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ORIGINAL ARTICLE

CT and clinical characteristics that predict risk of EGFR mutation in non-small cell lung cancer: a systematic review and meta-analysis

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Abstract

Introduction To systematically analyze CT and clinical characteristics to find out the risk factors of epidermal growth factor receptor (EGFR) mutation in non-small cell lung cancer (NSCLC). Then the significant characteristics were used to set up a mathematic model to predict EGFR mutation in NSCLC.

Materials and methods PubMed, Web of Knowledge and EMBASE up to August 17, 2018 were systematically searched for relevant studies that investigated the evidence of association between CT and clinical characteristics and EGFR mutation in NSCLC. After study selection, data extraction, and quality assessment, the pooled odds ratios (ORs) were calculated. Then from May 2017 to August 2018, all NSCLC received EGFR mutation examination and CT examination in our hospital were chosen to test the prediction model by receiver operating characteristic (ROC) curves.

Results Seventeen original studies met the inclusion criteria. The results showed that the ORs of ground-glass opacity (GGO), air bronchogram, pleural retraction, vascular convergence, smoking history, female gender were, respectively, 1.93 ($P=0.003$), 2.09 ($P=0.03$), 1.59 ($P<0.01$), 1.61 ($P=0.001$), 0.28 ($P<0.01$), 0.35 ($P<0.01$). The result of speculation, cavitation/bubble-like lucency, lesion shape, margin, pathological stage were, respectively, 1.19 ($P=0.32$), 0.99 ($P=0.97$), 0.82 ($P=0.42$), 1.02 ($P=0.90$), 0.77 ($P=0.30$). 121 NSCLC received EGFR mutation test were included to test the prediction model. The mathematical model based on the results of meta-analysis was: $0.74\times$air bronchogram $+0.46\times$pleural retraction $+0.48\times$vascular convergence $-1.27\times$non-smoking history $-1.05\times$female. The area under the ROC curve was 0.68.

Conclusion Based on the current evidence, GGO presence, air bronchogram, pleural retraction, vascular convergence were significant risk factors of EGFR mutation in NSCLC. And the prediction model can help to predict EGFR mutation status.

Keywords Spiral computed tomography · Epidermal growth factor receptor · Non-small cell lung carcinoma · Meta-analysis

Introduction

Lung cancer was the first cause of oncological death worldwide. Approximately 85% of lung cancers correspond to non-small lung cancer (NSCLC), divided principally in adenocarcinoma (ADC) (upto 50%) and squamous cell lung cancer (SCC) (30%) [1]. Most lung cancers diagnosed were at advanced stages that curative surgery was not available. Even early-stage lung cancers that received curative surgical resection are likely to experience recurrence or metastasis [2, 3]. The development of molecule-targeted therapies has revolutionized NSCLC therapy by affording better treatment effect and less toxicity than traditional chemotherapy [4]. The most common activated driver oncogene was epidermal growth factor receptor (EGFR), which is present in about 50% of Asian patients and upto 15% of white patients [5]. EGFR mutations are closely associated with a high response rate to treatment with EGFR tyrosine kinase inhibitor (TKI) [6].

Recent practice guidelines in oncology and pathology recommend that all locally advanced and metastatic NSCLC

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with ADC histology undergo testing for the most common targetable genetic abnormalities, such as EGFR mutation [7]; while getting tumor samples for EGFR mutation was risky and costly and not suitable for all patients. It would be very useful if EGFR mutation status could be identified without molecular examination. Further, due to the tumor heterogeneity, the tumor sample for mutation test may result as negative but may be truly positive [8, 9]. Many studies show that several clinical factors are associated with EGFR mutations, such as the female gender, nonsmokers, and East Asian origin [10]. Also many studies had shown that CT characteristics were associated with EGFR mutation, such as lesion shape, air bronchogram, ground-glass opacity (GGO) presence, while their results have some inconsistence [11, 12].

For our knowledge very few meta-analysis had summarized the association between different CT characteristics and EGFR mutation status [11]. Therefore we designed this study to sum up CT and clinical characteristics which can predict EGFR mutation in NSCLC. And a mathematical model was set up to test the predictive value of the results.

Materials and methods

This retrospective study was approved by the institutional review board. A systematic review of the literature was performed to summarize the evidence of association between CT and clinical characteristics and EGFR mutation in NSCLC. This manuscript was prepared using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [13].

Then from May 2017 to August 2018, all NSCLC received EGFR mutation examination and CT examination in our hospital were retrospectively chosen to test the prediction model which was made according to the meta-analysis result. All images (1.25 mm thickness, contrast material–enhanced) were viewed at lung window settings (width 1500 HU, level − 700 HU) on PACS. Two radiologists who have engaged in thoracic radiology for at least 5 years, blinded to the EGFR mutation status interpreted all CT images. In case of conflict judgments, consensus was reached by discussion.

Search strategy

We performed an unrestricted search in PubMed, Web of Knowledge and EMBASE upto August 17, 2018. The search terms "computed tomographic", "epidermal growth factor receptor mutation", "lung cancer" and their synonyms were combined without language restriction and medical subject headings (MeSH) were applied if available. Reference lists of retrieved articles and review articles were manually searched for other relevant studies. Two authors independently performed the search and reviewed all identified publications for inclusion, using predetermined criteria.

Inclusion criteria

Studies were included in this review if (1) all included cases were pathologically confirmed as lung cancer and received EGFR mutation examination, (2) chest CT was performed and systematically assessed for different CT and clinical characteristics, (3) at least one of the following CT characteristics: lesion shape, air bronchogram, margins, pleural retraction, vascular convergence, cavitation/bubble-like lucency, speculation, GGO presence and one of the clinical characteristics (gender or smoking history) was screened; (4) presentation of quantitative data [for example event rates or odds ratios (OR)] reflecting association between different CT characteristics and EGFR mutation conditions, (5) reports of lectures, conference papers, and animal experiments were excluded.

Data extraction and quality assessment

For each eligible study, the following data were extracted: (1) study characteristics: first author, publication year, country, study design. (2) Patient characteristics: age, gender, smoking history. (3) Pathological characteristics: histological type, pathological stage and EGFR mutation conditions. (4) CT characteristics: lesion size, lesion shape, air bronchogram, margins, pleural retraction, vascular convergence, cavitation/bubble-like lucency, speculation and GGO presence. (5) The value of OR and 95% confidence interval (CIs) or original dates to calculate OR value.

Methodologic quality of included studies was assessed using the Newcastle–Ottawa Scale [14]. Data extraction and quality assessment were carried out by two reviewers independently. In case of conflict judgments, consensus was reached by discussion.

Data analysis

ORs and corresponding 95% CIs were used to assess the strength of association between each CT or clinical characteristics and EGFR mutation.

Statistical heterogeneity was determined using the Q-test and I^2-test [15]. In the Q-test, at a level of $a = 0.1$, $P \leq 0.1$ indicates heterogeneity exists. The I^2-test with a value of 25%, 50%, and 75% indicate low heterogeneity, moderate heterogeneity and high heterogeneity. If $I^2 > 50\%$ or $P \leq 0.1$, the random-effects model (DerSimoniane–Laird model) was used. Otherwise, the fixed-effects model (Mantel–Haenszel model) was used. Publication bias was evaluated by Begg's funnel plot. $P > 0.05$ was considered as no publication bias

existed. Statistical analyses were performed using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA 12.0 (StataCorp, College Station).

A mathematical model was set up based on significant CT and clinical characteristics which were detected by meta-analysis multiplied the corresponding regression coefficients. Receiver operating characteristic (ROC) curves for the model were constructed and the available area under the curve (AUC) was calculated. The Youden Index was used to calculate the best cutoff. This analysis was performed using SPSS (version 21.0; SPSS Inc., IBM Co.).

Results

Study selection and characteristics

Seventeen original studies were retrieved from 2337 potential publications that assessed the relationship of CT characteristics and EGFR mutation in lung cancer. Figure 1 summarizes the screening process and reasons for exclusion.

All included studies were case–control studies. The characteristics of included studies are shown in Table 1. Different types of lung cancers (111 ADC, 25 SQC and 12 other types) were included in Usuda et al. [16]. Different types of NSCLC were included in Sabri et al. [17] and Kim et al. [18]. Only ADCs were included in the rest of included studies. Except Sabri et al. [17], Yano et al. [19] and Sugano et al. [20] detect EGFR mutations in exons 19 and 21, the other studies detect EGFR mutations in exons 18, 19, 20, and 21.

GGO presence and EGFR mutation

Eleven studies [7, 16, 17, 19–26] were included in the analysis of relationship between GGO presence and EGFR mutation states. In total 2226 cases with 595 GGO presence and 1631 GGO-negative cases were analyzed. In GGO presence group 346 (58.15%) EGFR mutations exist. In GGO-negative group 753 (46.17%) EGFR mutations exist. Except two studies, all other studies showed that GGO presence was a risk factor of EGFR mutations. The pooled OR was 1.93 (95% CI 1.24–2.99, $P=0.003$), which showed GGO presence was a significant risk factor of EGFR mutation (Fig. 2). A random-effect model was chosen for meta-analysis as significant heterogeneity ($I^2=65\%$, $P=0.001$) was observed. Funnel plot shows no publication bias exists ($P=0.33$).

Speculation and EGFR mutation

Eight studies [17–21, 27–29] were included in this analysis. 1591 cases with 994 positive speculation sign and 597 negative speculation signs were analyzed. 480 (48.29%) EGFR mutations existed in the speculation-positive group and 272 (45.56%) EGFR mutations existed in the speculation-negative group. Except two studies, all others showed that speculation-positive was related to EGFR mutation in NSCLC. The pooled OR was 1.19 (95% CI 0.84–1.69, $P=0.32$), which was not statistically significant

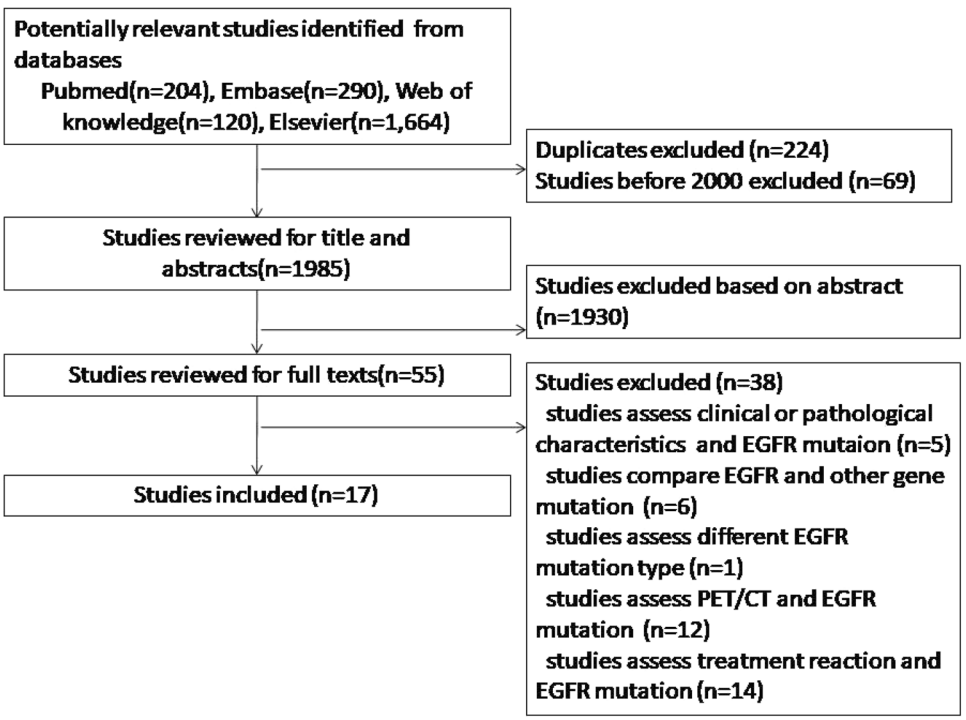

Fig. 1 Flow diagram of identification of relevant studies

Table 1 Characteristics of studies included in the meta-analysis

First author, year	Country	Design	Patients	Age range (years)	Lung cancer type	Samples for mutation test	EGFR mutation test	CT image slice thickness	CT and clinical characteristics	Overall quality
Yano, 2006	Japan	Case–control	80	40–86	ADC	Surgery	Exons 19, 21	1–2 mm	Vascular convergence, GGO presence, gender, smoking	8
Hsu, 2011	China	Case–control	162	34–86	Stage I ADC	Surgery	Exons 18–21	Unknown	GGO presence, gender, smoking	8
Sugano, 2010	Japan	Case–control	136	36–84	ADC	Surgery	Exons 19, 21	1–2 mm	GGO presence, spiculation, gender, smoking	8
Hsu, 2014	China	Case–control	149	32–89	Advanced ADC	Biopsy or surgery	Exons 18–21	1.25 mm, 1 mm	GGO presence, shape, margin, air bronchogram, gender, smoking	8
Usuda, 2014	Japan	Case–control	148	37–85	Lung cancer	Unclear	Exons 18–21	Unclear	GGO presence, gender, smoking	7
Zhou, 2015	China	Case–control	298	27–83	ADC	Unclear	Exons 18–21	0.625 mm	GGO presence, margin, spiculation, cavity, pleural retraction, gender, smoking	8
Dai, 2016	China	Case–control	204	Unclear	Stage IA ADC	Surgery	Exons 18–21	2 mm	Air bronchogram, margin, shape, spiculation, cavity, pleural retraction, vascular invasion, gender, smoking	8
Hasegawa, 2016	Japan	Case–control	263	38–90	ADC	Unclear	Exons 18–21	1 mm	Air bronchogram, pleural retraction, spiculation, cavity	8
Kim, 2016	Korea	Case–control	198	27–91	NSCLC	Surgery	Exons 18–21	0.625–1.5 mm	Margin, shape, spiculation, cavity, pleural retraction, gender, smoking	8
Liu, 2016	China	Case–control	385	30–80	ADC	Surgery	Exons 18–21	1.5 mm	Air bronchogram, margin, shape, spiculation, cavity, pleural retraction, vascular invasion, gender, smoking	9

Table 1 (continued)

First author, year	Country	Design	Patients	Age range (years)	Lung cancer type	Samples for mutation test	EGFR mutation test	CT image slice thickness	CT and clinical characteristics	Overall quality
Rizzo, 2016	Italy	Case–control	280	Unclear	ADC	Unclear	Exons 18–21	2 mm	GGO presence, air bronchogram, margin, shape, cavity, pleural retraction, gender, smoking	8
Sabri, 2016	England	Case–control	119	Unclear	NSCLC	Surgery	Exons 19, 21	3 mm or less	GGO presence, air bronchogram, spiculation, gender, smoking	8
Cao, 2017	China	Case–control	156	38–80	ADC	Biopsy and surgery	Exons 18–21	Unclear	GGO presence, air bronchogram, spiculation, shape, cavity, pleural retraction, vascular invasion, gender, smoking	8
Sacconi, 2017	Italy	Case–control	68	Unclear	Advanced ADC	Biopsy	Exons 18–21	1 mm	GGO presence, air bronchogram, margin, shape, pleural retraction, gender, smoking	8
Yang, 2015	China	Case–control	818	Unclear	ADC	Surgery	Exons 18–21	2 mm	GGO presence	9
Zhao, 2017	China	Case–control	282	33–87	ADC	Biopsy and surgery	Exons 18–21	0.5–7 mm	GGO presence, pleural retraction	9
Zou, 2017	China	Case–control	209	27–81	ADC	Unclear	Exons 18–21	1 mm	GGO presence, air bronchogram, margin, shape, cavity, pleural retraction, vascular invasion, gender, smoking	8

ADC adenocarcinoma, *NSCLC* non-small lung cancer, *GGO* ground-glass opacity

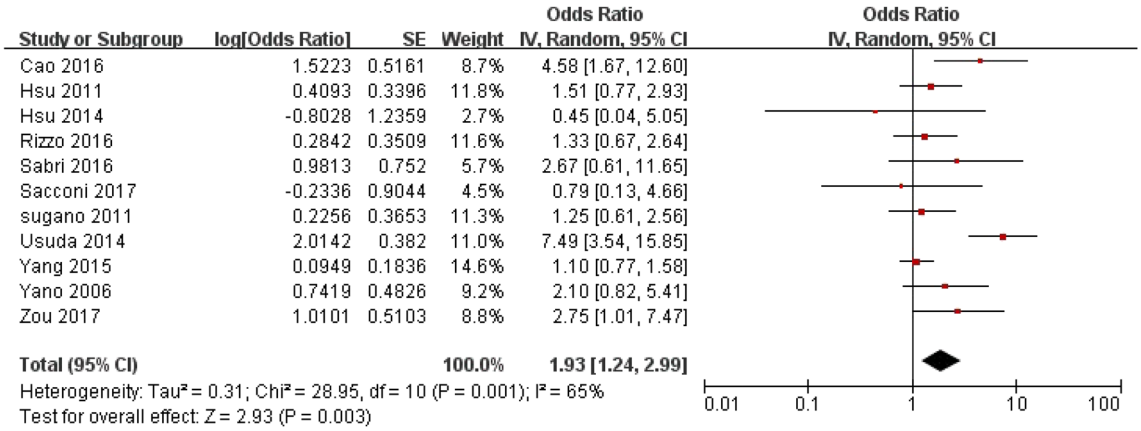

Fig. 2 Forest plots of the studies comparing tumors with and without GGO presence and EGFR mutation

(Supplement Figure 1). A random-effect model was chosen for meta-analysis as significant heterogeneity ($I^2 = 53\%$, $P = 0.04$) was observed. Funnel plot shows no publication bias exists ($P = 0.17$).

Air bronchogram and EGFR mutation

Eleven studies [7, 17, 21, 23, 24, 26–31] were included in this analysis. 2380 cases with 793 positive air bronchogram sign and 1587 negative air bronchogram sign were analyzed. 417(52.59%) EGFR mutations existed in the air bronchogram-positive group and 672 (42.34%) EGFR mutations existed in the negative group. Five studies with multivariate analysis showed that air bronchogram were independent risk factors of NSCLC. The pooled analysis showed that air bronchogram sign was a significant risk factor of EGFR mutation in NSCLC (OR 2.09, 95% CI 1.08–4.04, $P = 0.03$) (Fig. 3). A random-effect model was chosen for meta-analysis as significant heterogeneity ($I^2 = 94\%$, $P < 0.01$) was observed. Funnel plot shows publication bias exists ($P = 0.04$).

Pleural retraction and EGFR mutation

Eleven studies [7, 18–21, 24, 26–31] were included in this analysis. 2321 cases with 1132 positive pleural retraction sign and 1189 negative pleural retraction sign were analyzed. 595 (52.56%) EGFR mutations existed in the pleural retraction positive group and 448 (37.68%) EGFR mutations existed in the pleural retraction negative group. Five studies with multivariate analysis showed that pleural retraction were independent risk factor of NSCLC. The pooled analysis showed pleural retraction sign was a significant risk factor of EGFR mutation in NSCLC (OR 1.59, 95% CI 1.31–1.92, $P < 0.01$) (Fig. 4). A fixed-effect model was chosen for meta-analysis as low heterogeneity ($I^2 = 10\%$, $P = 0.35$) was observed. Funnel plot shows no publication bias exists ($P = 0.08$).

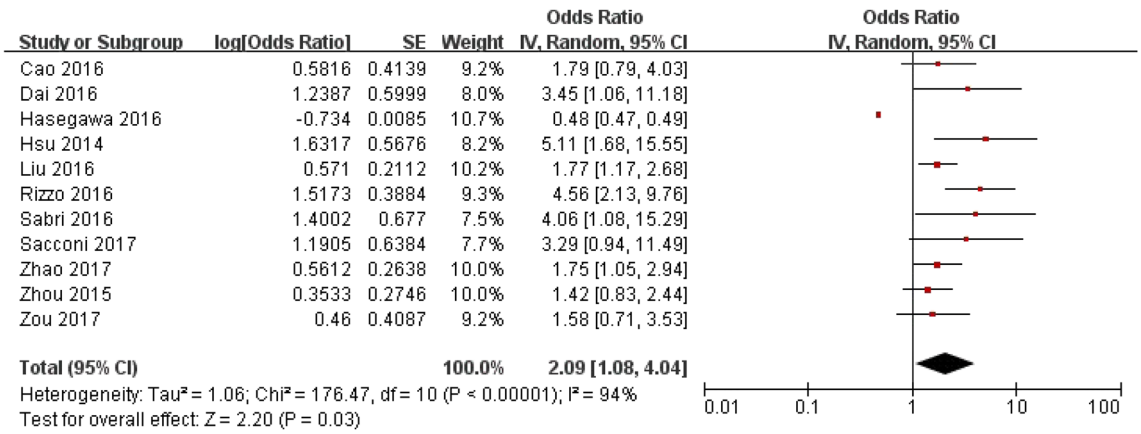

Fig. 3 Forest plots of the studies comparing tumors with and without air bronchogram and EGFR mutation

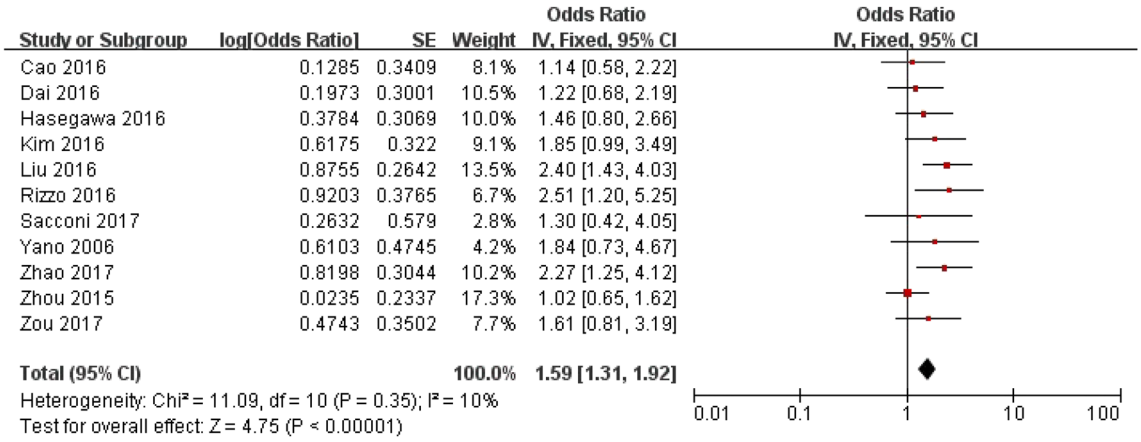

Fig. 4 Forest plots of the studies comparing tumors with and without pleural retraction and EGFR mutation

Cavitation/bubble-like lucency and EGFR mutation

Eight studies [7, 18, 21, 26–30] were included in this analysis. 1911 cases with 467 positive cavitation/bubble-like lucency sign and 1444 negative cavitation/bubble-like lucency sign were analyzed. 231 (49.46%) EGFR mutations existed in the cavitation/bubble-like lucency-positive group and 678 (46.95%) EGFR mutations existed in the cavitation/bubble-like lucency-negative group. Two studies with multivariate analysis showed that cavitation/bubble-like lucency sign were independent risk factors of NSCLC, while one study showed it was an independent protect factor of NSCLC. In our analysis cavitation/bubble-like lucency sign was a protect factor of EGFR mutation in NSCLC, but it was not statistically significant (OR 0.99, 95% CI 0.55–1.78, $P=0.97$) (Supplement Figure 2). A random-effect model was chosen for meta-analysis as significant heterogeneity ($I^2=78\%$, $P<0.01$) was observed. Funnel plot shows no publication bias exists ($P=0.053$).

Lesion shape and EGFR mutation

Seven studies [7, 18, 21, 23, 24, 26, 30] were included in this analysis. 1221 cases with 747 lesions with round shape and 474 lesions with irregular shape were analyzed. 354 (47.39%) EGFR mutations existed in the round shape group and 223 (47.04%) EGFR mutations existed in the irregular shape group. One study with multivariate analysis showed that irregular shape was an independent risk factor of NSCLC, and another study showed round shape was an independent protect factor of NSCLC. In our analysis round shape was a protect factor of EGFR mutation in NSCLC, but it was not statistically significant (OR 0.82, 95% CI 0.51–1.32, $P=0.42$) (Supplement Figure 3). A random-effect model was chosen for meta-analysis as significant heterogeneity ($I^2=61\%$, $P=0.02$) was observed. Funnel plot shows no publication bias exists ($P=0.08$).

Vascular convergence and EGFR mutation

Five studies [19, 21, 26, 28, 30] were included in this analysis. 973 cases with 464 positive vascular convergence sign and 509 negative vascular convergence sign were analyzed. 251 (54.09%) EGFR mutations existed in positive vascular convergence sign group and 258 (50.69%) EGFR mutations existed in negative vascular convergence sign group. Our study found vascular convergence sign was a significant risk factor of EGFR mutation in NSCLC (OR 1.61, 95% CI 1.20–2.16, $P=0.001$) (Fig. 5). A fixed-effect model was chosen for meta-analysis as low heterogeneity ($I^2=0\%$, $P=0.73$) was observed. Funnel plot shows no publication bias exists ($P=0.06$).

Margin and EGFR mutation

Five studies [7, 18, 23, 26, 30] were included in this analysis. 914 cases with 407 lesions with smooth margin and 507 lesions with lobulated or spiculated margin were analyzed. 209 (51.35%) EGFR mutations existed in smooth margin group and 242 (47.73%) EGFR mutations existed in lobulated or spiculated group. Two studies showed that smooth margin was risk factor of EGFR mutation in NSCLC, another three studies showed that smooth margin was a protect factor of EGFR mutation in NSCLC. Our analysis showed that smooth margin was a risk factor of EGFR mutation in NSCLC, while the result was not statistically significant (OR 1.02, 95% CI 0.74–1.40, $P=0.90$) (Supplement Figure 4). A fixed-effect model was chosen for meta-analysis as low heterogeneity ($I^2=0\%$, $P=0.66$) was observed. Funnel plot shows no publication bias exists ($P=0.06$).

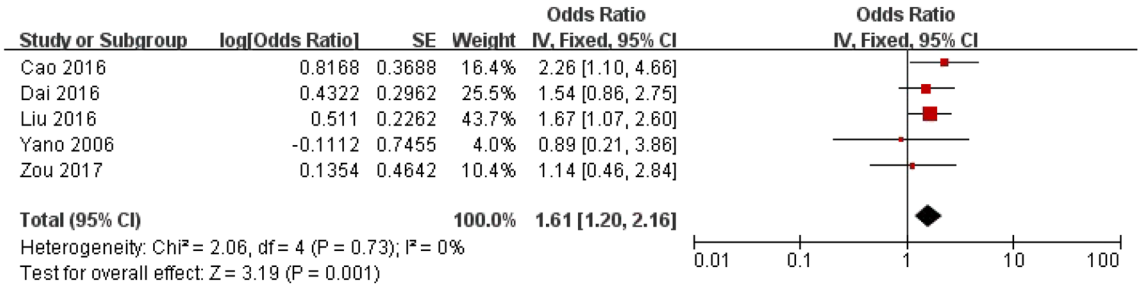

Fig. 5 Forest plots of the studies comparing tumors with and without vascular convergence and EGFR mutation

Smoking history and EGFR mutation

Thirteen studies [7, 16, 18–23, 26–30] in total of 2593 cases with 1531 patients smoked and 1062 patients never smoked were included in this analysis. 933 (60.94%) EGFR mutations existed in the smoking group and 319 (30.04%) EGFR mutations existed in the non-smoking group. All studies showed that NSCLC patients with a smoking history were less likely to have EGFR mutation. Our meta-analysis also showed that smoking was a protect factor of EGFR mutation in NSCLC (OR 0.28, 95% CI 0.21–0.36, $P<0.01$) (Supplement Figure 5). A random-effect model was chosen for meta-analysis as significant heterogeneity ($I^2=53\%$, $P=0.01$) was observed. Funnel plot shows no publication bias exists ($P=0.07$).

Gender and EGFR mutation

Thirteen studies [7, 16, 18–23, 27–31] were included in this analysis. 2628 patients with 1343 males and 1285 females were analyzed. 798 (58.75%) EGFR mutations existed in males and 319 (24.82%) EGFR mutations existed in females. All studies showed that females with NSCLC were more likely to have EGFR mutation. Our meta-analysis also showed that male was a protect factor of EGFR mutation in NSCLC (OR 0.35, 95% CI 0.29–0.41, $P<0.01$) (Supplement Figure 6). A fixed-effect model was chosen for meta-analysis as low heterogeneity ($I^2=36\%$, $P=0.10$) was observed. Funnel plot shows no publication bias exists ($P=0.27$).

Pathological stage and EGFR mutation

Nine studies [16, 18–21, 27–29, 31] in a total of 1987 cases with 1072 patients in stage I–II and 915 patients in stage III–IV were included in this analysis. 495 (46.18%) EGFR mutations existed in stage I–II group and 470 (51.37%) EGFR mutations existed in stage III–IV group. The pooled analysis showed that early stage was a protect factor of EGFR mutation in NSCLC, but the result was not statistically significant (OR 0.77, 95% CI 0.47–1.26, $P=0.30$) (Supplement Figure 7). A random-effect model was chosen for meta-analysis as significant heterogeneity ($I^2=80\%$, $P<0.01$) was observed. Funnel plot shows no publication bias exists ($P=0.74$).

Tumor size and EGFR mutation

Twelve studies analyzed the relationship between tumor size and EGFR mutation, while they defined tumor size for different meaning, such as the maximal diameter, average diameter. Because in most studies the tumor size was a continuous variable and no OR was shown, pooled analysis was not available. Some studies [16, 19–21, 23, 28] indicated that maximal diameter was significantly related to EGFR mutation, while one study [7] showed no relevant difference was found. Three studies [17, 18, 30] indicated that average diameter was significantly related to EGFR mutation, two studies [27, 29] had conflict result. Three studies [17, 20, 28] indicated that tumor size ≤ 3 cm/>3 cm was significantly related to EGFR mutation, one study [22] indicated that tumor size ≤ 2 cm/>2 cm was not significantly related to EGFR mutation.

Prediction model of EGFR mutation

121 NSCLC received EGFR mutation test. 65 NSCLC had EGFR mutation including 29 exon 19 deletion, 4 exon 20 insertion, 32 exon 21 missense. CT and clinical characteristics of all patients are shown in Table 2. The mathematical model based on the results of meta-analysis was: $0.74\times$air bronchogram $+0.46\times$pleural retraction $+0.48\times$vascular convergence $-1.27\times$non-smoking history $-1.05\times$female. The AUC of ROC curve was 0.68, the Youden Index was 0.34, the cutoff value was 0.47, and the best sensitivity and specificity for predicting EGFR mutation were 56.9% and 76.8%, respectively (Fig. 6).

Discussion

Although many original studies analyzed the relationship between CT characteristics and EGFR mutation in NSCLC, there are some conflicts in their results. Thus we conducted

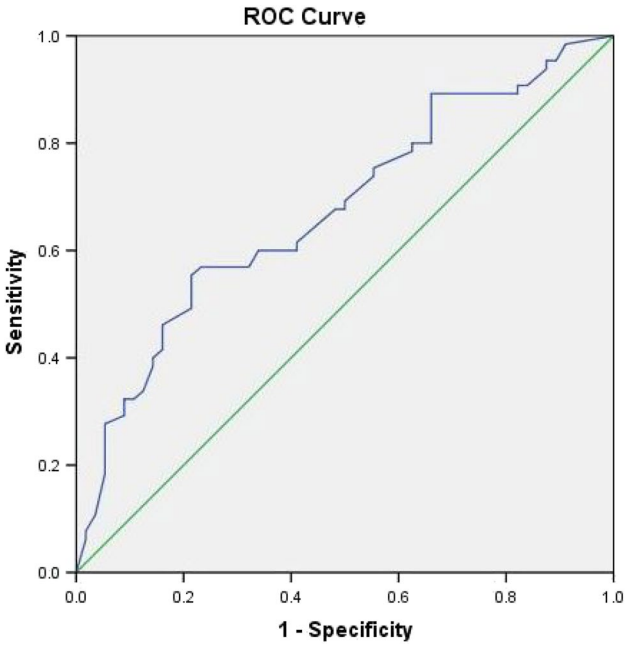

Fig. 6 ROC of the prediction score in the EGFR wild-type and mutation groups

Table 2 CT and clinical characteristics of included NSCLC patients

	EGFR mutation	Wild type
Gender		
Male	50	19
Female	15	37
Smoking history		
Yes	30	3
No	35	53
GGO		
Presence	27	27
Absence	38	29
Air bronchogram		
Presence	34	19
Absence	31	37
Pleural retraction		
Presence	34	24
Absence	31	32
Vascular convergence		
Presence	34	15
Absence	31	41

NSCLC non-small lung cancer, *GGO* ground-glass opacity

this meta-analysis to identify qualified studies to find out which CT characteristics were risk factors of EGFR mutation in NSCLC. We found that GGO presence, air bronchogram, pleural retraction, vascular convergence, non-smoking history and male gender were significant risk factors of EGFR mutation. Lesion shape, margin, cavitation/bubble-like lucency, and pathological stage were related to EGFR mutation, but the result was not statistically significant. According to the ROC curve the prediction model showed that these characteristics can help to predict EGFR mutation status of NSCLC. Although the sensitivity was not very high, the specificity reached 76.8%. This can help to exclude cases which have a lower possibility of EGFR mutation and help to reduce unnecessary test.

Some studies analyzed the relationship between radiomic characteristics and EGFR mutation in lung cancer. These studies showed that radiomic characteristics can predict EGFR mutation status. And radiomic characteristics combined with morphological characteristics can improve the prediction value a little [12, 28]. While extracting these radiomic characters was not as convenient as extracting morphological characteristics. We think these morphological characteristics extracted by viewing CT images can provide a rough information about EGFR mutation, then the one highly doubted to have gene mutation can have further radiomic analysis or gene mutation test.

GGO presence is notably higher in EGFR-mutated adenocarcinomas. Except Sacconi et al. [24] and Hsu et al. [22] all other included studies showed the same result. In these two studies, only advanced ADCs were included, which may include some bias. Because GGO more likely to occur in less-invasive ADC [32]. Many studies have reported that EGFR mutations were frequently associated with lepidic predominant ADC that commonly manifests as GGO-dominant lesion on CT [33, 34]. Exon 19 or 21 mutated adenocarcinomas show substantially higher GGO proportion than those of EGFR wild-type tumors [18, 33]. And the GGO percentage in tumors with exon 21 missense mutation was significantly higher than exon 19-mutation [33].

Air bronchogram was a significant risk factor of EGFR mutations. It is reported that lepidic predominant ADC show air bronchogram sign more often than other types [35]. Additionally, EGFR mutations were frequently associated with lepidic predominant ADC [33]. Maybe this is the reason why air bronchogram is a risk of EGFR mutation. While there was a lot of conflict in previous studies. Hasegawa et al. [27] and Sugano et al. [20] showed that air bronchogram was not related to EGFR mutations. Other studies showed air bronchogram was a risk factor of EGFR mutations [7, 17, 21, 23, 24, 26, 28–31], while only one study showed statistically significant [28].

Pleural retraction was also a significant risk factor of EGFR mutation. All included original studies showed that pleural retraction was related to EGFR mutation, while only a few results were statistically significant [28, 31]. Except Yano et al. [19], all other studies showed that vascular convergence was a risk factor of EGFR mutation, but only two studies were statistically significant [21, 28]. Pathological

stage was not significantly related to EGFR mutation. The maximal diameter may more likely predict EGFR mutation.

There were several limitations in this study. First, this study included patients from a different continent. Because of the limited cases in some continents, subgroup analysis is not available. Second, all included studies are retrospective studies that introduce a selection bias which may influence the final overall results. Third, CT scanning parameters and EGFR mutation detection methods are different in the original studies which may increase the inter study heterogeneity. Fourth, except for NSCLC, few other types of lung cancer were included in the original studies, which we cannot exclude. But these were just few of them, which would not make much difference to the results.

In conclusion, based on the current evidence, GGO presence, air bronchogram, pleural retraction, and vascular convergence were significant risk factors of EGFR mutation in NSCLC. Additionally the prediction model can help to exclude EGFR mutation-negative cases. This can help clinicians to select better examinations and further treatments for patients. Considering the study heterogeneity, more qualified studies need to be done in this area.

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Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

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