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Can ^{18}F-FDG PET/CT predict EGFR status in NSCLC patients? A systematic review and meta-analysis

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Key words ^{18}F-fluorodeoxyglucose; positron emission tomography/computed tomography; epidermal growth factor receptor; non-small cell lung cancer

Word count: 3032

Abstract

Objectives: This study aimed to explore the diagnostic significance of ^{18}F-FDG PET/CT for predicting the presence of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) patients.

Design: A systematic review and meta-analysis.

Data sources: The PubMed, EMBASE and Cochrane library databases were searched from the earliest available date to August 2019.

Eligibility criteria for selecting studies: The review included primary studies that compared mean SUV_{max} between wild-type and mutant EGFR, and evaluated the diagnostic value of ^{18}F-FDG PET/CT for prediction of EGFR status in NSCLC patients.

Data extraction and synthesis: The main purpose of the analysis was to assess the sensitivity and specificity, the DLR+ and DLR-, as well as the DOR. Each data point of the SROC graph was derived from a separate study. A pooled WMD was calculated using SUV_{max} extracted from the included studies. A random effects model was used for statistical analysis of the data and diagnostic performance for prediction was further assessed.

Results The pooled WMD of SUV_{max} between EGFR mutant and wild-type groups was -1.51 (95% CI: -2.16 - -0.87) from the 20 studies selected. Across 10 studies (2931 patients), the pooled sensitivity for ^{18}F-FDG PET/CT was 0.65 (95% CI 0.52–0.77) with a pooled specificity of 0.62 (95% CI 0.53–0.71). The overall DLR+ was 1.74 (95% CI 1.45–2.10) and DLR- was 0.55 (95% CI 0.41–0.74). The pooled DOR was 3.15 (95% CI 2.06-4.84). The area under the SROC curve was 0.68 (95% CI 0.64-0.72). The likelihood ratio scatter plot based on average sensitivity and specificity, was in the lower right quadrant.

Conclusion Meta-analysis results showed ^{18}F-FDG PET/CT had low pooled sensitivity and specificity. The low DOR and the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT should be used with caution when predicting EGFR mutations in NSCLC patients.

Article summary

Strengths and limitations

1. To our knowledge, this is the first review that systematically analyzes the diagnostic accuracy of ^{18}F-FDG PET/CT for predicting EGFR status.
2. Weight mean difference analysis was performed prior to inclusion of studies in the diagnostic accuracy meta-analysis.
3. High heterogeneous effect should be mentioned in the results interpretation.

Introduction

Lung cancer is a common malignant tumor that is associated with considerable social and economic burden. Global statistics show that among malignant tumors, morbidity and mortality from lung cancer ranks first in males, while in females lung cancer is second only to breast cancer [1]. Non-small cell lung cancer (NSCLC) accounts for 85–90% of lung cancers, with lung adenocarcinomas (LUAD) being the most diagnosed histological subtype of NSCLC [2]. In Asia, up to 50% of LUAD patients have activating mutations of the tyrosine kinase domain of epidermal growth factor receptor (EGFR) [3]. Tyrosine-kinase inhibitor (TKI), which targets EGFR kinase domain mutations, seems to trigger a form of oncogenic shock, resulting in a favorable response in NSCLC [4]. Therefore, identification of EGFR mutant has been considered a prognostic marker for TKI therapy in NSCLC. The standard approach to detecting EGFR status is genetic testing, which is based on tumor specimens captured by invasive needle biopsy. However, this method does not reflect the status of the entire tumor.

Image-based phenotyping, which provides a non-invasive method to visualize tumor phenotypic characteristics, is a promising tool for precision medicine [5]. The use of positron emission tomography/computed tomography (PET/CT) as a molecular imaging modality for precision medicine is unique. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT is widely used for cancer diagnosis and image-guided therapy. It has been reported that ^{18}F-FDG PET/CT can predict EGFR status in NSCLC patients, but this remains controversial. Some studies have confirmed that higher uptake of ^{18}F-FDG is predictive of mutant EGFR in NSCLC patients [6–8], while several studies have shown opposite result [9–11].

Although CT has been systematically analyzed to discover risk factors for EGFR mutations in NSCLC [12], ^{18}F-FDG PET/CT was used to predict other biological features or other genetic mutations of certain malignancies through meta-analysis [13–15]. To our knowledge, no meta-analysis has summarized the association between ^{18}F-FDG PET/CT and EGFR mutation status in NSCLC. The purpose of our study was to conduct a meta-analysis of the diagnostic performance of ^{18}F-FDG PET/CT in predicting EGFR mutations, thereby providing more evidence for precise treatment of NSCLC patients.

Methods

Screening of publications

A systematic review of publications relevant to PET and EGFR mutations in NSCLC was undertaken using the electronic databases of PubMed, Embase and the Cochrane library from the earliest available date of indexing up to August 31, 2019. A search algorithm based on combined terms was used: (1) "FDG" OR "Fluorodeoxyglucose" OR "2-Fluoro-2-deoxyglucose" OR "2-Fluoro-2-deoxy-D-glucose" and (2) "PET" OR "positron emission tomography" and (3) "Epidermal Growth Factor Receptor" OR "EGFR" OR "c-erbB-1" OR "erbB-1" OR "v-erbB" and (4) "pulmonary cancer" OR "pulmonary cancer" OR "lung neoplasm" OR "lung cancer" and (5) "mutation". In order to expand the scope of our search, we also screened the references of the included studies for other studies to include.

Inclusion of studies and data extraction

Only original articles focusing on ^{18}F-FDG PET/CT and EGFR status in NSCLC patients were eligible for inclusion. To compare the differences in ^{18}F-FDG uptake between EGFR mutant and wild-type patients, the publications that reported mean SUV_{max} and standard deviations (SD) of EGFR mutant and wild-type groups were first selected. Next, articles using ^{18}F-FDG PET/CT to predict EGFR status in NSCLC patients were included based on whether they provided sufficient data to re-evaluate the sensitivity and specificity, or provided absolute data including true-positive, true-negative, false-positive and false-negative without data overlap. Duplicate publications and publications that do not contain original data, such as case reports, conference papers, review articles and letters, were excluded. Non-relevant studies and basic research were also excluded. Two researchers independently reviewed the abstracts of the selected articles using the above inclusion criteria. The same researchers independently evaluated the full text to determine whether they were eligible for final inclusion.

Quality assessment and publication bias

For WMD analysis, risk of bias, including random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting were assessed. Publication bias was assessed using a funnel plot, and plot asymmetry was considered to be suggestive of publication bias. For diagnostic performance analysis, the Quality Assessment of Diagnostic Accuracy

Studies-2 (QUADAS-2) tool was employed to assess the risk of bias in diagnostic accuracy studies. The tool consisted of four domains of risk of bias, including patient selection, index test, reference standard and flow and timing. Publication bias was evaluated using a funnel plot and Egger's regression test.

Data synthesis and analysis

A pooled weighted mean difference (WMD) was calculated through SUV_{max} extracted from the retrieved articles. A random effects model was used for statistical analysis of the data. Pooled data were displayed using forest plots and presented with 95% confidence intervals (CI). An I^2 test was performed to analysis the heterogeneity between studies (I^2 value > 50% was considered significant). Diagnostic performance for prediction was further assessed. The main purpose was to assess the sensitivity and specificity, the positive and negative diagnostic likelihood ratios (DLR+ and DLR-, respectively), as well as the diagnostic odds ratio (DOR). Publication bias was evaluated using a Deeks' funnel plot of the effective sample size. The bivariate model allowed us to incorporate the correlation that might exist between the logit-transformed values of paired sensitivity and specificity across studies. Each data point of the summary receiver operator characteristic (SROC) graph was derived from a separate study. Based on these points, the smooth SROC curve was formed to reveal the accuracy of the pooled measures. The likelihood ratio scatter plots graphically showed summary spots of likelihood ratios obtained from the average sensitivity and specificity. Statistical analyses were performed using STATA 15.1 (StataCorp LP, College Station, TX) and RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark). $p \leq 0.05$ was considered statistically significant.

Results

Literature search and selection of studies

The comprehensive search yielded 431 records for analysis. Records with duplicate titles and abstracts (69) were excluded. Additionally, 30 review articles, 122 conference abstracts, 8 basic research articles, 89 case reports, editorials, notes or surveys and 75 non-relevant or other language studies were excluded. The remaining 33 full-text articles were further assessed for eligibility. For calculating pooled WMD, 13 articles were excluded due to insufficient data and 20 studies were included. For the pooled DOR analysis, 20 articles were excluded due to insufficient data and 3 articles were excluded due to inconsistent results according to pooled

WMD results (^{18}F-FDG uptake was significantly lower in EGFR mutant group). The remaining 10 studies were included in the meta-analysis. The detailed procedure of study selection is shown in Figure 1.

Study description and publication bias

A total of 4341 patients were included in the analysis comparing SUV_{max} between the EGFR mutant and wild-type groups. The patients were enrolled retrospectively in all 20 of the included studies. The pooled comparison of the studies demonstrated that ^{18}F-FDG uptake was significantly lower in the EGFR mutant group (WMD -1.51; 95% CI -2.16 - -0.87; $p < 0.00001$; $I^2 = 78\%$, Figure 2). The most common domains with reporting deficiencies related to the patient selection, as there was no random sequence generation for retrospective studies (Figure 3A). Visual analysis of the funnel plot was not suggestive of publication bias using Egger's test ($p = 0.994$; Figure 3B). The principal characteristics of the included 20 studies are shown in Table 1. In order to predict presence of EGFR mutations in NSCLC patients, a total of 2931 patients were included in the analysis, including 1686 male and 1245 female cases. The average age was 63 years old, 88.6% had LUAD and 43.1% were smokers. All 10 studies enrolled patients retrospectively. The incidence rate of EGFR mutation was 42.4% with a range of 21.0%–57.5%. SUV_{max} was used for interpretation of ^{18}F-FDG PET/CT to predict the EGFR mutation status. The principal characteristics of the 10 included studies are shown in Table 1. Most of the observational studies demonstrated a low risk of bias as assessed by the QUADAS-2 tool (Figure 4A). Deek's funnel plot asymmetry tests were performed to assess a possible publication bias. No significant bias was found ($p = 0.13$; Figure 4B).

Diagnostic effectiveness of ^{18}F-FDG PET/CT

The diagnostic effectiveness of ^{18}F-FDG PET/CT in predicting EGFR mutation in NSCLC patients was meta-analyzed across 10 studies. The pooled sensitivity was 0.65 (95% CI 0.52–0.77) with heterogeneity ($I^2 = 91.29$, 95% CI 87.23–95.35, $p = 0.00$). The pooled specificity was 0.62 (95% CI 0.53–0.71) with heterogeneity ($I^2 = 93.05$, 95% CI 90.01–96.08, $p = 0.00$; Figure 5). DLR syntheses gave an overall DLR+ of 1.74 (95% CI 1.45–2.10) and DLR− of 0.55 (95% CI 0.41–0.74; Figure 6). The pooled DOR was 1.15 (95% CI 0.72-1.58) and 3.15 (95% CI 2.06-4.84; Figure 6). The AUC obtained from SROC was 0.68 (95% CI 0.64-0.72; Figure 7A).

Likelihood ratio scatter plot

The summary value of likelihood ratios obtained from the average sensitivity and specificity shown in the likelihood ratio scatter plot (Figure 7B) was located in the lower right quadrant, which indicated that ^{18}F-FDG PET/CT may not be useful for predicting whether there is an EGFR mutation (when positive) or not (when negative).

Discussion

In light of the advances in the precise treatment of lung cancer, identifying targetable mutations at the time of diagnosis has become the key to determining the best treatment strategies. The EGFR mutation is an important molecular subtype of NSCLC, which is highly sensitive to anti-EGFR TKI therapy. The clinical outcome of the NSCLC patients harboring EGFR alteration was significantly improved by three different generations of EGFR TKIs. The identification of the EGFR mutation led to an important paradigm shift in the treatment and survival of NSCLC patients. Tissue biopsy is the current gold standard for genetic identification and analysis. Unfortunately, this procedure usually results in failure or poor reproducibility due to insufficient materials. Another emerging strategy is plasma genotyping through “liquid biopsy”, a technique that can identify target mutant gene in circulating cell-free tumor DNA. However, inconsistencies between EGFR mutation status obtained from plasma and tumor DNA samples has also been found [16]. Moreover, neither biopsies nor plasma samples can provide accurate anatomical information such as position, size, boundary and relationship with adjacent structures of the tumors, which is critical for clinical treatment planning and response assessment.

Molecular imaging is an attractive option for evaluating NSCLC patients receiving targeted treatment because it can noninvasively observe the molecular and genomic characteristics of the tumor. As a typical molecular imaging technique, ^{18}F-FDG PET/CT can identify areas of increased metabolic activity by measuring ^{18}F-FDG uptake in many malignancies including NSCLC. Semi-quantitative parameters can be used for PET image analysis, with SUV_{max} being the most effective and commonly used parameter. ^{18}F-FDG PET/CT has also been used in the assessment of genetic status.

Previous studies on the value of ^{18}F-FDG PET in predicting EGFR status have been conflicting. Accumulation of ^{18}F-FDG was reported to be lower in NSCLC patients, which can be used to predict EGFR status. Na et al. first reported that patients with low SUV_{max} were more

likely to have EGFR mutations than those with high SUV_{max}. When using 9.2 as the cut-off value, the specificity and sensitivity reached 72% and 67%, respectively[17]. Lee et al. concluded that ^{18}F-FDG avidity had no significant clinical value in predicting EGFR status, while the univariate analysis showed SUV_{max} was significantly correlated with EGFR mutation using 11.7 as the cut-off value [18]. Cho et al. also found that mutant EGFR had relatively lower glycolysis compared with wild-type EGFR. A cut-off SUV_{max} value of 9.6 had the highest sensitivity (79.3 %) in predicting EGFR mutation [19]. Research by Guan et al. showed that ^{18}F-FDG uptake values could effectively predict the EGFR mutation status of NSCLC patients. ROC curve analysis revealed the AUC was 0.65 with the SUV_{max} value of 8.1 as the cut-off point [20]. Next, other studies further demonstrated that low SUV_{max} was a significant predictor of EGFR mutations using different cut off values [6, 7, 21–23]. Chen et al. demonstrated that using 9.92 as the SUV_{max} cut-off point can best discriminate the EGFR mutation status with an AUC of 0.75, and they identified that the mechanism responsible for the decreased FDG uptake associated with mutant EGFR was through the NOX4/ROS/GLUT1 axis [8].

However, multiple groups have reported no association between SUV_{max} and EGFR status. Mak et al. reported that high normalized SUV_{max} only correlated with the EFGR wild-type genotype [24]. Moreover, several studies have reported conflicting results. Huang et al. found that a higher ^{18}F-FDG uptake with a SUV_{max} cut-off value of 9.5 correlates with the presence of EGFR mutations [9]. Ko et al. showed a trend of higher SUV_{max} in patients with an EGFR mutation, with an optimal cut-off was 6 [11]. Kanmaz et al. made a similar conclusion, with an SUV_{max} cut-off value of 13.65 as the predictor [10].

For the conflicting information from the above studies, comparison of mean SUV_{max} between EGFR mutant and wild-type was first pooled with WMD to determine the relationship between EGFR status and FDG uptake. According to result of WMD meta-analysis, ^{18}F-FDG uptake was significantly lower in the EGFR mutant group. Thus, only studies that reported lower ^{18}F-FDG uptake for prediction of EGFR mutation in NSCLC patients were included in the DOR analysis. The meta-analysis showed low pooled sensitivity and specificity for prediction. The low DOR as well as the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT might not be useful—or, at least, should be used with caution—for predicting EGFR mutations in NSCLC patients. In addition, the obvious heterogeneity, especially for the main parameters, indicated that the differences between studies cannot be ignored and conclusion should be drawn carefully.

To improve diagnostic efficacy, recent studies focused on ^{18}F-FDG PET/CT radiomics [25, 26]. Radiomics refers to the extraction of quantitative characteristics from medical images [27]. The PET/CT-based radiomic characteristics showed good performance in the prediction of EGFR mutation in NSCLC patients [28]. Although the predication efficacy improved, its clinical application requires additional studies to confirm and optimize. Beyond ^{18}F-FDG, novel radiotracers have also been investigated. ^{18}F-MPG PET/CT was demonstrated to be a valid strategy for stratifying NSCLC patients with EGFR-activating mutations for EGFR-TKI treatment [29]. Other promising studies are under way to translate these novel approaches into the clinic to guide effective precision therapy for NSCLC patients.

The main limitation of this study is the high level of heterogeneity. However, this can be addressed using a random effects model. The first area of heterogeneity is related to NSCLC subtypes. LUAD is the main pathological type of NSCLC, but even within LUAD, there are different subtypes. For example, alveolar carcinoma demonstrates relatively low ^{18}F-FDG uptake. Second, SUV_{max} is the most stable and commonly used index, but there are many factors that affect SUV_{max}, including tumor size, glucose level, image acquisition and reconstruction. Third, the number of studies included in this study was small, especially for subgroup analysis. To further study these issues, an increased number of high-quality studies need to be carried out in the future.

Conclusion

Our meta-analysis results showed that ^{18}F-FDG PET/CT had low pooled sensitivity and specificity for EGFR mutation prediction. The low DOR and the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT might not be useful—or, at least, that it should be used with caution—for predicting EGFR mutations in NSCLC patients.

Author contributions

BD is the first author. BL and YL obtained funding. BD and YL designed the study. BD and SW collected and analyzed the data. BD drafted the manuscript. BD and YL contributed to the interpretation of the results and critical revision of the manuscript for important intellectual

content, and approved the final version of the manuscript. All authors have read and approved the final manuscript. BD and YL are the study guarantors.

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Competing interests

We have read and understood the BMJ policy on declaration of interests and declare that we have no competing interests.

Data sharing

No additional data are available

Patient and public involvement

No patient involved

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Table 1 Characteristics of the included studies

Authors	Year	Country	Study design	Patient number	Age (mean)	Gender (M/F)	Smoker	LUAD	Genetic test	EGFR mutant /wild-type	^{18}F-FDG injection dose	Cut-off value	Meta-analysis
Caicedo et al [30]	2014	Spain	R	102	62	62/40	73	90	PCR	22/80	NA	NA	WMD
Chen et al [8]	2019	China	R	157	66	84/73	68	144	PCR	54/103	481 MBq	9.92	WMD/ DOR
Cho et al [19]	2016	Korea	R	61	61	33/28	29	58	PCR	30/31	5.5 MBq/kg	9.6	WMD/ DOR
Choi et al [31]	2012	Korea	R	163	60	99/64	73	130	PCR	57/106	5.18 MBq/kg	NA	WMD
Choi et al [32]	2013	Korea	R	331	62	158/173	145	331	PCR	156/175	5.18 MBq/kg	NA	WMD
Chung et al [33]	2010	Korea	R	106	64	63/43	60	97	PCR	42/64	4.8 MBq/kg	NA	WMD
Gu et al [21]	2017	China	R	210	59	132/78	90	161	PCR	70/140	5.18 MBq/kg	9	DOR
Guan et al [20]	2016	China	R	316	60	216/100	162	242	PCR	126/190	NA	8.1	WMD/ DOR
Huang et al [9]	2010	China	R	77	62	44/33	16	77	PCR	49/28	370MBq	NA	WMD

Kanmaz et al [10]	2016	Turkey	R	218	62	151/67	155	218	PCR	63/155	3.7~5.2 MBq/kg	NA	WMD
Kim et al [34]	2016	Korea	R	198	62	113/85	68	183	PCR	101/97	5.18 MBq/kg	NA	WMD
Kim et al [35]	2018	Korea	R	232	64	104/128	93	232	PCR	132/100	5.18 MBq/kg	NA	WMD
Lee et al [18]	2015	Korea	R	206	68	148/58	71	135	PCR	47/159	481 MBq	11.7	DOR
Lee et al [36]	2015	China	R	71	65	33/38	19	71	PCR	48/23	370 MBq	NA	WMD
Lv et al [23]	2018	China	R	808	59	468/340	310	731	PCR	371/437	5.5 MBq/kg	7	WMD/ DOR
Mak et al[24]	2011	USA	R	100	65	39/61	73	90	PCR	24/76	5.55~7.4MBq	NA	WMD
Minamimoto et al [37]	2017	USA	R	127	67	NA	NA	127	PCR	32/95	12~17 mCi	NA	WMD
Na et al [17]	2010	Korea	R	100	64	68/32	57	53	PCR	21/79	370 MBq	9.2	DOR
Qiang et al [38]	2016	China	R	97	65	50/47	51	97	PCR	44/53	7.4 MBq/kg	NA	WMD
Suárez-Piñera et al [39]	2018	Spain	R	106	71	NA	NA	106	PCR	24/82	5.29 MBq/kg	NA	WMD

Takamochi et al [22]	2017	Japan	R	734	68	367/367	363	734	PCR	334/400	3.5 MBq/kg	2.69	WMD/ DOR
Yang et al [6]	2019	China	R	200	61	108/92	68	200	PCR	115/85	3.7~6.66 MBq/kg	6.15	WMD/ DOR
Zhu et al [7]	2018	China	R	139	62	62/77	46	139	PCR	74/65	4.2 MBq/kg	11.19	WMD/ DOR

LUAD, Lung adenocarcinoma; WMD, weighted mean difference; DOR, diagnostic odds ratio.

Figure 1 Publication screening flowchart.

Figure 2 Forest plot for analysis of ^{18}F-FDG uptake in EGFR mutant versus wild-type in NSCLC patients.

Figure 3 A: Risk of bias of included studies. **B:** funnel plot of SUV_{max} in EGFR mutant versus wild-type in NSCLC patients.

Figure 4 A: Assessment of risk of bias of the included studies using QUADAS-2 tool. **B**: Deeks's funnel plot of asymmetry test for publication bias showed no significant bias was found. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; WMD: weighted mean difference; ESS: effective sample size.

Figure 5 Forest plot of pooled sensitivity and specificity of ^{18}F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.

Figure 6 Forest plot of pooled positive, negative DLR and DOR of ^{18}F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.

Figure 7 A: Summary receiver operating characteristic (SROC) curves of ^{18}F-FDG PET/CT for predicting EGFR mutations in NSCLC patients. **B**: Likelihood ratio scatter plot of ^{18}F-FDG PET/CT predicting EGFR mutations in NSCLC patients.

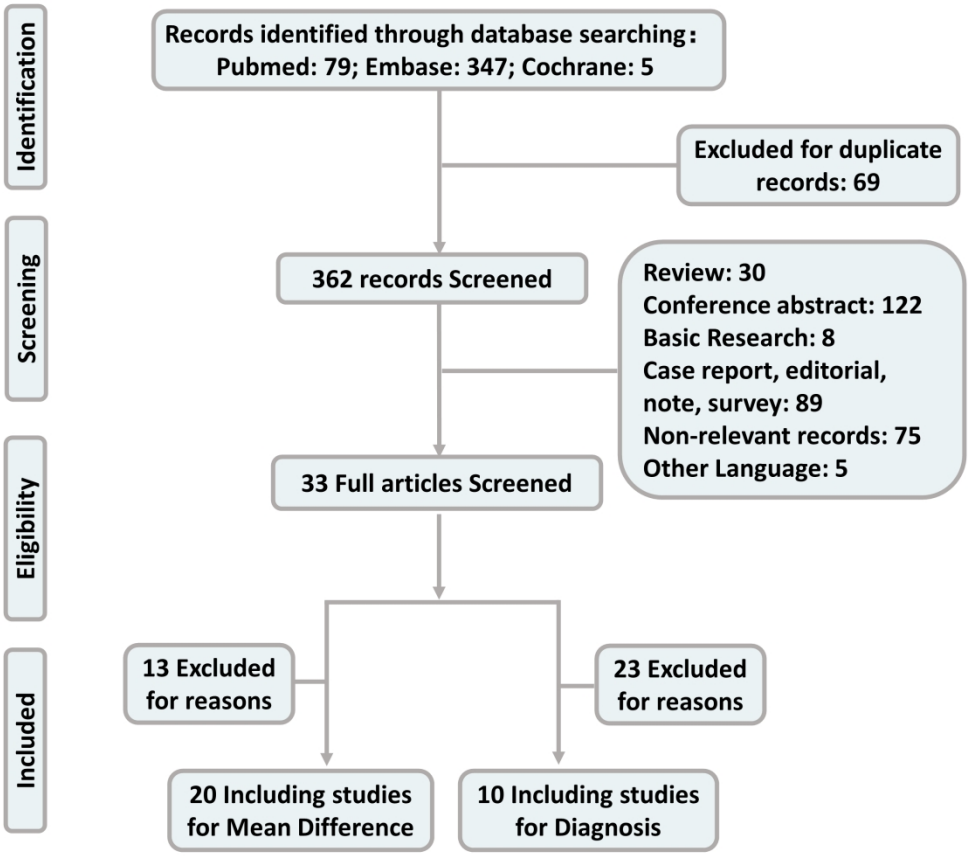

Figure 1 Publication screening flowchart.

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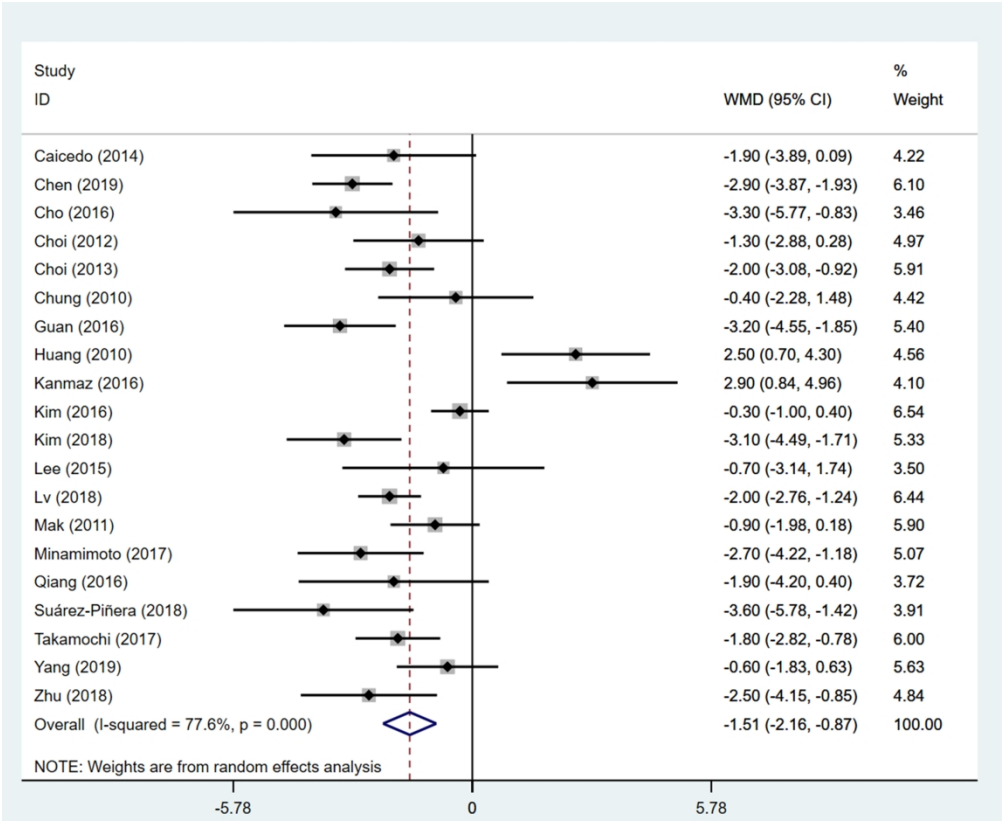

Figure 2 Forest plot for analysis of 18F-FDG uptake in EGFR mutant versus wild-type in NSCLC patients.

221x181mm (300 x 300 DPI)

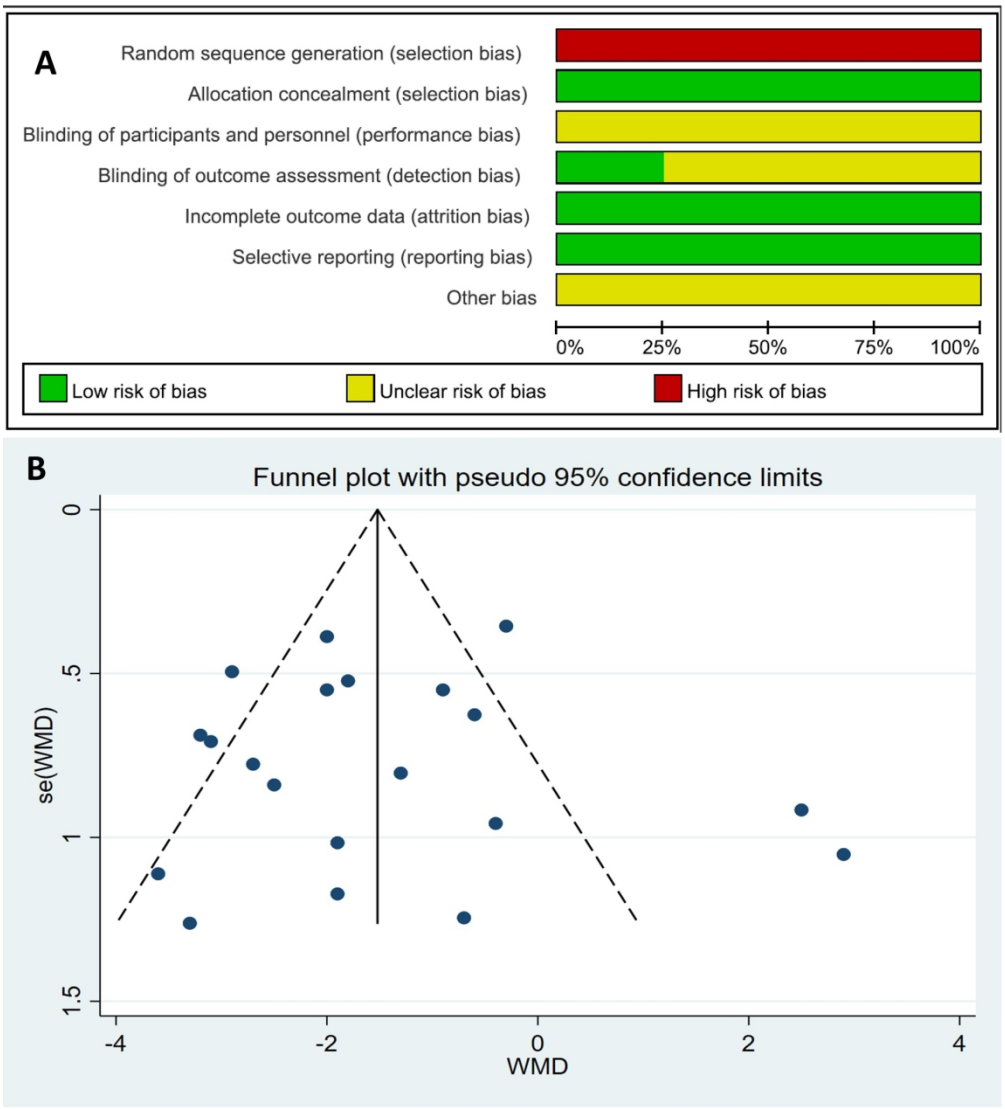

Figure 3 A: Risk of bias of included studies. B: funnel plot of SUVmax in EGFR mutant versus wild-type in NSCLC patients.

171x190mm (300 x 300 DPI)

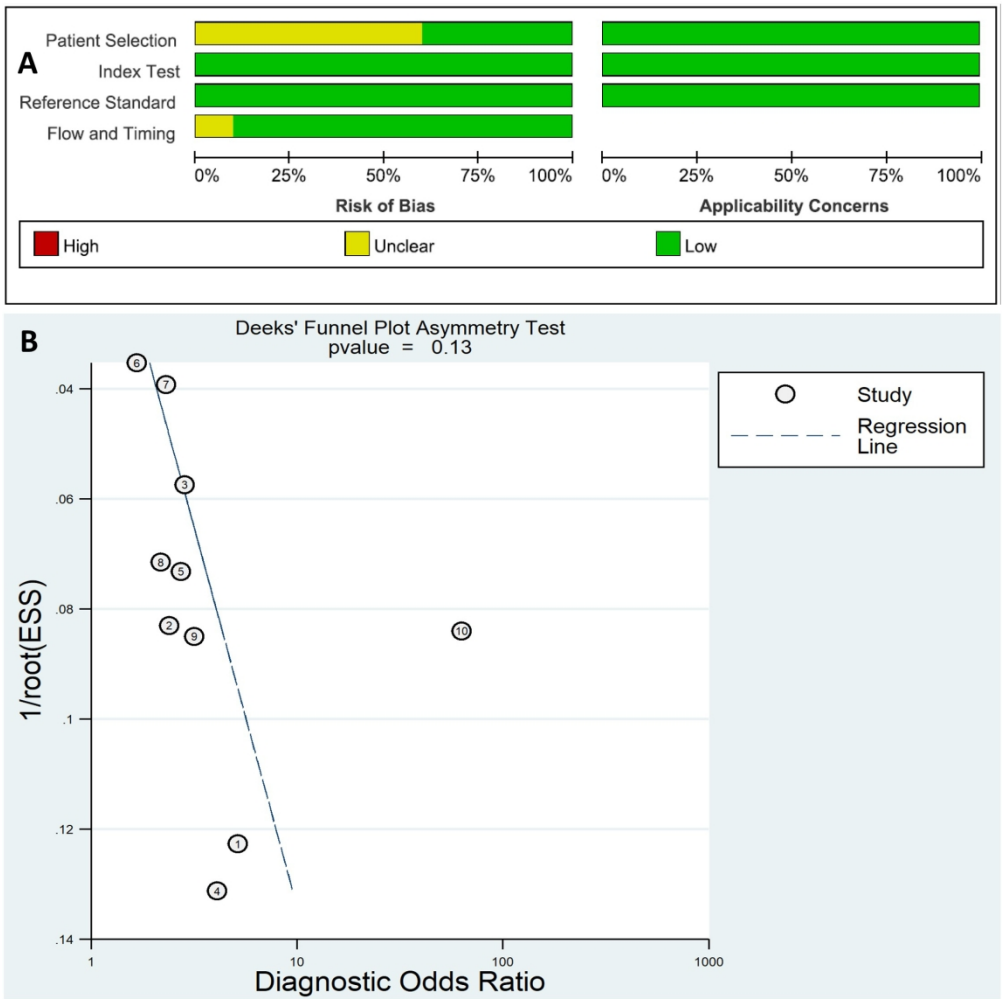

Figure 4 A: Assessment of risk of bias of the included studies using QUADAS-2 tool. B: Deeks's funnel plot of asymmetry test for publication bias showed no significant bias was found. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; WMD: weighted mean difference; ESS: effective sample size.

187x187mm (300 x 300 DPI)

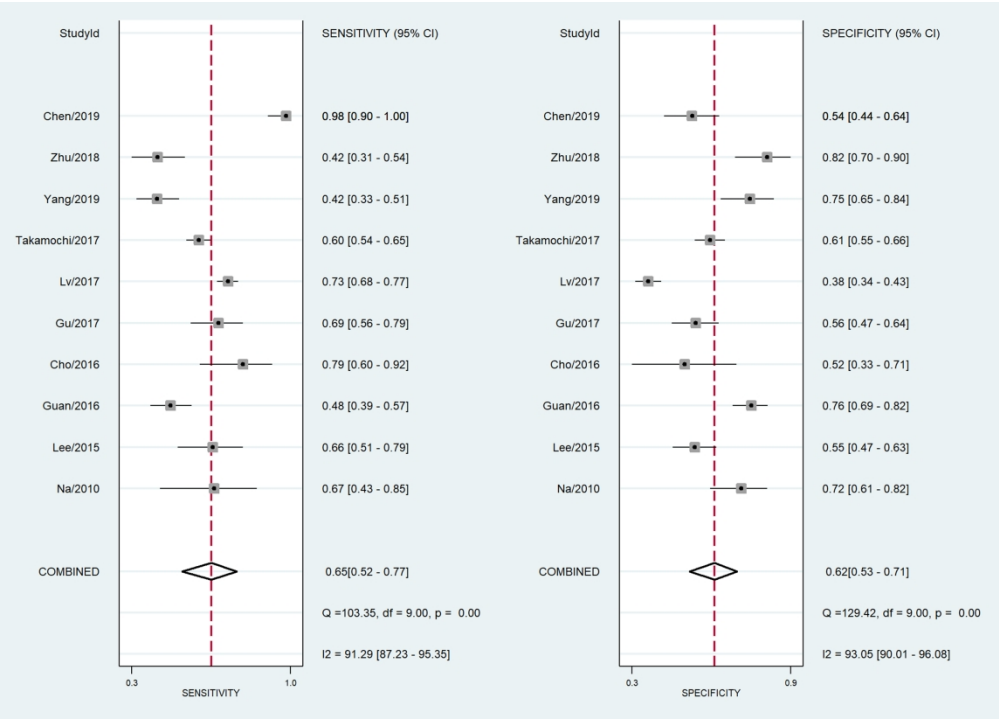

Figure 5 Forest plot of pooled sensitivity and specificity of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.

253x181mm (300 x 300 DPI)

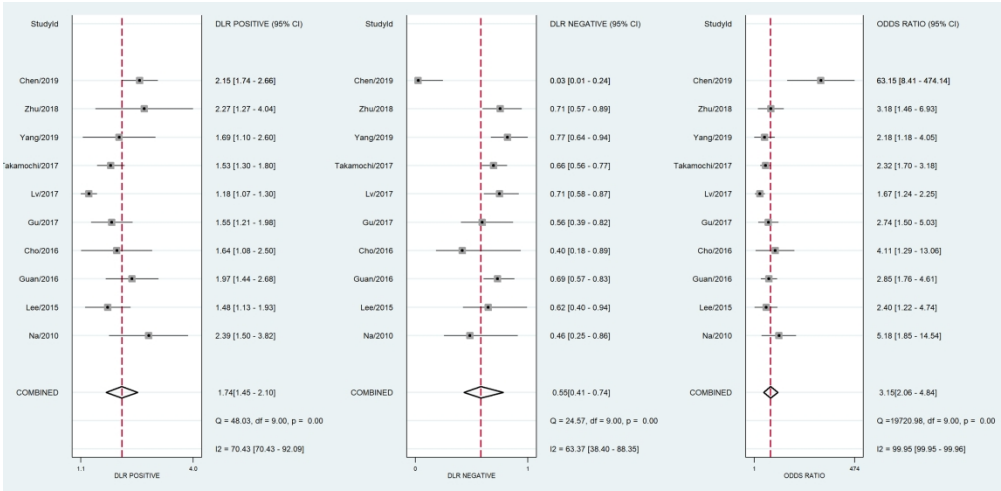

Figure 6 Forest plot of pooled positive, negative DLR and DOR of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.

312x152mm (300 x 300 DPI)

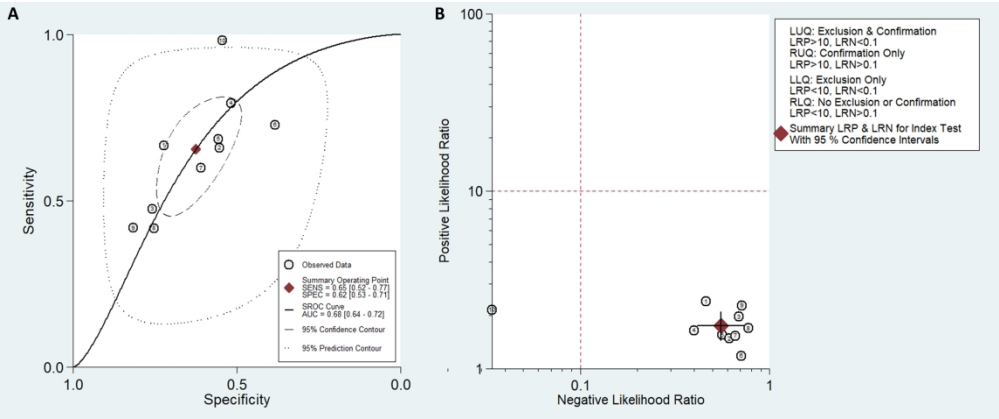

Figure 7 A: Summary receiver operating characteristic (SROC) curves of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients. B: Likelihood ratio scatter plot of 18F-FDG PET/CT predicting EGFR mutations in NSCLC patients.

338x140mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4, 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 4, 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 6; Figure 3,4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 6; Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 6; Figure 2，5, 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 6; Figure 3，4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 6; Figure 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 7,8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Can 18F-FDG PET/CT predict EGFR status in non-small cell lung cancer patients? A systematic review and meta-analysis

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Primary Subject Heading:	Diagnostics
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Keywords:	Nuclear radiology < RADIOLOGY & IMAGING, Respiratory tract tumours < ONCOLOGY, GENETICS

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Can ^{18}F-FDG PET/CT predict EGFR status in non-small cell lung cancer patients? A systematic review and meta-analysis

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Key words ^{18}F-fluorodeoxyglucose; positron emission tomography/computed tomography; epidermal growth factor receptor; non-small cell lung cancer

Word count: 5626

Abstract

Objectives: This study aimed to explore the diagnostic significance of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) for predicting the presence of epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer (NSCLC) patients.

Design: A systematic review and meta-analysis.

Data sources: The PubMed, EMBASE and Cochrane library databases were searched from the earliest available date to December 2020.

Eligibility criteria for selecting studies: The review included primary studies that compared the mean maximum of standard uptake value (SUV_{max}) between wild-type and mutant *EGFR*, and evaluated the diagnostic value of ^{18}F-FDG PET/CT using SUV_{max} for prediction of *EGFR* status in NSCLC patients.

Data extraction and synthesis: The main analysis was to assess the sensitivity and specificity, the positive diagnostic likelihood ratio (DLR+) and DLR-, as well as the diagnostic odds ratio (DOR) of SUV_{max} in prediction of *EGFR* mutations. Each data point of the summary receiver operator characteristic (SROC) graph was derived from a separate study. A random effects model was used for statistical analysis of the data, and then diagnostic performance for prediction was further assessed.

Results: Across 15 studies (3574 patients), the pooled sensitivity for ^{18}F-FDG PET/CT was 0.70 (95% CI 0.60-0.79) with a pooled specificity of 0.59 (95% CI 0.52-0.66). The overall DLR+ was 1.74 (95% CI 1.49–2.03) and DLR- was 0.50 (95% CI 0.38–0.65). The pooled DOR was 3.50 (95% CI 2.37-5.17). The area under the SROC curve was 0.68 (95% CI 0.64-0.72). The likelihood ratio scatter plot based on average sensitivity and specificity was in the lower right quadrant.

Conclusion Meta-analysis results showed ^{18}F-FDG PET/CT had low pooled sensitivity and specificity. The low DOR and the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT should be used with caution when predicting *EGFR* mutations in NSCLC patients.

Article summary

Strengths and limitations

1. To our knowledge, this is the first review that systematically analyzes the diagnostic accuracy of ^{18}F-FDG PET/CT for predicting *EGFR* status.
2. Weight mean difference analysis was performed prior to inclusion of studies in the diagnostic accuracy meta-analysis.
3. High heterogeneous effect should be mentioned in the results interpretation.

Introduction

Lung cancer is a common malignant tumor that is associated with considerable social and economic burden. Global statistics show that among malignant tumors, morbidity and mortality from lung cancer ranks first in males, while in females lung cancer is second only to breast cancer [1]. Non-small cell lung cancer (NSCLC) accounts for 85–90% of lung cancers, with lung adenocarcinomas (LUAD) being the most diagnosed histological subtype of NSCLC [2]. In Asia, up to 50% of LUAD patients have activating mutations of the tyrosine kinase domain of epidermal growth factor receptor (*EGFR*) [3]. Tyrosine-kinase inhibitor (TKI), which targets *EGFR* kinase domain mutations, seems to trigger a form of oncogenic shock, resulting in a favorable response in NSCLC [4]. Therefore, it was considered that *EGFR* mutations have a predictive role for TKI administration in NSCLC. The standard approach to detecting *EGFR* status is genetic testing, which is based on tumor specimens captured by resection, fine needle aspiration or biopsy. However, this method does not reflect the status of the entire tumor, and usually results in failure or poor reproducibility due to insufficient materials. Liquid biopsy can identify target mutant gene in circulating cell-free tumor DNA, which is sometimes inconsistencies with specimens biopsy, limiting it clinical application.

Image-based phenotyping, which provides a non-invasive method to visualize tumor phenotypic characteristics, is a promising tool for precision medicine [5]. X-ray computed tomography (CT) imaging have been systematically analyzed to discover anatomical risk factors for *EGFR* mutations prediction in NSCLC [6]. The use of positron emission tomography/ computed tomography (PET/CT) as a molecular imaging modality for precision medicine is unique. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT that can provide information on glucose metabolism is widely used for cancer diagnosis and image-guided therapy. It has been reported that ^{18}F-FDG PET/CT can predict *EGFR* status in NSCLC patients, but this remains controversial. Some studies have confirmed that higher uptake of ^{18}F-FDG is predictive of mutant *EGFR* in NSCLC patients [7–9], while several studies have shown opposite result [10–12]. A systematic review is meaningful to clarify this point.

Although ^{18}F-FDG PET/CT was used to predict many biological features or other genetic mutations of certain malignancies through meta-analysis [13–15], as far as we know, no meta-analysis has summarized the association between ^{18}F-FDG PET/CT and *EGFR* mutation status in

NSCLC. The purpose of our study was to conduct a meta-analysis of the diagnostic performance of ^{18}F-FDG PET/CT in predicting *EGFR* mutations, thereby providing more evidence for precise treatment of NSCLC patients.

Methods

Patient and public involvement statement

This study was a systematic review and meta-analysis. Ethics committee approval was not necessary because all data were carefully extracted from existing literature. In addition, neither patients nor the public were involved in the design and planning of the study.

Screening of publications

A systematic review of publications relevant to PET and *EGFR* mutations in NSCLC was undertaken using the electronic databases of PubMed, Embase and the Cochrane library from the earliest available date of indexing up to December 31, 2020. A search algorithm based on combined terms was used: (1) "FDG" OR "Fluorodeoxyglucose" OR "2-Fluoro-2-deoxyglucose" OR "2-Fluoro-2-deoxy-D-glucose" and (2) "PET" OR "positron emission tomography" and (3) "Epidermal Growth Factor Receptor" OR "*EGFR*" OR "c-erbB-1" OR "erbB-1" OR "v-erbB" and (4) "pulmonary cancer" OR "pulmonary cancer" OR "lung neoplasm" OR "lung cancer" and (5) "mutation" (see online supplementary file for further details on search strategy). In order to expand the scope of our search, we also screened the references of the included studies for other studies to include.

Inclusion of studies and data extraction

Only original articles focusing on ^{18}F-FDG PET/CT and *EGFR* status in NSCLC patients were eligible for inclusion. To compare the differences in ^{18}F-FDG uptake between *EGFR* mutant and wild-type patients, the publications that reported the mean maximum of standard uptake value (SUV_{max}) and standard deviations (SD) of *EGFR* mutant and wild-type groups were first selected. Next, articles using ^{18}F-FDG PET/CT to predict *EGFR* status in NSCLC patients were included based on whether they provided sufficient data to re-evaluate the sensitivity and specificity, or provided absolute data including true-positive, true-negative, false-positive and false-negative without data overlap. Duplicate publications and publications that do not contain original data,

such as case reports, conference papers, review articles and letters, were excluded. Non-relevant studies and basic research were also excluded. Only English article were evaluated. Two researchers independently reviewed the abstracts of the selected articles using the above inclusion criteria. When there were disagreements between authors, a consensus was reached through a third author was consulted. The same researchers independently evaluated the full text to determine whether they were eligible for final inclusion.

Quality assessment and publication bias

For pooled weighted mean difference (WMD) analysis, risk of bias, including random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting were assessed. Publication bias was assessed using a funnel plot, and plot asymmetry was considered to be suggestive of publication bias. For diagnostic performance analysis, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was employed to assess the risk of bias in diagnostic accuracy studies. The tool consisted of four domains of risk of bias, including patient selection, index test, reference standard and flow and timing. Publication bias was evaluated using a funnel plot and Egger's regression test.

Data synthesis and analysis

A WMD was calculated through SUV_{max} extracted from the retrieved articles. A random effects model was used for statistical analysis of the data. Pooled data were displayed using forest plots and presented with 95% confidence intervals (CI). An I^2 test was performed to analysis the heterogeneity between studies (I^2 value > 50% was considered significant). Diagnostic performance for prediction was further assessed. The main purpose was to assess the sensitivity and specificity, the positive and negative diagnostic likelihood ratios (DLR+ and DLR-, respectively), as well as the diagnostic odds ratio (DOR). Publication bias was evaluated using a Deeks' funnel plot of the effective sample size. The bivariate model allowed us to incorporate the correlation that might exist between the logit-transformed values of paired sensitivity and specificity across studies. Each data point of the summary receiver operator characteristic (SROC) graph was derived from a separate study. Based on these points, the smooth SROC curve was formed to reveal the accuracy of the pooled measures. The likelihood ratio scatter plots graphically showed summary spots of likelihood ratios obtained from the average

sensitivity and specificity. Statistical analyses were performed using STATA 15.1 (StataCorp LP, College Station, TX) and RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark). $p \leq 0.05$ was considered statistically significant.

Results

Literature search and selection of studies

The comprehensive search yielded 545 records for analysis. Records with duplicate titles and abstracts (89) were excluded. Additionally, 36 review articles, 144 conference abstracts, 13 basic research articles, 120 case reports, editorials, notes and surveys, 86 non-relevant records and 10 other language studies were excluded. The remaining 47 full-text articles were further assessed for eligibility. For calculating pooled WMD, 24 articles were excluded due to insufficient data and 23 studies were included. For the pooled DOR analysis, 29 articles were excluded due to insufficient data and 3 articles were excluded due to inconsistent results according to pooled WMD results (^{18}F-FDG uptake was significantly lower in *EGFR* mutant group; the pooled sensitivity, specificity and DOR were also calculated without these 3 studies exclusion). The remaining 15 studies were included in the meta-analysis. The detailed procedure of study selection is shown in Figure 1.

Study description and publication bias

All included patients were taken ^{18}F-FDG PET/CT examination and EGFR gene test. EGFR mutations analysis was carried out on tissue specimens obtained from resection, aspiration or biopsy. A total of 5220 patients were included in the WMD analysis, and SUV_{max} between the *EGFR* mutant and wild-type groups were compared. The patients were enrolled retrospectively in all 23 of the included studies. The pooled comparison of the studies demonstrated that ^{18}F-FDG uptake was significantly lower in the *EGFR* mutant group (WMD -1.73; 95% CI -2.34 - -1.12; $p < 0.05$; $I^2 = 78.2\%$, Figure 2). The most common domains with reporting deficiencies related to the patient selection, as there was no random sequence generation for retrospective studies (Figure 3A). Visual analysis of the funnel plot was not suggestive of publication bias using Egger's test ($p = 0.786$; Figure 3B). The principal characteristics of the included 23 studies are shown in Table 1.

In order to predict presence of *EGFR* mutations in NSCLC patients, a total of 3574 patients were included in the analysis, including 2046 male and 1528 female cases. The average age was 62.9

years old, 90.3% had LUAD and 42.8% were smokers. All 15 studies enrolled patients retrospectively. The incidence rate of *EGFR* mutation was 41.2% with a range of 21.0%–57.5%. SUV_{max} was used for interpretation of ^{18}F-FDG PET/CT to predict the *EGFR* mutation status. The principal characteristics of the 15 included studies are also shown in Table 1. Most of the observational studies demonstrated a low risk of bias as assessed by the QUADAS-2 tool (Figure 4A). Deek's funnel plot asymmetry tests were performed to assess a possible publication bias. No significant bias was found (p = 0.089; Figure 4B).

Table 1 Characteristics of the included studies

Authors	Year	Country	Study design	Patient number	Age (mean)	Gender (M/F)	Smoker	LUAD	Genetic test	*EGFR* mutant /wild-type	^{18}F-FDG injection dose	Cut-off value	Meta-analysis
Caicedo et al [16]	2014	Spain	R	102	62	62/40	73	90	PCR	22/80	NA	NA	WMD
Chen et al [9]	2019	China	R	157	66	84/73	68	144	PCR	54/103	481 MBq	9.92	WMD/ DOR
Cho et al [17]	2016	Korea	R	61	61	33/28	29	58	PCR	30/31	5.5 MBq/kg	9.6	WMD/ DOR
Choi et al [18]	2012	Korea	R	163	60	99/64	73	130	PCR	57/106	5.18 MBq/kg	NA	WMD
Choi et al [19]	2013	Korea	R	331	62	158/173	145	331	PCR	156/175	5.18 MBq/kg	NA	WMD
Chung et al [20]	2010	Korea	R	106	64	63/43	60	97	PCR	42/64	4.8 MBq/kg	NA	WMD
Gao et al [21]	2020	China	R	167	58	87/80	67	162	PCR	72/94	370 MBq	11.5	DOR
Gu et al [22]	2017	China	R	210	59	132/78	90	161	PCR	70/140	5.18 MBq/kg	9	DOR
Guan et al [23]	2016	China	R	316	60	216/100	162	242	PCR	126/190	NA	8.1	WMD/ DOR
Hong et al [24]	2020	Korea	R	134	69	89/45	76	134	PCR	62/72	52/7MBq/kg	9.6	WMD/ DOR
Huang et al [10]	2010	China	R	77	62	44/33	16	77	PCR	49/28	370MBq	NA	WMD
Kanmaz et al [11]	2016	Turkey	R	218	62	151/67	155	218	PCR	63/155	3.7~5.2 MBq/kg	NA	WMD
Kim et al [25]	2016	Korea	R	198	62	113/85	68	183	PCR	101/97	5.18 MBq/kg	NA	WMD
Kim et al [26]	2018	Korea	R	232	64	104/128	93	232	PCR	132/100	5.18 MBq/kg	NA	WMD
Lee et al [27]	2015	Korea	R	206	68	148/58	71	135	PCR	47/159	481 MBq	11.7	DOR
Lee et al [28]	2015	China	R	71	65	33/38	19	71	PCR	48/23	370 MBq	NA	WMD
Liao et al [29]	2020	China	R	191	63	101/90	65	191	PCR	63/128	3.7 MBq/kg	7.78	DOR
Lv et al [30]	2018	China	R	808	59	468/340	310	731	PCR	371/437	5.5 MBq/kg	7	WMD/ DOR

Liu et al [31]	2017	China	R	87	60	49/38	32	78	PCR	41/46	NA	10.4	DOR
Mak et al[32]	2011	USA	R	100	65	39/61	73	90	PCR	24/76	5.55~7.4MBq	NA	WMD
Minamimoto et al [33]	2017	USA	R	127	67	NA	NA	127	PCR	32/95	12~17 mCi	NA	WMD
Mu et al [34]	2020	China, USA	R	681	63	378/303	315	567	PCR	312/369	NA	NA	WMD
Na et al [35]	2010	Korea	R	100	64	68/32	57	53	PCR	21/79	370 MBq	9.2	DOR
Qiang et al [36]	2016	China	R	97	65	50/47	51	97	PCR	44/53	7.4 MBq/kg	NA	WMD
Suárez-Piñera et al [37]	2018	Spain	R	106	71	NA	NA	106	PCR	24/82	5.29 MBq/kg	NA	WMD
Takamochi et al [38]	2017	Japan	R	734	68	367/367	363	734	PCR	334/400	3.5 MBq/kg	2.69	WMD/ DOR
Whi et al [39]	2020	Korea	R	64	66	34/30	25	64	PCR	29/35	5.18 MBq/kg	9.5	WMD/ DOR
Yang et al [7]	2019	China	R	200	61	108/92	68	200	PCR	115/85	3.7~6.66 MBq/kg	6.15	WMD/ DOR
Zhu et al [8]	2018	China	R	139	62	62/77	46	139	PCR	74/65	4.2 MBq/kg	11.19	WMD/ DOR

LUAD, Lung adenocarcinoma; WMD, weighted mean difference; DOR, diagnostic odds ratio.

Diagnostic effectiveness of ^{18}F-FDG PET/CT

The diagnostic effectiveness of ^{18}F-FDG PET/CT in predicting *EGFR* mutation in NSCLC patients was meta-analyzed across 15 studies. The pooled sensitivity was 0.70 (95% CI 0.60-0.79) with heterogeneity (I^2 = 90.86, 95% CI 87.38–94.34, $p < 0.05$). The pooled specificity was 0.59 (95% CI 0.52-0.66) with heterogeneity (I^2 = 91.43, 95% CI 88.23–94.63, $p < 0.05$; Figure 5). DLR syntheses gave an overall DLR+ of 1.74 (95% CI 1.49–2.03) and DLR− of 0.50 (95% CI 0.38–0.65; Figure 6). The pooled DOR was 3.50 (95% CI 2.37-5.17; Figure 6). The area under curve (AUC) obtained from SROC was 0.68 (95% CI 0.64-0.72; Figure 7A). Lower pooled sensitivity, specificity and DOR were shown with the three studies included in the prediction of EGFR mutations in NSCLC patients (see online supplementary file Figure S1).

Likelihood ratio scatter plot

The summary value of likelihood ratios obtained from the average sensitivity and specificity shown in the likelihood ratio scatter plot (Figure 7B) was located in the lower right quadrant, which indicated that ^{18}F-FDG PET/CT may not be useful for predicting whether there is an *EGFR* mutation (when positive) or not (when negative).

Discussion

In light of the advances in the precise treatment of lung cancer, identifying targetable mutations at the time of diagnosis has become the key to determining the best treatment strategies. The *EGFR* mutation is an important molecular subtype of NSCLC, which is highly sensitive to anti-*EGFR* TKI therapy. The clinical outcome of the NSCLC patients harboring *EGFR* alteration was significantly improved by three different generations of *EGFR* TKIs. The identification of the *EGFR* mutation led to an important paradigm shift in the treatment and survival of NSCLC patients. Tissue biopsy is the current gold standard for genetic identification and analysis. Unfortunately, this procedure usually results in failure or poor reproducibility due to insufficient materials. Another emerging strategy is plasma genotyping through "liquid biopsy", a technique that can identify target mutant gene in circulating cell-free tumor DNA. However, inconsistencies between *EGFR* mutation status obtained from plasma and tumor DNA samples has also been found [40]. Moreover, neither biopsies nor plasma samples can provide accurate anatomical information such as position, size, boundary and relationship with adjacent structures of the tumors, which is critical for clinical treatment planning and response assessment.

Molecular imaging is an attractive option for evaluating NSCLC patients receiving targeted treatment because it can noninvasively observe the molecular and genomic characteristics of the tumor. As a typical molecular imaging technique, ^{18}F-FDG PET/CT can identify areas of increased metabolic activity by measuring ^{18}F-FDG uptake in many malignancies including NSCLC. Semi-quantitative parameters can be used for PET image analysis, with SUV_{max} being the most effective and commonly used parameter. ^{18}F-FDG PET/CT has also been used in the assessment of genetic status.

Previous studies on the value of ^{18}F-FDG PET in predicting *EGFR* status have been conflicting. Accumulation of ^{18}F-FDG was reported to be lower in NSCLC patients, which can be used to predict *EGFR* status. Na et al. first reported that patients with low SUV_{max} were more likely to have *EGFR* mutations than those with high SUV_{max}. When using 9.2 as the cut-off value, the specificity and sensitivity reached 72% and 67%, respectively[35]. Lee et al. concluded that ^{18}F-FDG avidity had no significant clinical value in predicting *EGFR* status, while the univariate analysis showed SUV_{max} was significantly correlated with *EGFR* mutation using 11.7 as the cut-off value [27]. Cho et al. also found that mutant *EGFR* had relatively lower glycolysis compared

with wild-type *EGFR*. A cut-off SUV_{max} value of 9.6 had the highest sensitivity (79.3 %) in predicting *EGFR* mutation [17]. Research by Guan et al. showed that ^{18}F-FDG uptake values could effectively predict the *EGFR* mutation status of NSCLC patients. ROC curve analysis revealed the AUC was 0.65 with the SUV_{max} value of 8.1 as the cut-off point [23]. Next, other studies further demonstrated that low SUV_{max} was a significant predictor of *EGFR* mutations using different cut off values [7, 8, 22, 30, 38]. Chen et al. demonstrated that using 9.92 as the SUV_{max} cut-off point can best discriminate the *EGFR* mutation status with an AUC of 0.75, and they identified that the mechanism responsible for the decreased FDG uptake associated with mutant *EGFR* was through the NOX4/ROS/GLUT1 axis [9].

However, multiple groups have reported no association between SUV_{max} and *EGFR* status. Mak et al. reported that high normalized SUV_{max} only correlated with the EFGR wild-type genotype [32]. Moreover, several studies have reported conflicting results. Huang et al. found that a higher ^{18}F-FDG uptake with a SUV_{max} cut-off value of 9.5 correlates with the presence of *EGFR* mutations [10]. Ko et al. showed a trend of higher SUV_{max} in patients with an *EGFR* mutation, with an optimal cut-off was 6 [12]. Kanmaz et al. made a similar conclusion, with an SUV_{max} cut-off value of 13.65 as the predictor [11].

For the conflicting information from the above studies, comparison of mean SUV_{max} between *EGFR* mutant and wild-type was first pooled with WMD to determine the relationship between *EGFR* status and FDG uptake. According to result of WMD meta-analysis, ^{18}F-FDG uptake was significantly lower in the *EGFR* mutant group. Thus, studies that reported higher ^{18}F-FDG uptake for prediction of *EGFR* mutation in NSCLC patients were excluded in the DOR analysis. The meta-analysis showed low pooled sensitivity of 70% and specificity of 59% for prediction. The low DOR of 0.68 as well as the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT might not be useful—or, at least, should be used with caution—for predicting *EGFR* mutations in NSCLC patients. In addition, the obvious heterogeneity, especially for the main parameters, indicated that the differences between studies cannot be ignored and conclusion should be drawn carefully.

To improve diagnostic efficacy, more ^{18}F-FDG PET/CT semi-quantitative parameters including metabolic tumor volume and total glucose glycolysis were investigated to potentially predict EGFR mutations [20, 29]. Recent studies also focused on ^{18}F-FDG PET/CT radiomics [41, 42]. Radiomics refers to the extraction of quantitative characteristics from medical images

[43]. The PET/CT-based radiomic characteristics showed good performance in the prediction of *EGFR* mutation in NSCLC patients [34, 44]. Although the predication efficacy improved, its clinical application requires additional studies to confirm and optimize. Beyond ^{18}F-FDG, novel radiotracers have also been investigated. ^{18}F-MPG PET/CT was demonstrated to be a valid strategy for stratifying NSCLC patients with *EGFR*-activating mutations for *EGFR*-TKI treatment [45], but this radiotracer is not routinely available. Other promising studies are under way to translate these novel approaches into the clinic to guide effective precision therapy for NSCLC patients.

The main limitation of this study is the high level of heterogeneity. However, this can be addressed using a random effects model. The first area of heterogeneity is related to NSCLC subtypes. LUAD is the main pathological type of NSCLC, but even within LUAD, there are different subtypes. For example, alveolar carcinoma demonstrates relatively low ^{18}F-FDG uptake. Second, SUV_{max} is the most stable and commonly used index, but there are many factors that affect SUV_{max}, including tumor size, glucose level, image acquisition and reconstruction, especially for different PET/CT equipment with different acquisition parameters. Third, the number of studies included in this study was small, especially for subgroup analysis. To further study these issues, an increased number of high-quality studies need to be carried out in the future.

Conclusion

Our meta-analysis results showed that ^{18}F-FDG PET/CT had low pooled sensitivity and specificity for *EGFR* mutation prediction. The low DOR and the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT might not be useful—or, at least, that it should be used with caution—for predicting *EGFR* mutations in NSCLC patients.

Author contributions

BD is the first author. BD and YL obtained funding. BD, XL and YL designed the study. BD, YC, GL and SW collected and analyzed the data. BD drafted the manuscript. BD and YL contributed to the interpretation of the results and critical revision of the manuscript for

important intellectual content, and approved the final version of the manuscript. All authors have read and approved the final manuscript. BD and YL are the study guarantors.

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Competing interests

We have read and understood the BMJ policy on declaration of interests and declare that we have no competing interests.

Data sharing

No additional data are available

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Figure 1 Publication screening flowchart.

Figure 2 Forest plot for analysis of ^{18}F-FDG uptake in *EGFR* mutant versus wild-type in NSCLC patients.

Figure 3 A: Risk of bias of included studies. **B:** funnel plot of SUV_{max} in *EGFR* mutant versus wild-type in NSCLC patients.

Figure 4 A: Assessment of risk of bias of the included studies using QUADAS-2 tool. **B**: Deeks's funnel plot of asymmetry test for publication bias showed no significant bias was found. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; WMD: weighted mean difference; ESS: effective sample size.

Figure 5 Forest plot of pooled sensitivity and specificity of ^{18}F-FDG PET/CT for predicting *EGFR* mutations in NSCLC patients.

Figure 6 Forest plot of pooled positive, negative DLR and DOR of ^{18}F-FDG PET/CT for predicting *EGFR* mutations in NSCLC patients.

Figure 7 A: Summary receiver operating characteristic (SROC) curves of ^{18}F-FDG PET/CT for predicting *EGFR* mutations in NSCLC patients. **B**: Likelihood ratio scatter plot of ^{18}F-FDG PET/CT predicting *EGFR* mutations in NSCLC patients.

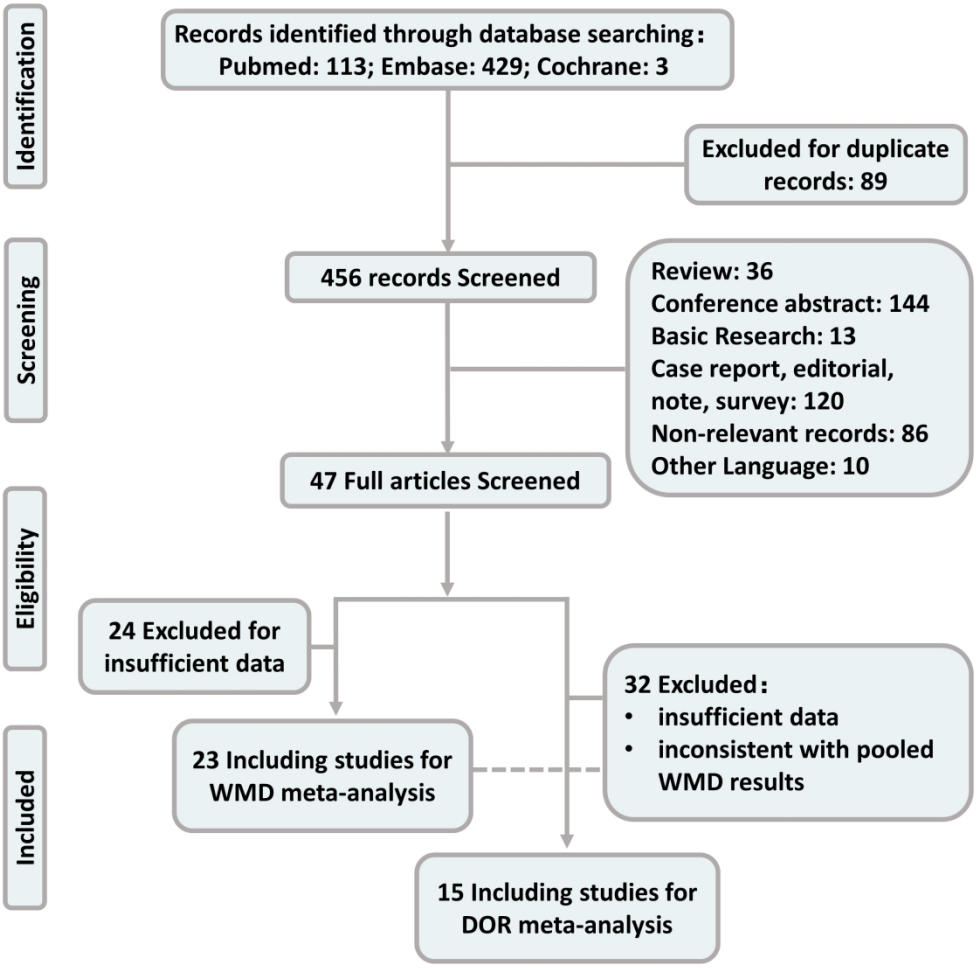

Figure 1 Publication screening flowchart.

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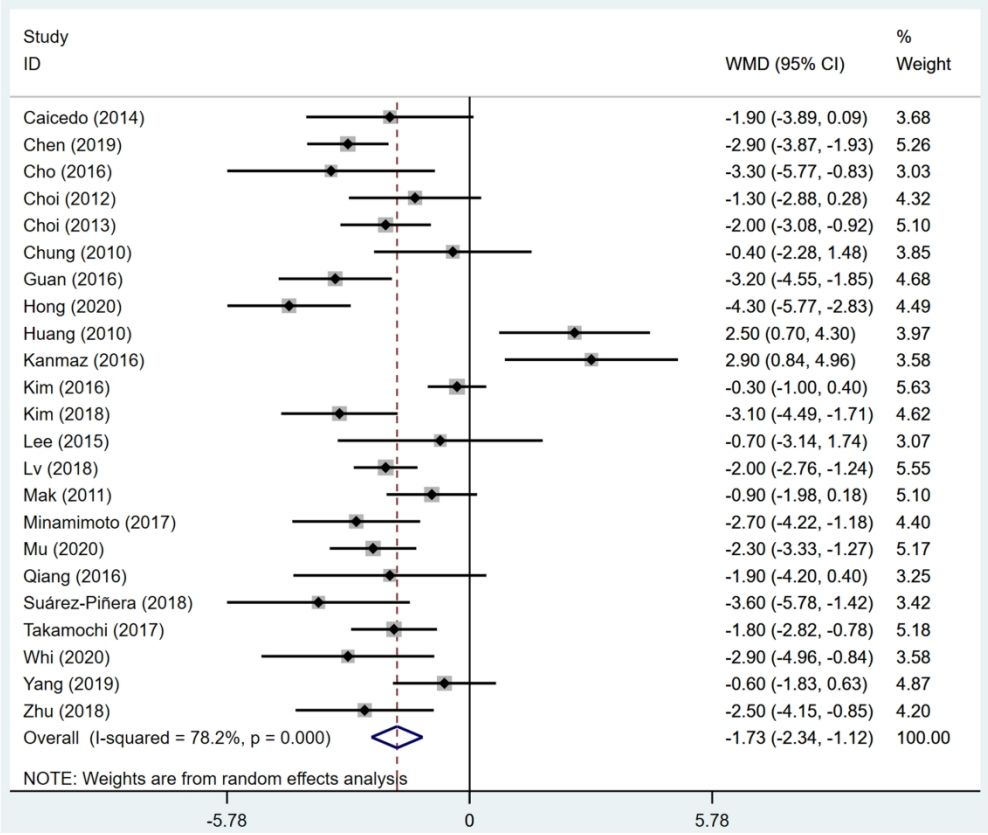

Figure 2 Forest plot for analysis of 18F-FDG uptake in EGFR mutant versus wild-type in NSCLC patients.

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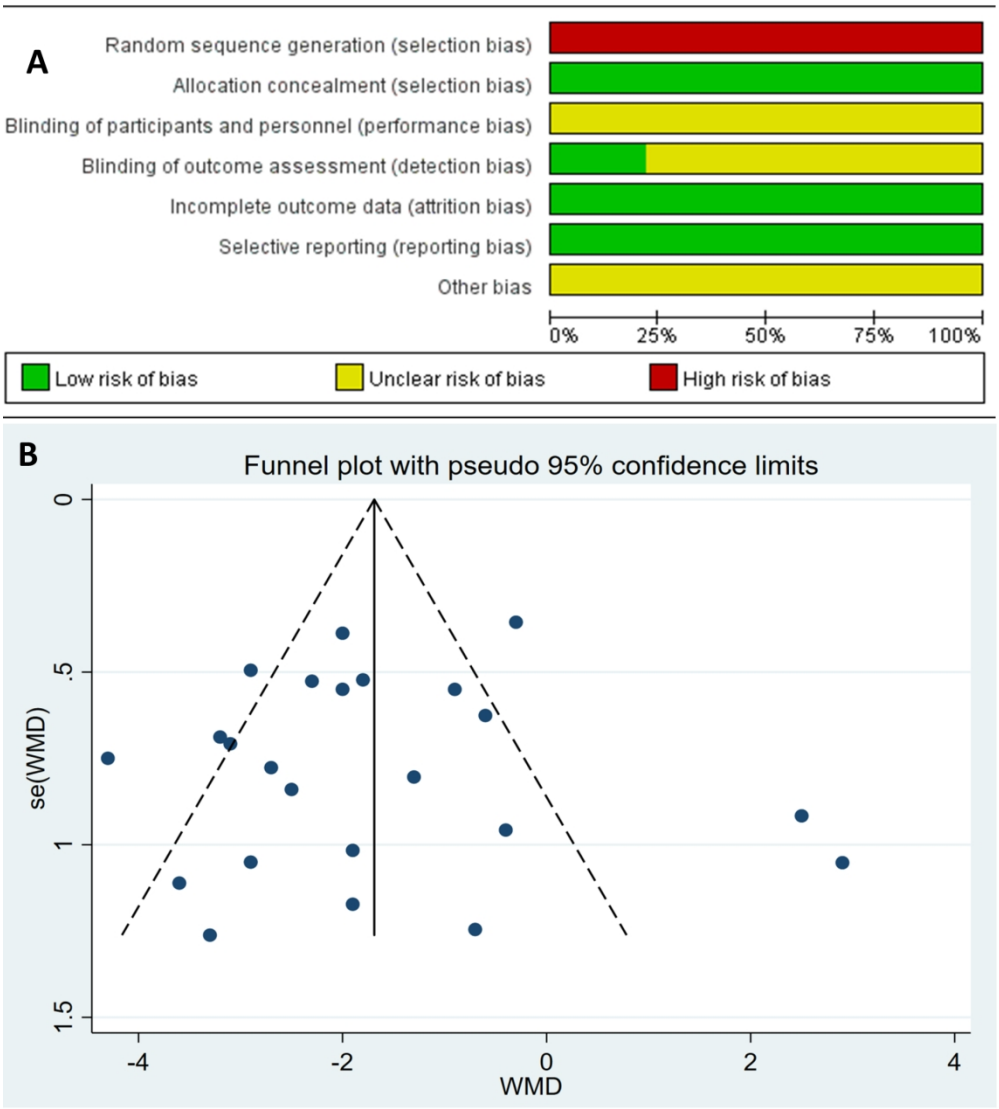

Figure 3 A: Risk of bias of included studies. B: funnel plot of SUVmax in EGFR mutant versus wild-type in NSCLC patients.

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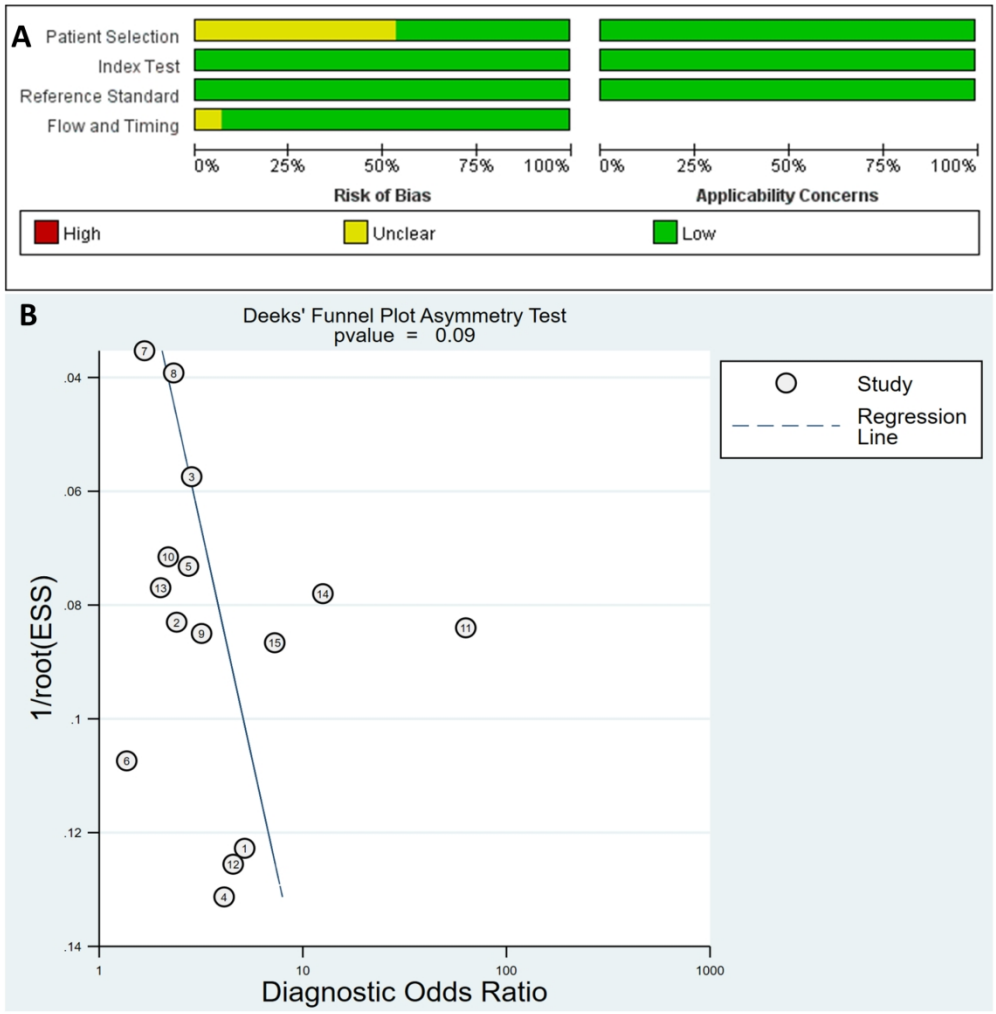

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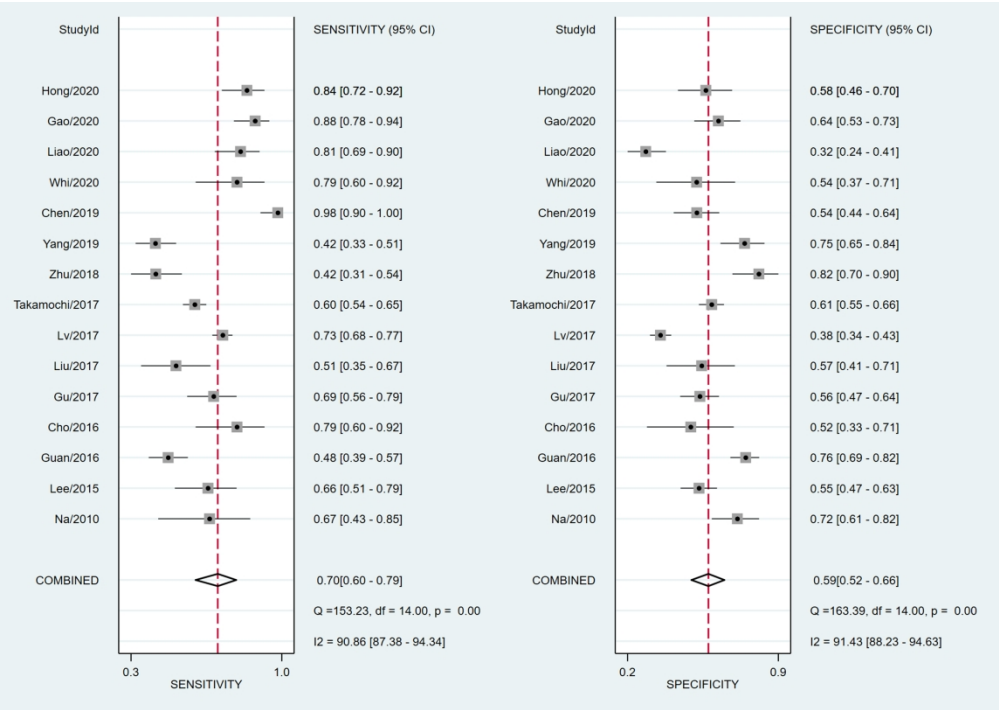

Figure 5 Forest plot of pooled sensitivity and specificity of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.

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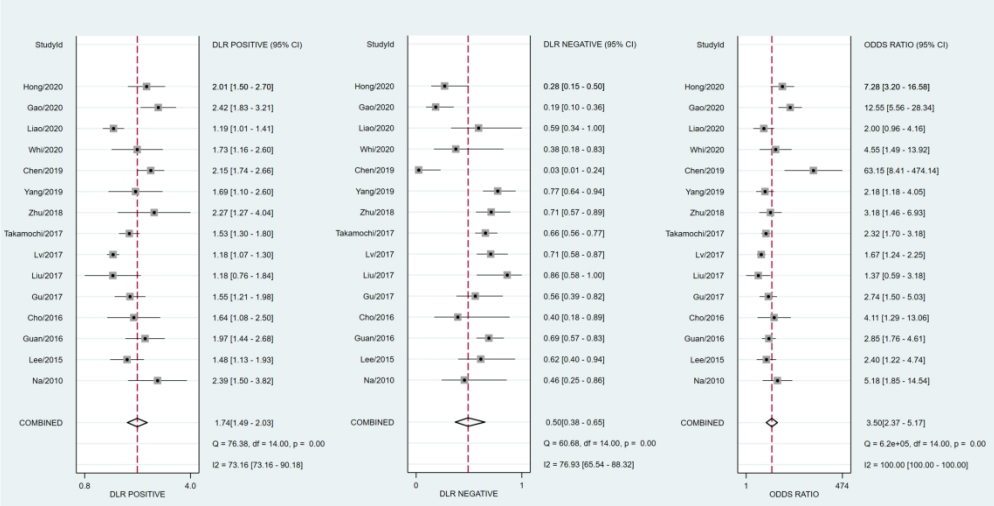


Figure 6 Forest plot of pooled positive, negative DLR and DOR of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.

338x171mm (300 x 300 DPI)

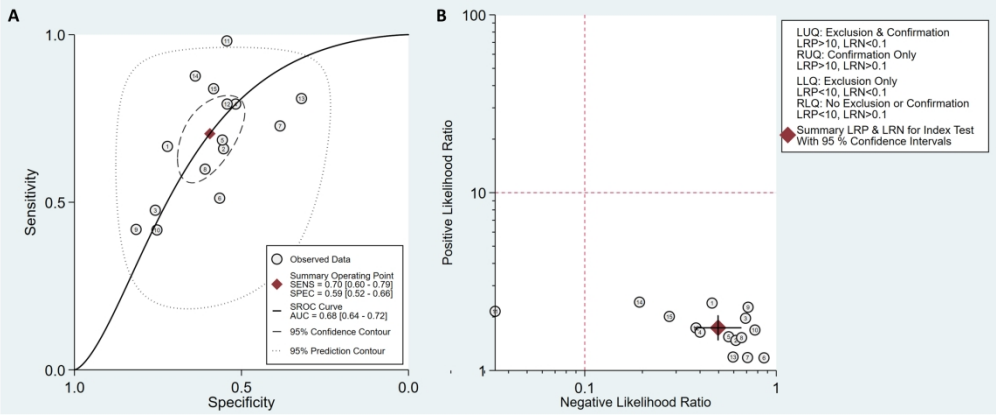


Figure 7 A: Summary receiver operating characteristic (SROC) curves of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients. B: Likelihood ratio scatter plot of 18F-FDG PET/CT predicting EGFR mutations in NSCLC patients.

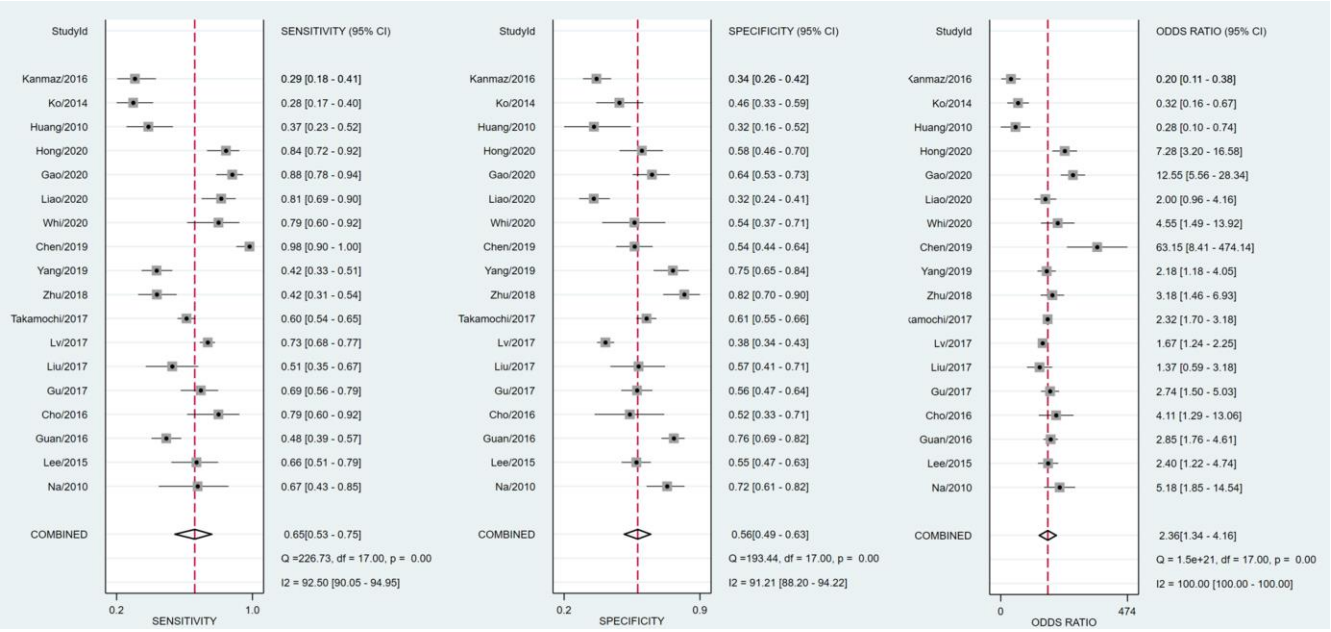
332x137mm (300 x 300 DPI)

Supplementary Appendix

1. **Search Strategy** (used in PubMed)

((((((((Epidermal Growth Factor Receptor) OR EGFR)) OR c-erbB-1) OR erbB-1) OR v-erbB))
AND (((((((FDG) OR Fluorodeoxyglucose) OR 2-Fluoro-2-deoxyglucose) OR 2-Fluoro-2-deoxy-D-glucose))
AND ((Positron Emission Tomography) OR PET)) AND ((((pulmonary Neoplasm) OR pulmonary cancer)) OR
((lung neoplasm) OR lung cancer))))) AND Mutation

2. **Figure S1** Forest plot of pooled sensitivity, specificity and DOR of ^{18}F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5, 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5, 6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 7; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 7; Figure 3,4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 8; Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 9; Figure 2，5, 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 7; Figure 3，4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 9; Figure 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10,11,12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 12

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 13

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Can 18F-FDG PET/CT predict EGFR status in non-small cell lung cancer patients? A systematic review and meta-analysis

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Can ^{18}F-FDG PET/CT predict EGFR status in non-small cell lung cancer patients? A systematic review and meta-analysis

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Key words ^{18}F-fluorodeoxyglucose; positron emission tomography/computed tomography; epidermal growth factor receptor; non-small cell lung cancer

Word count: 5527

Abstract

Objectives: This study aimed to explore the diagnostic significance of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) for predicting the presence of epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer (NSCLC) patients.

Design: A systematic review and meta-analysis.

Data sources: The PubMed, EMBASE and Cochrane library databases were searched from the earliest available date to December 2020.

Eligibility criteria for selecting studies: The review included primary studies that compared the mean maximum of standard uptake value (SUV_{max}) between wild-type and mutant *EGFR*, and evaluated the diagnostic value of ^{18}F-FDG PET/CT using SUV_{max} for prediction of *EGFR* status in NSCLC patients.

Data extraction and synthesis: The main analysis was to assess the sensitivity and specificity, the positive diagnostic likelihood ratio (DLR+) and DLR-, as well as the diagnostic odds ratio (DOR) of SUV_{max} in prediction of *EGFR* mutations. Each data point of the summary receiver operator characteristic (SROC) graph was derived from a separate study. A random effects model was used for statistical analysis of the data, and then diagnostic performance for prediction was further assessed.

Results: Across 15 studies (3574 patients), the pooled sensitivity for ^{18}F-FDG PET/CT was 0.70 (95% CI 0.60-0.79) with a pooled specificity of 0.59 (95% CI 0.52-0.66). The overall DLR+ was 1.74 (95% CI 1.49–2.03) and DLR- was 0.50 (95% CI 0.38–0.65). The pooled DOR was 3.50 (95% CI 2.37-5.17). The area under the SROC curve was 0.68 (95% CI 0.64-0.72). The likelihood ratio scatter plot based on average sensitivity and specificity was in the lower right quadrant.

Conclusion Meta-analysis results showed ^{18}F-FDG PET/CT had low pooled sensitivity and specificity. The low DOR and the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT should be used with caution when predicting *EGFR* mutations in NSCLC patients.

Article summary

Strengths and limitations

1. To our knowledge, this is the first review that systematically analyzes the diagnostic accuracy of ^{18}F-FDG PET/CT for predicting *EGFR* status.
2. Weight mean difference analysis was performed prior to inclusion of studies in the diagnostic accuracy meta-analysis.
3. High heterogeneous effect should be mentioned in the results interpretation.

Introduction

Lung cancer is a common malignant tumor that is associated with considerable social and economic burden. Global statistics show that among malignant tumors, morbidity and mortality from lung cancer ranks first in males, while in females lung cancer is second only to breast cancer [1]. Non-small cell lung cancer (NSCLC) accounts for 85–90% of lung cancers, with lung adenocarcinomas (LUAD) being the most diagnosed histological subtype of NSCLC [2]. In Asia, up to 50% of LUAD patients have activating mutations of the tyrosine kinase domain of epidermal growth factor receptor (*EGFR*) [3]. Tyrosine-kinase inhibitor (TKI), which targets *EGFR* kinase domain mutations, seems to trigger a form of oncogenic shock, resulting in a favorable response in NSCLC [4]. The clinical outcome of the NSCLC patients harboring *EGFR* alteration was significantly improved by three different generations of *EGFR* TKIs. Therefore, *EGFR* mutations are considered to have a predictive role in the success of TKI treatment in NSCLC. The standard approach to detecting *EGFR* status is genetic testing, which is based on tumor specimens captured by resection, fine needle aspiration or biopsy. However, this method does not reflect the status of the entire tumor, and usually results in failure or poor reproducibility due to insufficient materials. Liquid biopsy can identify mutant target gene in circulating cell-free tumor DNA, which is sometimes inconsistent with specimens biopsy [5], limiting it clinical application. Moreover, neither biopsies nor plasma samples can provide accurate anatomical information such as position, size, boundary and relationship with adjacent structures of the tumors, which is critical for clinical treatment planning and response assessment.

Image-based phenotyping, which provides a non-invasive method to visualize tumor phenotypic characteristics, is a promising tool for precision medicine [6]. X-ray computed tomography (CT) imaging have been systematically analyzed to discover anatomical risk factors for *EGFR* mutations prediction in NSCLC [7]. Molecular imaging is an attractive option for evaluating NSCLC patients receiving targeted treatment because it can noninvasively capture the molecular and genomic characteristics of the tumor. The use of positron emission tomography/ computed tomography (PET/CT) as a molecular imaging modality for precision medicine is unique. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT can provide information on glucose metabolism and is widely used for cancer diagnosis and image-guided therapy. Semi-quantitative parameters can be used for PET image analysis, with the mean maximum of standard uptake

value (SUV_{max}) being the most effective and commonly used parameter. It has been reported that ^{18}F-FDG PET/CT can predict *EGFR* status in NSCLC patients, but this remains controversial. Some studies have confirmed that higher uptake of ^{18}F-FDG is predictive of mutant *EGFR* in NSCLC patients [8–10], while several other studies have shown the opposite result [11–13]. A systematic review is needed to clarify this point.

Although ^{18}F-FDG PET/CT was used to predict many biological features or other genetic mutations of certain malignancies through meta-analysis [14–16], as far as we know, no meta-analysis has summarized the association between ^{18}F-FDG PET/CT and *EGFR* mutation status in NSCLC. The purpose of our study was to conduct a meta-analysis of the diagnostic performance of ^{18}F-FDG PET/CT in predicting *EGFR* mutations, thereby providing more evidence for precise treatment of NSCLC patients.

Methods

Screening of publications

A systematic review of publications relevant to PET and *EGFR* mutations in NSCLC was undertaken using the electronic databases of PubMed, Embase and the Cochrane library from the earliest available date of indexing up to December 31, 2020. A search algorithm based on combined terms was used: (1) “FDG” OR “Fluorodeoxyglucose” OR “2-Fluoro-2-deoxyglucose” OR “2-Fluoro-2-deoxy-D-glucose” and (2) “PET” OR “positron emission tomography” and (3) “Epidermal Growth Factor Receptor” OR “*EGFR*” OR “c-erbB-1” OR “erbB-1” OR “v-erbB” and (4) “pulmonary cancer” OR “pulmonary cancer” OR “lung neoplasm” OR “lung cancer” and (5) “mutation” (see online supplementary file for further details on search strategy). In order to expand the scope of our search, we also screened the references of the included studies for other studies to include.

Inclusion of studies and data extraction

Only original articles focusing on ^{18}F-FDG PET/CT and *EGFR* status in NSCLC patients were eligible for inclusion. To compare the differences in ^{18}F-FDG uptake between *EGFR* mutant and wild-type patients, the publications that reported SUV_{max} and standard deviations (SD) of *EGFR* mutant and wild-type groups were first selected. Next, articles using ^{18}F-FDG PET/CT to predict *EGFR* status in NSCLC patients were included based on whether they provided sufficient data to

re-evaluate the sensitivity and specificity, or provided absolute data including true-positive, true-negative, false-positive and false-negative without data overlap. Duplicate publications and publications that do not contain original data, such as case reports, conference papers, review articles and letters, were excluded. Non-relevant studies and basic research were also excluded. Only English article were evaluated. Two researchers independently reviewed the abstracts of the selected articles using the above inclusion criteria. When there were disagreements between authors, a consensus was reached through a third author who was consulted. The same researchers independently evaluated the full text to determine whether they were eligible for final inclusion.

Quality assessment and publication bias

For pooled weighted mean difference (WMD) analysis, risk of bias, including random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting were assessed. Publication bias was assessed using a funnel plot, and plot asymmetry was considered to be suggestive of publication bias. For diagnostic performance analysis, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was employed to assess the risk of bias in diagnostic accuracy studies. The tool consisted of four domains of risk of bias, including patient selection, index test, reference standard and flow and timing. Publication bias was evaluated using a funnel plot and Egger's regression test.

Data synthesis and analysis

A WMD was calculated through SUV_{max} extracted from the retrieved articles. A random effects model was used for statistical analysis of the data. Pooled data were displayed using forest plots and presented with 95% confidence intervals (CI). An I^2 test was performed to analysis the heterogeneity between studies (I^2 value > 50% was considered significant). Diagnostic performance for prediction was further assessed. The main purpose was to assess the sensitivity and specificity, the positive and negative diagnostic likelihood ratios (DLR+ and DLR-, respectively), as well as the diagnostic odds ratio (DOR). Publication bias was evaluated using a Deeks' funnel plot of the effective sample size. The bivariate model allowed us to incorporate the correlation that might exist between the logit-transformed values of paired sensitivity and specificity across studies. Each data point of the summary receiver operator characteristic

(SROC) graph was derived from a separate study. Based on these points, the smooth SROC curve was formed to reveal the accuracy of the pooled measures. The likelihood ratio scatter plots graphically showed summary spots of likelihood ratios obtained from the average sensitivity and specificity. Statistical analyses were performed using STATA 15.1 (StataCorp LP, College Station, TX) and RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark). $p \leq 0.05$ was considered statistically significant.

Patient and public involvement statement

Neither patients nor the public were involved in the design and planning of the study.

Results

Literature search and selection of studies

The comprehensive search yielded 545 records for analysis. Records with duplicate titles and abstracts (89) were excluded. Additionally, 36 review articles, 144 conference abstracts, 13 basic research articles, 120 case reports, editorials, notes and surveys, 86 non-relevant records and 10 other language studies were excluded. The remaining 47 full-text articles were further assessed for eligibility. For calculating pooled WMD, 24 articles were excluded due to insufficient data and 23 studies were included. For the pooled DOR analysis, 29 articles were excluded due to insufficient data and 3 articles were excluded due to inconsistent results according to pooled WMD results (^{18}F-FDG uptake was significantly lower in *EGFR* mutant group; the pooled sensitivity, specificity and DOR were also calculated without excluding the 3 studies). The remaining 15 studies were included in the meta-analysis. The detailed procedure of study selection is shown in Figure 1.

Study description and publication bias

All included patients underwent a ^{18}F-FDG PET/CT examination and EGFR gene test. EGFR mutations analysis was carried out on tissue specimens obtained from resection, aspiration or biopsy. A total of 5220 patients were included in the WMD analysis, and SUV_{max} between the *EGFR* mutant and wild-type groups were compared. The patients were enrolled retrospectively in all 23 of the included studies. The pooled comparison of the studies demonstrated that ^{18}F-

FDG uptake was significantly lower in the *EGFR* mutant group (WMD -1.73; 95% CI -2.34 - -1.12; $p < 0.05$; $I^2 = 78.2\%$, Figure 2). The most common domains with reporting deficiencies related to the patient selection, as there was no random sequence generation for retrospective studies (Figure 3A). Visual analysis of the funnel plot was not suggestive of publication bias using Egger's test ($p = 0.786$; Figure 3B). The principal characteristics of the included 23 studies are shown in Table 1.

In order to predict presence of *EGFR* mutations in NSCLC patients, a total of 3574 patients were included in the analysis, including 2046 male and 1528 female cases. The average age was 62.9 years old, 90.3% had LUAD and 42.8% were smokers. All 15 studies enrolled patients retrospectively. The *EGFR* mutation incidence rate was 41.2% with a range of 21.0%–57.5%. SUV_{max} was used for interpretation of ^{18}F-FDG PET/CT to predict the *EGFR* mutation status. The principal characteristics of the 15 included studies are also shown in Table 1. Most of the observational studies demonstrated a low risk of bias as assessed by the QUADAS-2 tool (Figure 4A). Deek's funnel plot asymmetry tests were performed to assess a possible publication bias. No significant bias was found ($p = 0.089$; Figure 4B).

Table 1 Characteristics of the included studies

Authors	Year	Country	Study design	Patient number	Age (mean)	Gender (M/F)	Smoker	LUAD	Genetic test	*EGFR* mutant /wild-type	^{18}F-FDG injection dose	Cut-off value	Meta-analysis
Caicedo et al [17]	2014	Spain	R	102	62	62/40	73	90	PCR	22/80	NA	NA	WMD
Chen et al [10]	2019	China	R	157	66	84/73	68	144	PCR	54/103	481 MBq	9.92	WMD/ DOR
Cho et al [18]	2016	Korea	R	61	61	33/28	29	58	PCR	30/31	5.5 MBq/kg	9.6	WMD/ DOR
Choi et al [19]	2012	Korea	R	163	60	99/64	73	130	PCR	57/106	5.18 MBq/kg	NA	WMD
Choi et al [20]	2013	Korea	R	331	62	158/173	145	331	PCR	156/175	5.18 MBq/kg	NA	WMD
Chung et al [21]	2010	Korea	R	106	64	63/43	60	97	PCR	42/64	4.8 MBq/kg	NA	WMD
Gao et al [22]	2020	China	R	167	58	87/80	67	162	PCR	72/94	370 MBq	11.5	DOR
Gu et al [23]	2017	China	R	210	59	132/78	90	161	PCR	70/140	5.18 MBq/kg	9	DOR
Guan et al [24]	2016	China	R	316	60	216/100	162	242	PCR	126/190	NA	8.1	WMD/ DOR
Hong et al [25]	2020	Korea	R	134	69	89/45	76	134	PCR	62/72	52/7MBq/kg	9.6	WMD/ DOR
Huang et al [11]	2010	China	R	77	62	44/33	16	77	PCR	49/28	370MBq	NA	WMD

Kanmaz et al [12]	2016	Turkey	R	218	62	151/67	155	218	PCR	63/155	3.7~5.2 MBq/kg	NA	WMD
Kim et al [26]	2016	Korea	R	198	62	113/85	68	183	PCR	101/97	5.18 MBq/kg	NA	WMD
Kim et al [27]	2018	Korea	R	232	64	104/128	93	232	PCR	132/100	5.18 MBq/kg	NA	WMD
Lee et al [28]	2015	Korea	R	206	68	148/58	71	135	PCR	47/159	481 MBq	11.7	DOR
Lee et al [29]	2015	China	R	71	65	33/38	19	71	PCR	48/23	370 MBq	NA	WMD
Liao et al [30]	2020	China	R	191	63	101/90	65	191	PCR	63/128	3.7 MBq/kg	7.78	DOR
Lv et al [31]	2018	China	R	808	59	468/340	310	731	PCR	371/437	5.5 MBq/kg	7	WMD/ DOR
Liu et al [32]	2017	China	R	87	60	49/38	32	78	PCR	41/46	NA	10.4	DOR
Mak et al[33]	2011	USA	R	100	65	39/61	73	90	PCR	24/76	5.55~7.4MBq	NA	WMD
Minamimoto et al [34]	2017	USA	R	127	67	NA	NA	127	PCR	32/95	12~17 mCi	NA	WMD
Mu et al [35]	2020	China, USA	R	681	63	378/303	315	567	PCR	312/369	NA	NA	WMD
Na et al [36]	2010	Korea	R	100	64	68/32	57	53	PCR	21/79	370 MBq	9.2	DOR
Qiang et al [37]	2016	China	R	97	65	50/47	51	97	PCR	44/53	7.4 MBq/kg	NA	WMD
Suárez-Piñera et al [38]	2018	Spain	R	106	71	NA	NA	106	PCR	24/82	5.29 MBq/kg	NA	WMD
Takamochi et al [39]	2017	Japan	R	734	68	367/367	363	734	PCR	334/400	3.5 MBq/kg	2.69	WMD/ DOR
Whi et al [40]	2020	Korea	R	64	66	34/30	25	64	PCR	29/35	5.18 MBq/kg	9.5	WMD/ DOR
Yang et al [8]	2019	China	R	200	61	108/92	68	200	PCR	115/85	3.7~6.66 MBq/kg	6.15	WMD/ DOR
Zhu et al [9]	2018	China	R	139	62	62/77	46	139	PCR	74/65	4.2 MBq/kg	11.19	WMD/ DOR

LUAD, Lung adenocarcinoma; WMD, weighted mean difference; DOR, diagnostic odds ratio.

Diagnostic effectiveness of ^{18}F-FDG PET/CT

The diagnostic effectiveness of ^{18}F-FDG PET/CT in predicting *EGFR* mutation in NSCLC patients was meta-analyzed across 15 studies. The pooled sensitivity was 0.70 (95% CI 0.60-0.79) with heterogeneity (I^2 = 90.86, 95% CI 87.38–94.34, $p < 0.05$). The pooled specificity was 0.59 (95% CI 0.52-0.66) with heterogeneity (I^2 = 91.43, 95% CI 88.23–94.63, $p < 0.05$; Figure 5). DLR syntheses gave an overall DLR+ of 1.74 (95% CI 1.49–2.03) and DLR− of 0.50 (95% CI 0.38–0.65; Figure 6). The pooled DOR was 3.50 (95% CI 2.37-5.17; Figure 6). The area under curve (AUC) obtained from SROC was 0.68 (95% CI 0.64-0.72; Figure 7A). Lower pooled

sensitivity, specificity and DOR were shown with the three studies included in the prediction of EGFR mutations in NSCLC patients (see online supplementary file Figure S1).

Likelihood ratio scatter plot

The summary value of likelihood ratios obtained from the average sensitivity and specificity shown in the likelihood ratio scatter plot (Figure 7B) was located in the lower right quadrant, which indicated that ^{18}F-FDG PET/CT may not be useful for predicting whether there is an *EGFR* mutation (when positive) or not (when negative).

Discussion

In light of the advances in the precise treatment of lung cancer, identifying targetable mutations at the time of diagnosis has become the key to determining the best treatment strategies. The identification of the *EGFR* mutation led to an important paradigm shift in the treatment and survival of NSCLC patients. A typical molecular imaging technique, ^{18}F-FDG PET/CT has been used in prediction of *EGFR* status in NSCLC patients. However, various studies have published contradictory results. This is the first systematic review and meta-analysis to summarize current evidence for the use of ^{18}F-FDG PET/CT to predict EGFR status in NSCLC patients. The principal findings of this meta-analysis showed low sensitivity and specificity of ^{18}F-FDG PET/CT in the prediction of EGFR mutations.

Previous studies on the value of ^{18}F-FDG PET in predicting *EGFR* status have been conflicting. Accumulation of ^{18}F-FDG was reported to be lower in NSCLC patients, which can be used to predict *EGFR* status. Na et al. first reported that patients with low SUV_{max} were more likely to have *EGFR* mutations than those with high SUV_{max}. When using 9.2 as the cut-off value, the specificity and sensitivity reached 72% and 67%, respectively[36]. Lee et al. concluded that ^{18}F-FDG avidity had no significant clinical value in predicting *EGFR* status, while the univariate analysis showed that SUV_{max} was significantly correlated with *EGFR* mutation using 11.7 as the cut-off value [28]. Cho et al. also found that mutant *EGFR* had relatively lower glycolysis compared with wild-type *EGFR*. A cut-off SUV_{max} value of 9.6 had the highest sensitivity (79.3 %) in predicting *EGFR* mutations [18]. Research by Guan et al. showed that ^{18}F-FDG uptake values could effectively predict the *EGFR* mutation status of NSCLC patients. ROC curve analysis revealed the AUC was 0.65, with an SUV_{max} value of 8.1 as the cut-off point [24].

Next, other studies further demonstrated that low SUV_{max} was a significant predictor of *EGFR* mutations using different cut off values [8, 9, 23, 31, 39]. Chen et al. demonstrated that using 9.92 as the SUV_{max} cut-off point can best discriminate the *EGFR* mutation status with an AUC of 0.75, and they identified that the mechanism responsible for the decreased FDG uptake associated with mutant *EGFR* was through the NOX4/ROS/GLUT1 axis [10]. However, multiple groups have reported no association between SUV_{max} and *EGFR* status. Mak et al. reported that high normalized SUV_{max} only correlated with the EFGR wild-type genotype [33]. Moreover, several studies have reported conflicting results. Huang et al. found that a higher ^{18}F-FDG uptake with a SUV_{max} cut-off value of 9.5 correlates with the presence of *EGFR* mutations [11]. While Ko et al. showed a trend of higher SUV_{max} in patients with an *EGFR* mutation, with an optimal cut-off was 6 [13]. Kanmaz et al. made a similar conclusion, with an SUV_{max} cut-off value of 13.65 as the predictor [12].

Our results indicated the ^{18}F-FDG PET/CT has low sensitivity and specificity in predicting EGFR mutations. Comparison of mean SUV_{max} between *EGFR* mutant and wild-type was first pooled with WMD to determine the relationship between *EGFR* status and FDG uptake. According to result of WMD meta-analysis, ^{18}F-FDG uptake was significantly lower in the *EGFR* mutant group. Thus, studies that reported higher ^{18}F-FDG uptake for prediction of *EGFR* mutation in NSCLC patients were excluded in the DOR analysis. The meta-analysis showed low pooled sensitivity of 70% and specificity of 59% for prediction. The low DOR of 0.68 as well as the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT might not be useful—or, at least, should be used with caution—for predicting *EGFR* mutations in NSCLC patients. In addition, the obvious heterogeneity, especially for the main parameters, indicated that the differences between studies cannot be ignored and conclusion should be drawn carefully.

Many efforts have been made to improve prediction efficacy, which may be the direction of future research. More ^{18}F-FDG PET/CT semi-quantitative parameters including metabolic tumor volume and total glucose glycolysis were investigated to potentially predict EGFR mutations [21, 30]. Recent studies also focused on ^{18}F-FDG PET/CT radiomics [41, 42]. Radiomics refers to the extraction of quantitative characteristics from medical images [43]. The PET/CT-based radiomic characteristics showed good performance in the prediction of *EGFR* mutations in NSCLC patients [35, 44]. Although the predication efficacy improved, its clinical application requires

additional studies to confirm and optimize. Beyond ^{18}F-FDG, novel radiotracers have also been investigated. ^{18}F-MPG PET/CT was demonstrated to be a valid strategy for stratifying NSCLC patients with *EGFR*-activating mutations for *EGFR*-TKI treatment [45], but this radiotracer is not routinely available. Other promising studies are under way to translate these novel approaches into the clinic to guide effective precision therapy for NSCLC patients.

Strengths and limitations

The strength of this study is that the conflicting results were first analyzed using WMD analysis, so that a more reasonable meta-analysis can be performed on the accuracy of the diagnosis. The high level of heterogeneity is the main limitation. However, this can be addressed using a random effects model. The first area of heterogeneity is related to NSCLC subtypes. LUAD is the main pathological type of NSCLC, but even within LUAD, there are different subtypes. For example, alveolar carcinoma demonstrates relatively low ^{18}F-FDG uptake. Second, SUV_{max} is the most stable and commonly used index, but there are many factors that affect SUV_{max}, including tumor size, glucose level, and image acquisition and reconstruction, especially for different PET/CT equipment with different acquisition parameters. Third, the number of studies included in this study was small, especially for subgroup analysis. To further study these issues, an increased number of high-quality studies need to be carried out in the future.

Conclusion

Our meta-analysis results showed that ^{18}F-FDG PET/CT had low pooled sensitivity and specificity for *EGFR* mutation prediction. The low DOR and the likelihood ratio scatter plot indicated that ^{18}F-FDG PET/CT might not be useful—or, at least, that it should be used with caution—for predicting *EGFR* mutations in NSCLC patients.

Ethics statement

This study was a systematic review and meta-analysis. Ethics committee approval was not necessary because all data were carefully extracted from existing literature.

Author contributions

BD is the first author. BD and YL obtained funding. BD, XL and YL designed the study. BD, YC, GL and SW collected and analyzed the data. BD drafted the manuscript. BD and YL contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content, and approved the final version of the manuscript. All authors have read and approved the final manuscript. BD and YL are the study guarantors.

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Competing interests

We have read and understood the BMJ policy on declaration of interests and declare that we have no competing interests.

Data sharing

No additional data are available

References

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Figure 1 Publication screening flowchart.

Figure 2 Forest plot for analysis of ^{18}F-FDG uptake in *EGFR* mutant versus wild-type in NSCLC patients.

Figure 3 A: Risk of bias of included studies. **B:** funnel plot of SUV_{max} in *EGFR* mutant versus wild-type in NSCLC patients.

Figure 4 A: Assessment of risk of bias of the included studies using QUADAS-2 tool. **B**: Deeks's funnel plot of asymmetry test for publication bias showed no significant bias was found. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; WMD: weighted mean difference; ESS: effective sample size.

Figure 5 Forest plot of pooled sensitivity and specificity of ^{18}F-FDG PET/CT for predicting *EGFR* mutations in NSCLC patients.

Figure 6 Forest plot of pooled positive, negative DLR and DOR of ^{18}F-FDG PET/CT for predicting *EGFR* mutations in NSCLC patients.

Figure 7 A: Summary receiver operating characteristic (SROC) curves of ^{18}F-FDG PET/CT for predicting *EGFR* mutations in NSCLC patients. **B**: Likelihood ratio scatter plot of ^{18}F-FDG PET/CT predicting *EGFR* mutations in NSCLC patients.

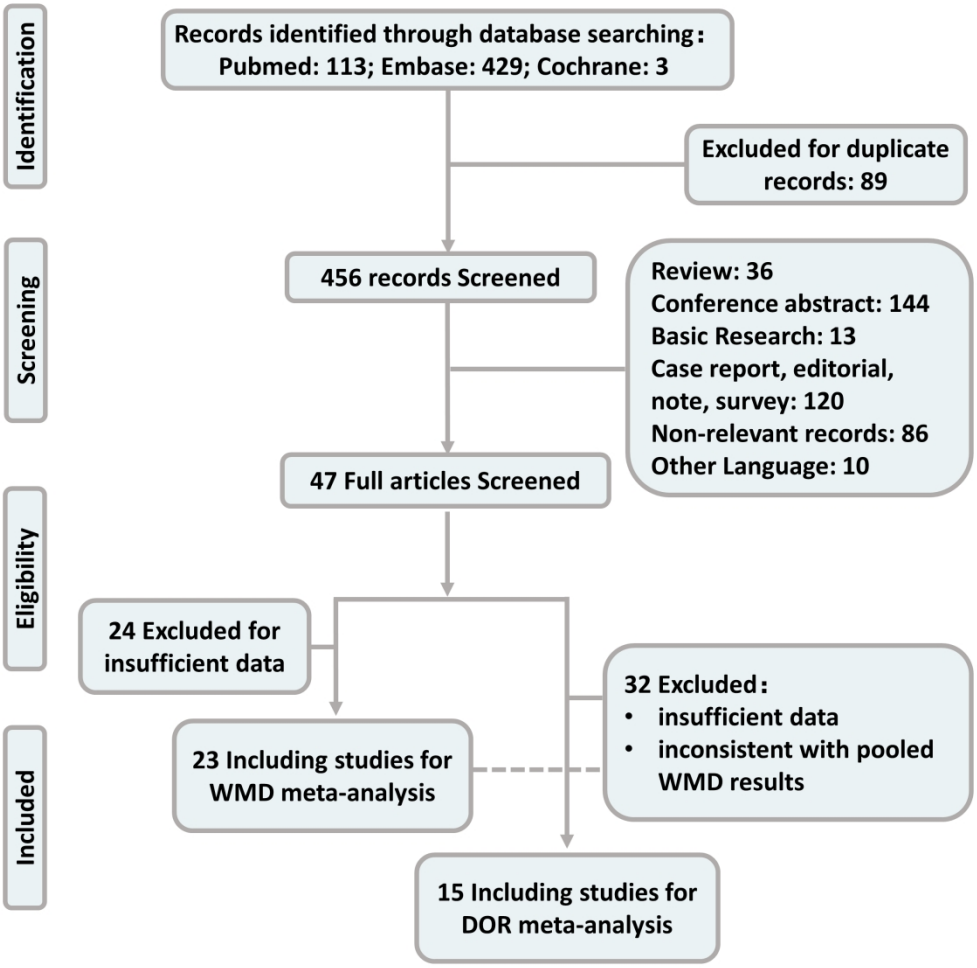

Figure 1 Publication screening flowchart.

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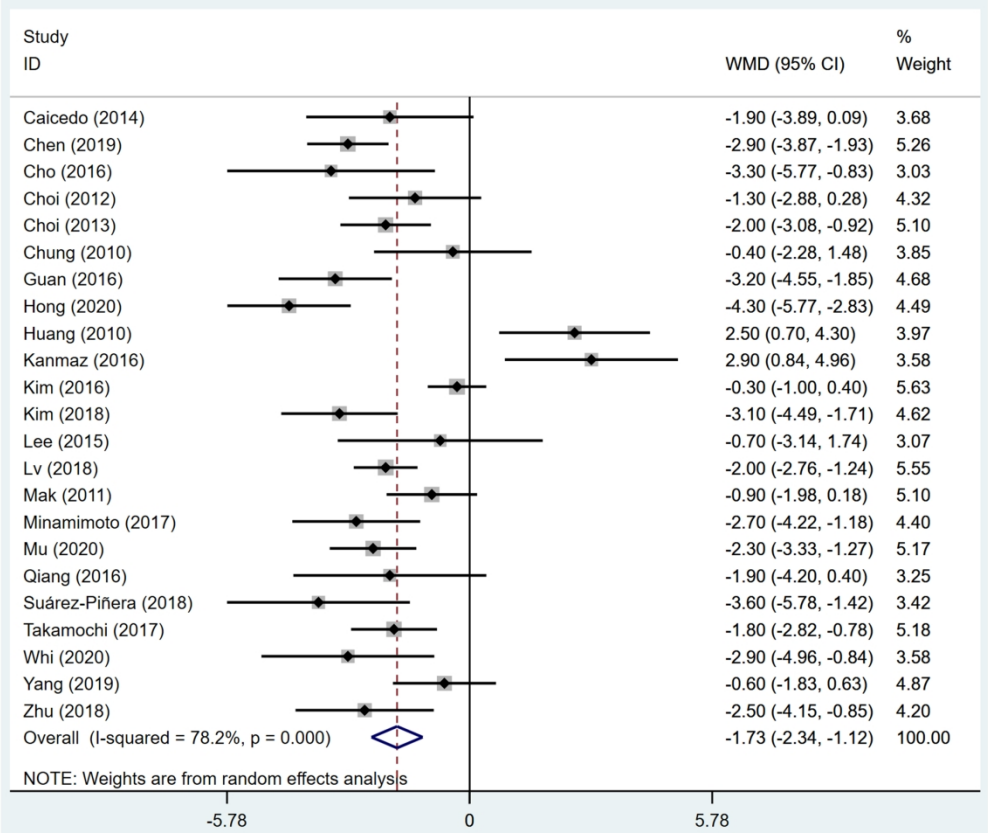

Figure 2 Forest plot for analysis of 18F-FDG uptake in EGFR mutant versus wild-type in NSCLC patients.

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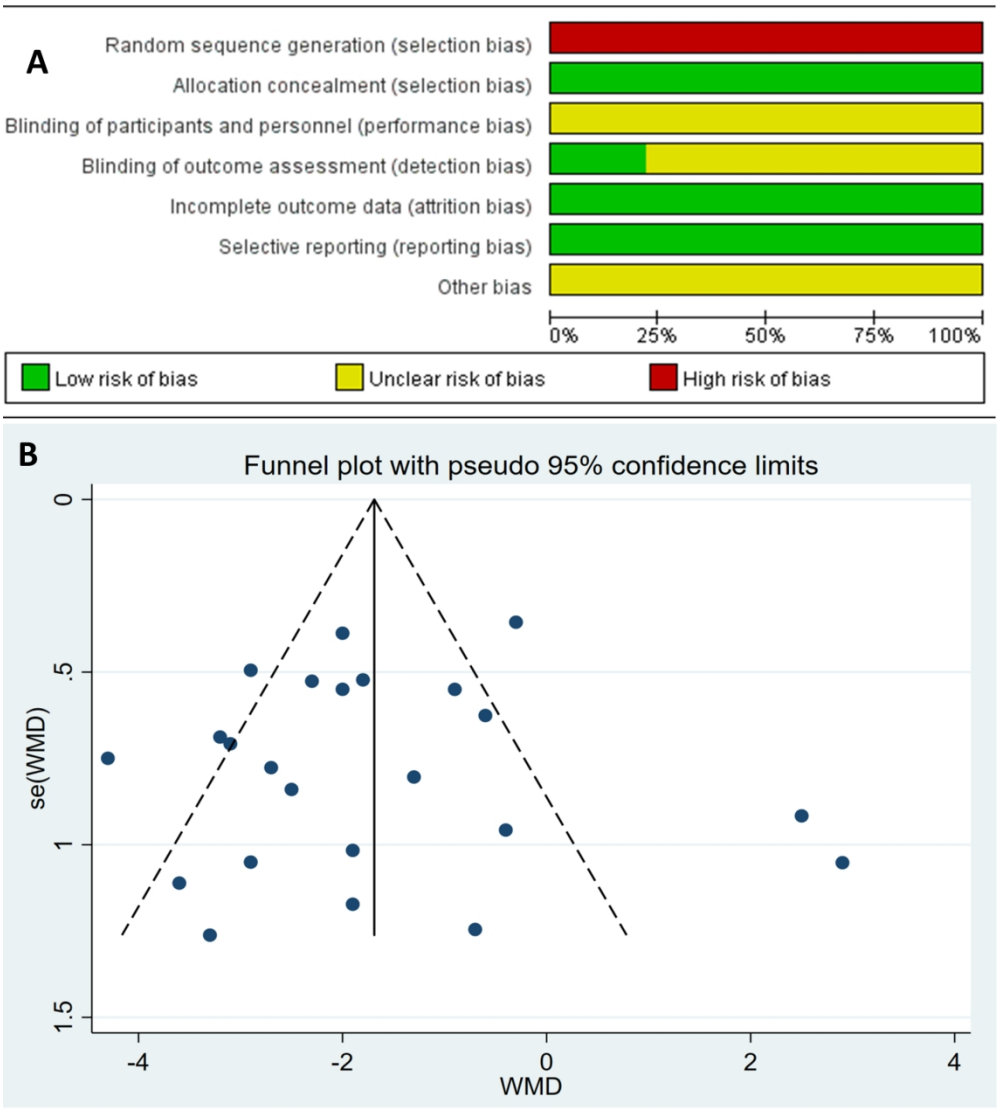

Figure 3 A: Risk of bias of included studies. B: funnel plot of SUVmax in EGFR mutant versus wild-type in NSCLC patients.

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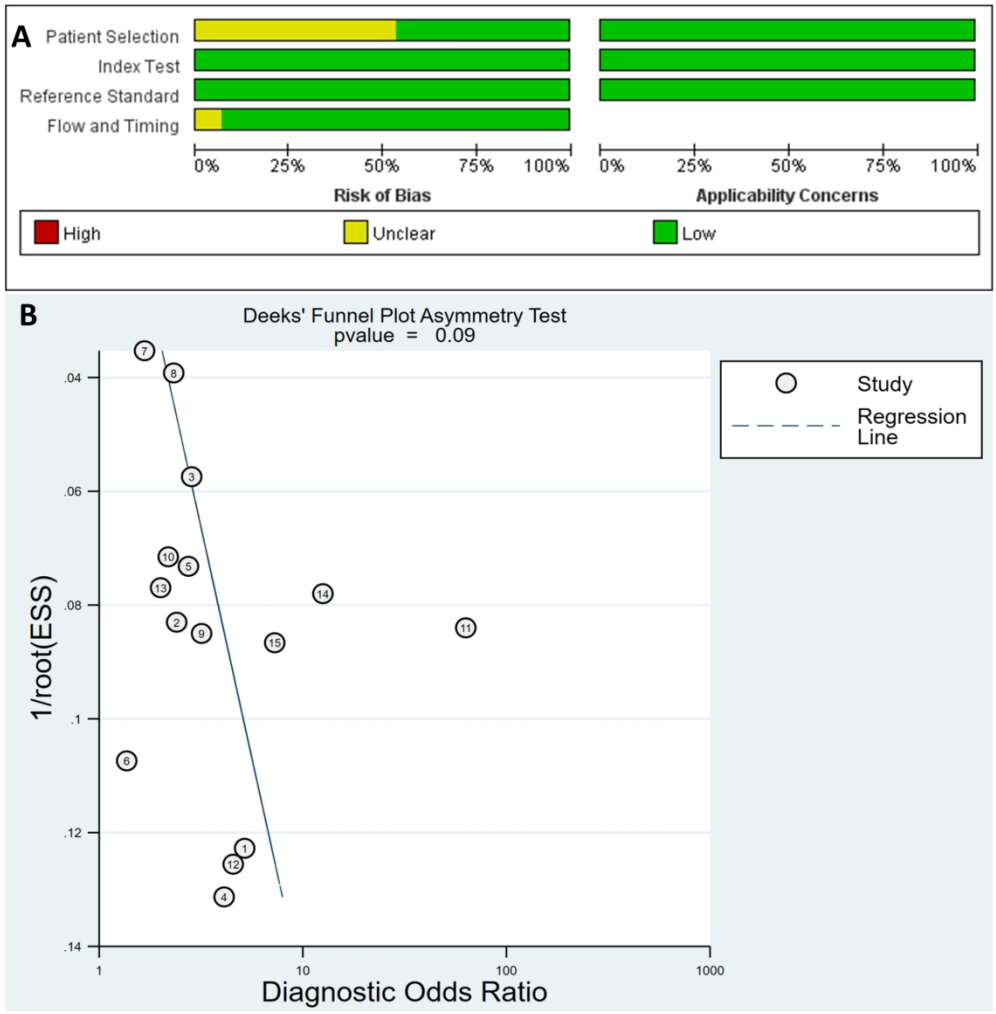


Figure 4 A: Assessment of risk of bias of the included studies using QUADAS-2 tool. B: Deeks's funnel plot of asymmetry test for publication bias showed no significant bias was found. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; WMD: weighted mean difference; ESS: effective sample size.

187x190mm (300 x 300 DPI)

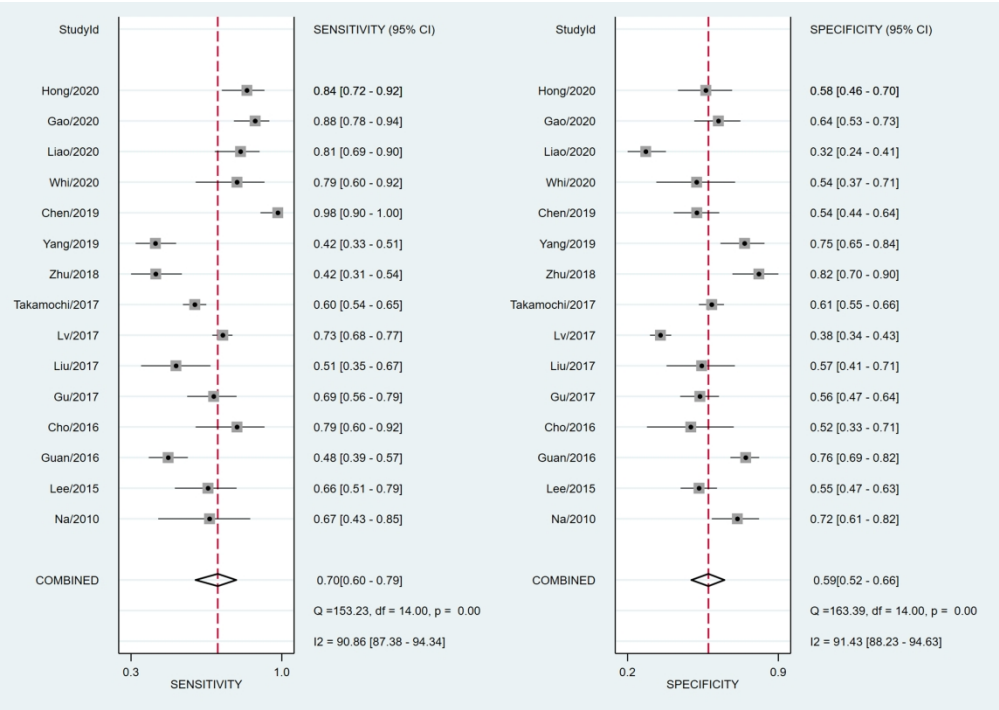


Figure 5 Forest plot of pooled sensitivity and specificity of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.

268x190mm (300 x 300 DPI)

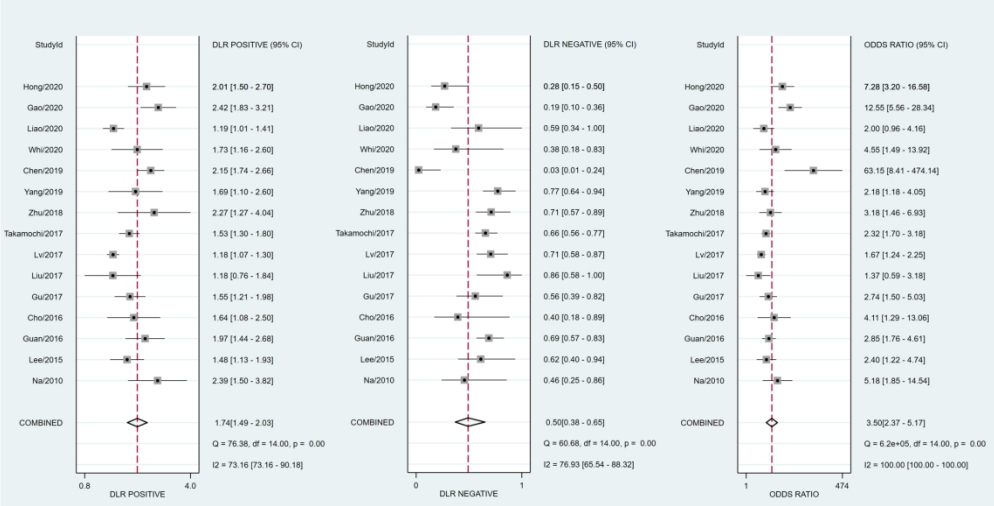


Figure 6 Forest plot of pooled positive, negative DLR and DOR of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.

338x171mm (300 x 300 DPI)

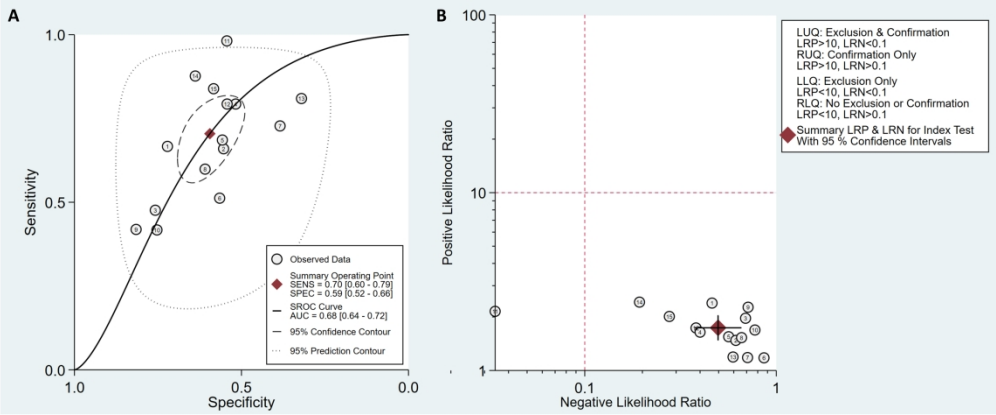


Figure 7 A: Summary receiver operating characteristic (SROC) curves of 18F-FDG PET/CT for predicting EGFR mutations in NSCLC patients. B: Likelihood ratio scatter plot of 18F-FDG PET/CT predicting EGFR mutations in NSCLC patients.

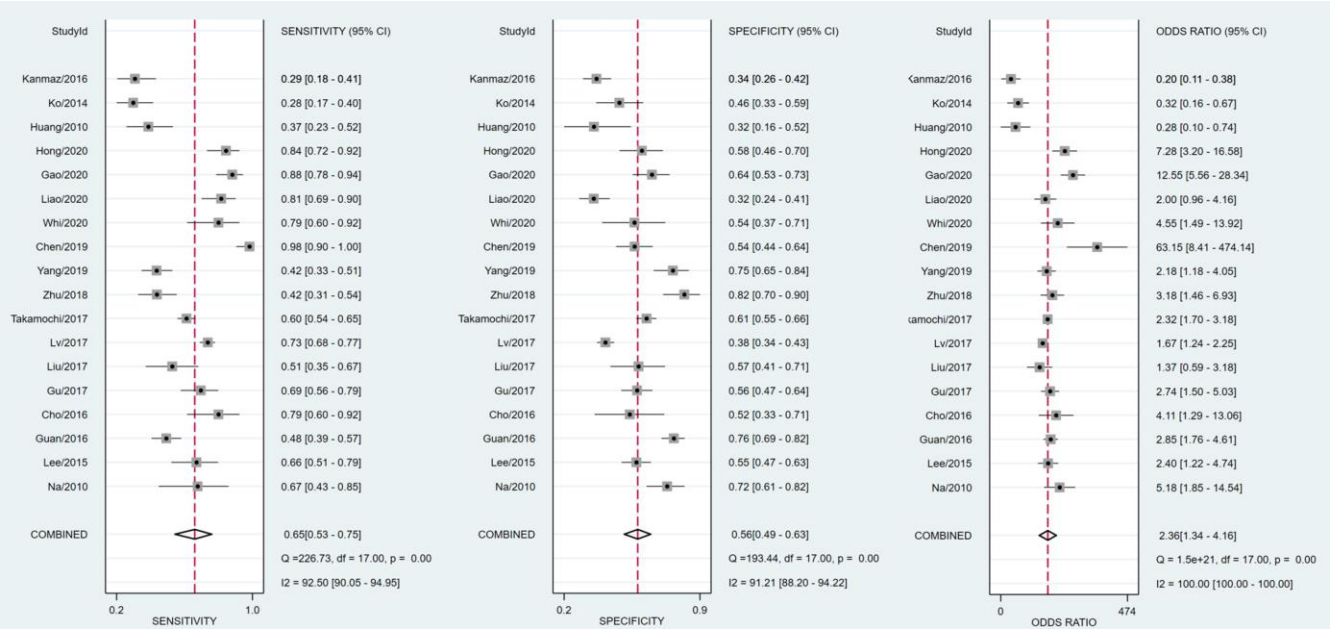
332x137mm (300 x 300 DPI)

Supplementary Appendix

1. **Search Strategy** (used in PubMed)

((((((((Epidermal Growth Factor Receptor) OR EGFR)) OR c-erbB-1) OR erbB-1) OR v-erbB))
AND (((((((FDG) OR Fluorodeoxyglucose) OR 2-Fluoro-2-deoxyglucose) OR 2-Fluoro-2-deoxy-D-glucose))
AND ((Positron Emission Tomography) OR PET)) AND ((((pulmonary Neoplasm) OR pulmonary cancer)) OR
((lung neoplasm) OR lung cancer))))) AND Mutation

2. **Figure S1** Forest plot of pooled sensitivity, specificity and DOR of ^{18}F-FDG PET/CT for predicting EGFR mutations in NSCLC patients.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5, 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5, 6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 7; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 7; Figure 3,4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 8; Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 9; Figure 2，5, 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 7; Figure 3，4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 9; Figure 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10,11,12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 12

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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