI: 0.53 to 1.52; heterogeneity, P=0.000, I^2=82.4%; *Figure 9*). *Table 2* summarized the results of all subgroups.

Publication bias

The funnel plot and Egger's test were performed for the overall comparison. No obvious visual asymmetry was observed in funnel plots (*Figure 10*) for DFS, and the P values of the Egger's test were greater than 0.05.

Discussion

Due to the predictive value to EGFR-TKI, EGFR mutation plays a crucial role in precision medicine. Except for its contribution to predict the response to EGFR-TKI, EGFR mutations are anticipated to have inherent prognostic implication. A prior research indicated that EGFR may be a positive prognostic factor for survival in patients with advanced NSCLC (35). In addition, the effect of EGFR mutations on the prognosis of resected NSCLC has been reported by previous studies, but the results were disputed. A meta-analysis is required to integrate all available results to provide further insight on this controversial issue. Combined with the available data provided by the included studies, our results supported the assumption that EGFR mutations have no prognostic value in complete resected NSCLC, but significant heterogeneity was observed.

A previous study has suggested that the status of EGFR mutations was associated with sensitivity to chemotherapy (37), however, it is difficult to determine the

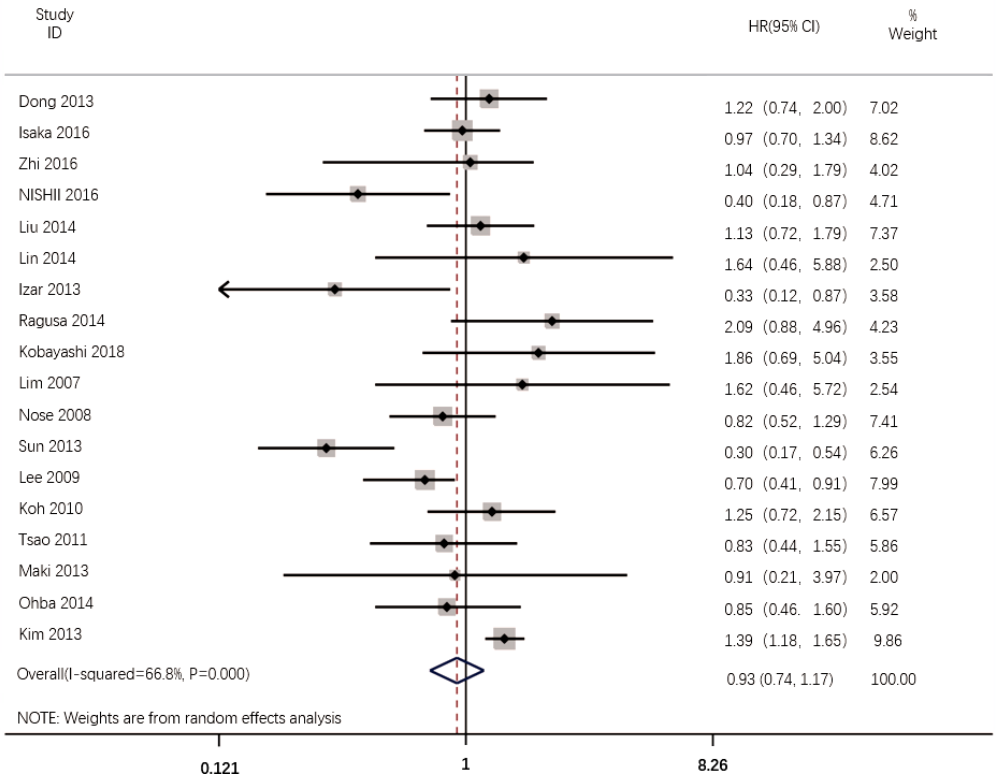

Figure 2 Forest plot of the pooled HRs for DFS by overall population. DFS, disease-free survival; HR, hazard ratio.

prognostic value of EGFR mutations when patients have received adjuvant treatment. Thus, we carried out subgroup analyses in patients with stage I NSLCL who rarely receive adjuvant therapy. Interestingly, our results show that there is no significant different in DFS between the EGFR-mutated patients and those with wild type in stage I subgroup (HR 0.82, 95% CI: 0.5 to 1.33), which is consistent with the overall result. This result implies that EGFR mutation may not an independent prognostic factor for DFS.

Our study found no significant difference in DFS between patients with mutant-type EGFR and those with wild-type which is consistent with a previous meta-analysis (38). It suggested that EGFR mutations may merely play a detrimental role in advanced stage and may not have much impact on early stages of NSCLC. However, the population of this study is mixed with significant heterogeneity ($P<0.01$, $I^2=66.8\%$). After carried out a subgroup analyses by tumor type, we suspect that it was the tumor type resulted in the heterogeneity.

Several studies have showed that patients with advanced NSCLC harboring Ex19 mutations have better OS than those with Ex21 mutations treated with EGFR-TKI (39-41). Moreover, a prior study showed advanced NSCLC patients harboring Ex19 mutations have shown better responses to chemotherapy than those with Ex21 deletions (42). Conversely, a recently published study from Tetsuya Isaka (43) reported that Ex21 adenocarcinoma were low grade with a lepidic growth pattern, whereas wild-type tumors were high grade and contained solid and papillary components with vascular invasion; Ex19 tumors were intermediate grade (44). This finding is consistent with the findings of Yang *et al.* (44) which showed that Ex21 adenocarcinomas had a higher ratio of ground-glass opacity than Ex19 tumors (43). In the present study, patients with 19del potentially had inferior DFS to those with L858R but the result did not reach statistical significance (HR 1.38, 95% CI: 0.76 to 2.52). As stated above, we surmise that the result may be confused by chemotherapy which is a subsequent treatment after surgery for patients with stage II–III disease.

Our study gives further evidence to support previous assumptions that EGFR mutations had no impact on the prognosis of resected NSCLC. However, there are several limitations. First, this is a retrospective analysis, prospective analysis is needed to further illustrate these issues. Second, since follow-up time of each study was not the same,

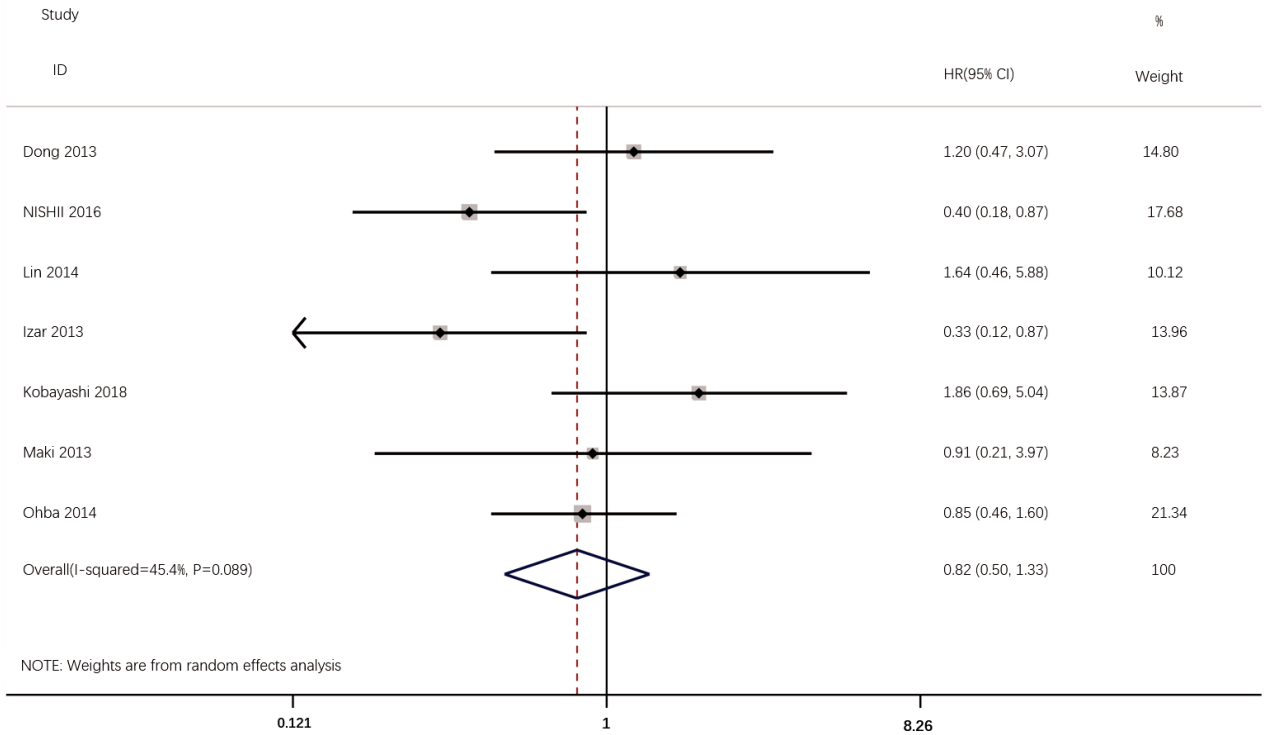

Figure 3 Forest plot of the pooled HRs for DFS by stage I subgroup. DFS, disease-free survival; HR, hazard ratio.

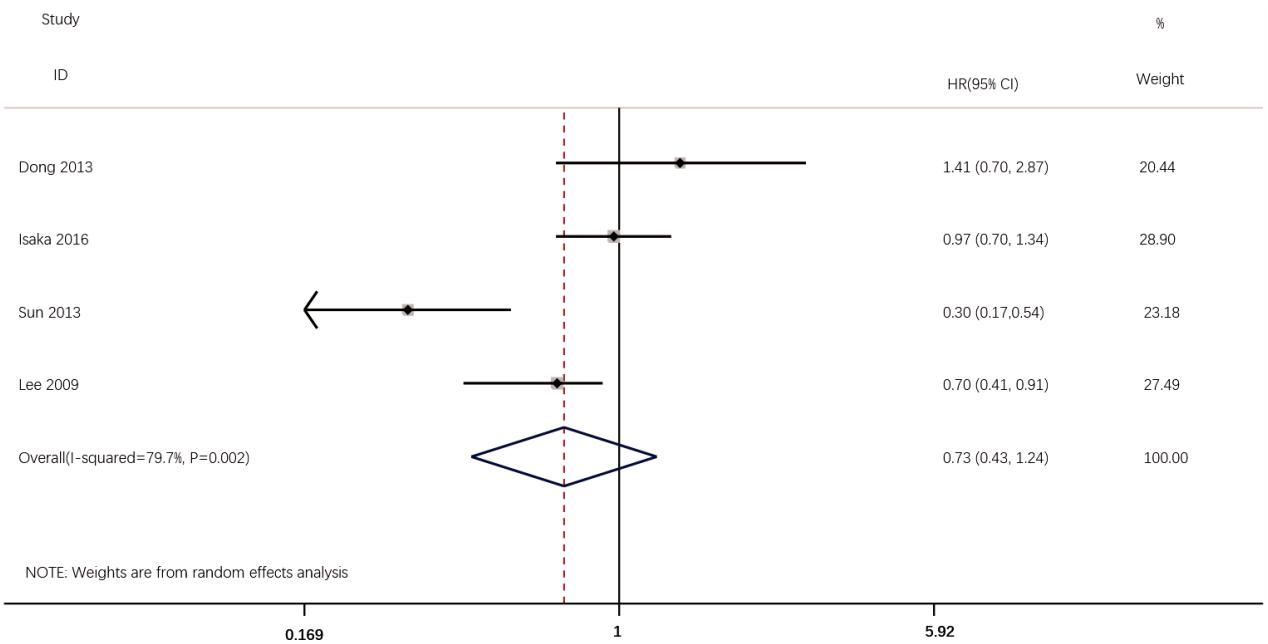

Figure 4 Forest plot of the pooled HRs for DFS by stage II–III subgroup. DFS, disease-free survival; HR, hazard ratio.

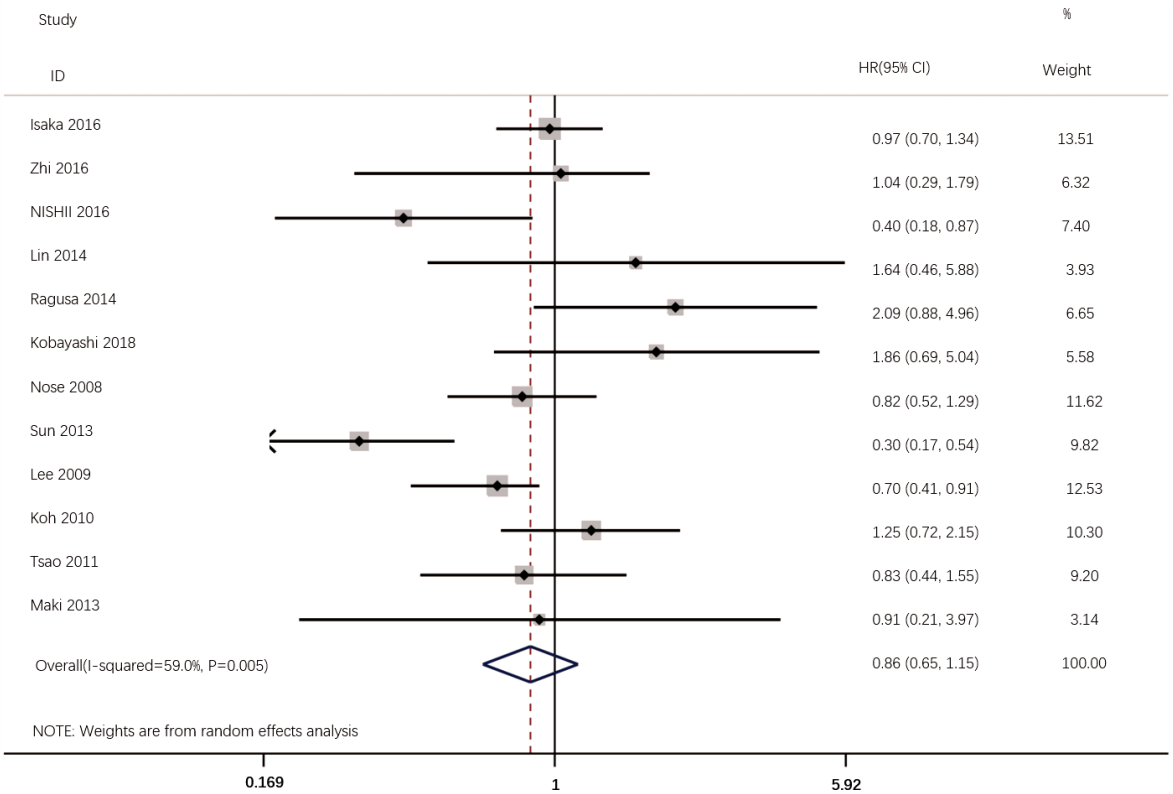

Figure 5 Forest plot of the pooled HRs for DFS by retrospective test EGFR status subgroup. DFS, disease-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor.

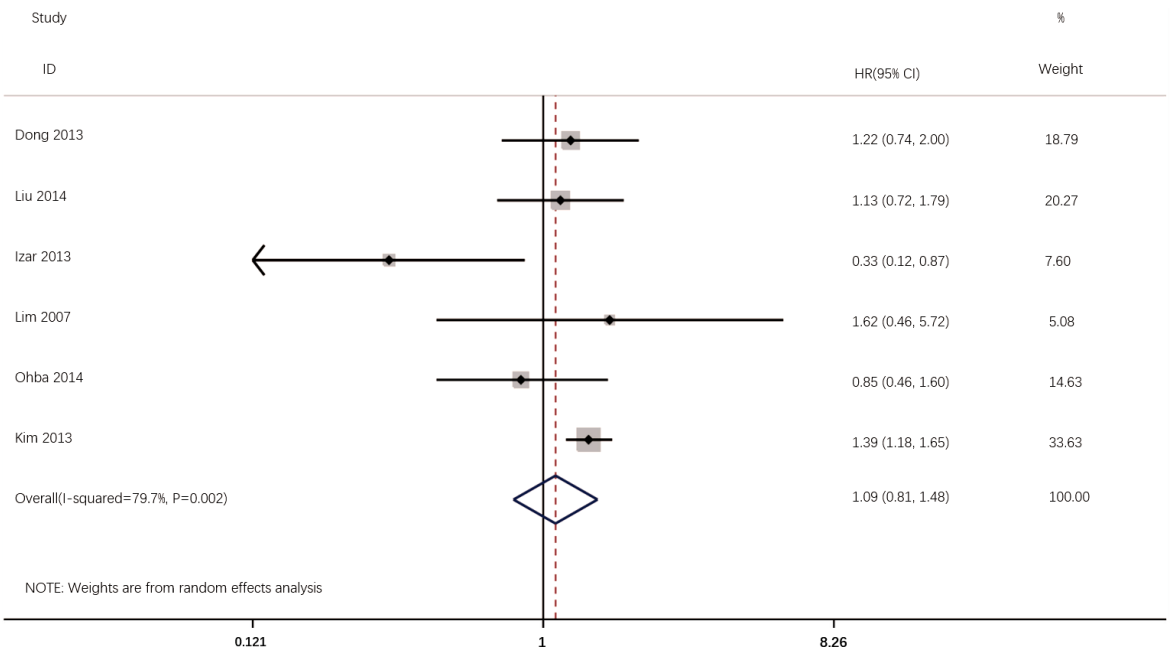

Figure 6 Forest plot of the pooled HRs for DFS by retrospective review EGFR status subgroup. DFS, disease-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor.

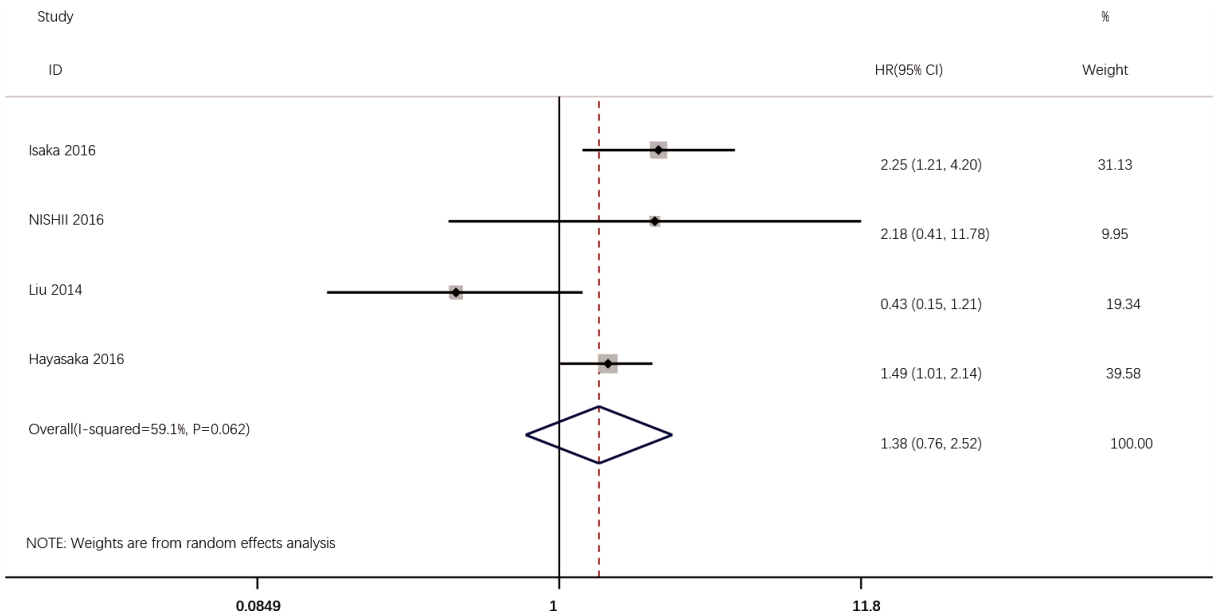

Figure 7 Forest plot of the pooled HRs for DFS by 19del or L858R subgroup. DFS, disease-free survival; HR, hazard ratio.

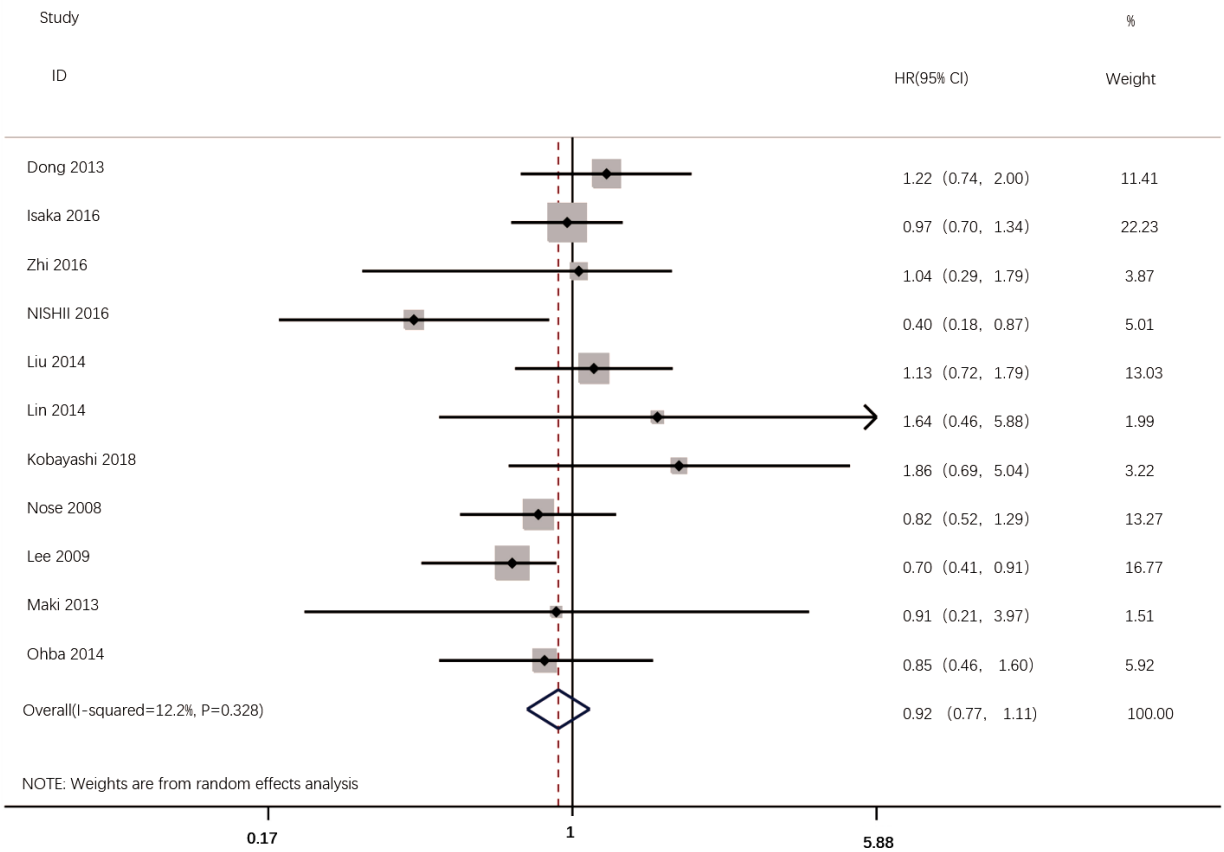

Figure 8 Forest plot of the pooled HRs for DFS by adenocarcinoma subgroup. DFS, disease-free survival; HR, hazard ratio.

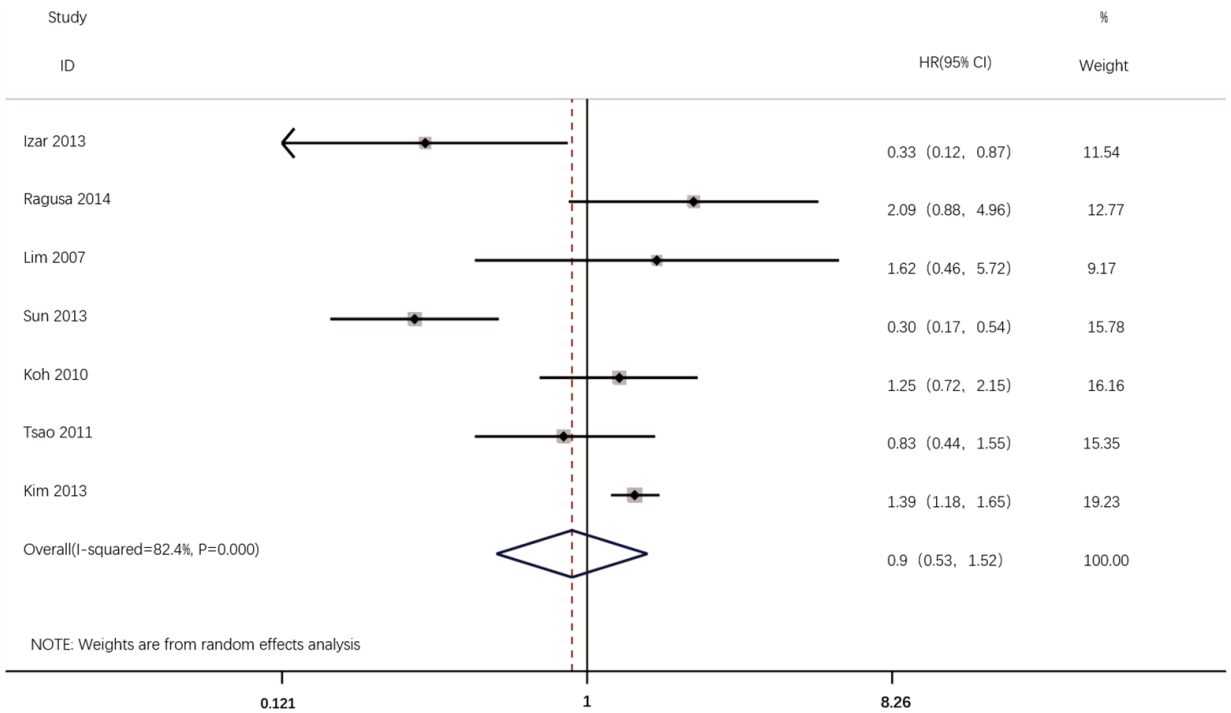

Figure 9 Forest plot of the pooled HRs for DFS by NSCLC subgroup. DFS, disease-free survival; HR, hazard ratio; NSCLC, non-small cell lung cancer.

Table 2 Subgroup analysis on DFS among cancer patients according to EGFR status

Subgroup	HR	95% CI	P
Stage			
I	0.82	0.50 to 1.33	0.423
II–III	0.94	0.56 to 1.57	0.243
EGFR type			
19del or L858R	1.38	0.76 to 2.52	0.288
The selection method of the EGFR status			
Retrospective test	0.86	0.65 to 1.15	0.316
Retrospective review	1.09	0.81 to 1.48	0.567
Race			
Asian	0.94	0.74 to 1.19	0.6
Caucasian	0.85	0.34 to 2.16	0.71
Tumor type			
Adenocarcinoma	0.92	0.77 to 1.11	0.379
NSCLC	0.90	0.53 to 1.52	0.694

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; HR, hazard ratio.

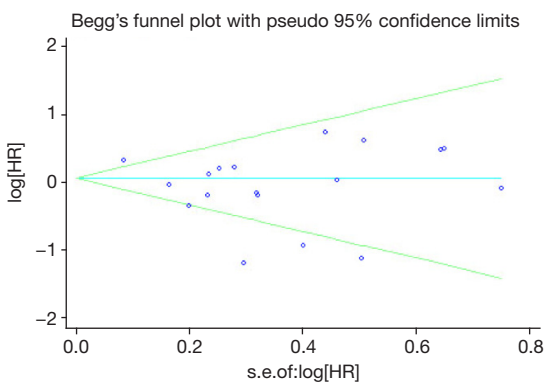

Figure 10 Funnel plot for publication bias. The two oblique lines indicate the pseudo 95% CI.

significant heterogeneity was observed. In addition, we can't avoid the influence of the adjuvant chemotherapy or postoperative radiotherapy based on the original reports. Further studies are necessary.

Conclusions

In summary, our results demonstrated that EGFR mutations

showed no prognostic value in primary resected NSCLC. When deciding treatment strategy for postoperative (especially stage I) patients, there is no evidence support difference between mutated and wild-type patients. However, 19 del might be a negative factor through indirect reason, which may require more strict management. We strongly encourage reporting the specific prognostic impacts of different mutation types.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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