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

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ABSTRACT

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

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 patients with NSCLC.

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 OR (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 to 0.79) with a pooled specificity of 0.59 (95% CI 0.52 to 0.66). The overall DLR+ was 1.74 (95% CI 1.49 to 2.03) and DLR− was 0.50 (95% CI 0.38 to 0.65). The pooled DOR was 3.50 (95% CI 2.37 to 5.17). The area under the SROC curve was 0.68 (95% CI 0.64 to 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 patients with NSCLC.

Strengths and limitations of this study

- ► To our knowledge, this is the first review that systematically analyses the diagnostic accuracy of ^{18}F-fluorodeoxyglucose/CT for predicting epidermal growth factor receptor status.
- ► Weight mean difference analysis was performed prior to inclusion of studies in the diagnostic accuracy meta-analysis.
- ► High heterogeneous effect should be mentioned in the results interpretation.

INTRODUCTION

Lung cancer is a common malignant tumour that is associated with considerable social and economic burden. Global statistics show that among malignant tumours, 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 patients with LUAD 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 favourable response in NSCLC.[4] The clinical outcome of the patients with NSCLC harbouring *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 tumour specimens captured by resection, fine needle aspiration or biopsy. However, this method does not reflect the status of the entire tumour, and usually results in failure or poor reproducibility due to insufficient materials. Liquid biopsy can identify mutant target gene in circulating cell-free tumour 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 tumours, which is critical for clinical treatment planning and response assessment.

Image-based phenotyping, which provides a non-invasive method to visualise tumour phenotypic characteristics, is a promising tool for precision medicine.[6] X-ray CT imaging have been systematically analysed to discover anatomical risk factors for *EGFR* mutations prediction in NSCLC.[7] Molecular imaging is an attractive option for evaluating patients with NSCLC receiving targeted treatment because it can non-invasively capture the molecular and genomic characteristics of the tumour. The use of positron emission 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 patients with NSCLC, but this remains controversial. Some studies have confirmed that higher uptake of ^{18}F-FDG is predictive of mutant *EGFR* in patients with NSCLC,[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 summarised 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 patients with NSCLC.

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 31 December 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 supplemental 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 patients with NSCLC 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 SD of *EGFR* mutant and wild-type groups were first selected. Next, articles using ^{18}F-FDG PET/CT to predict *EGFR* status in patients with NSCLC 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 articles 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

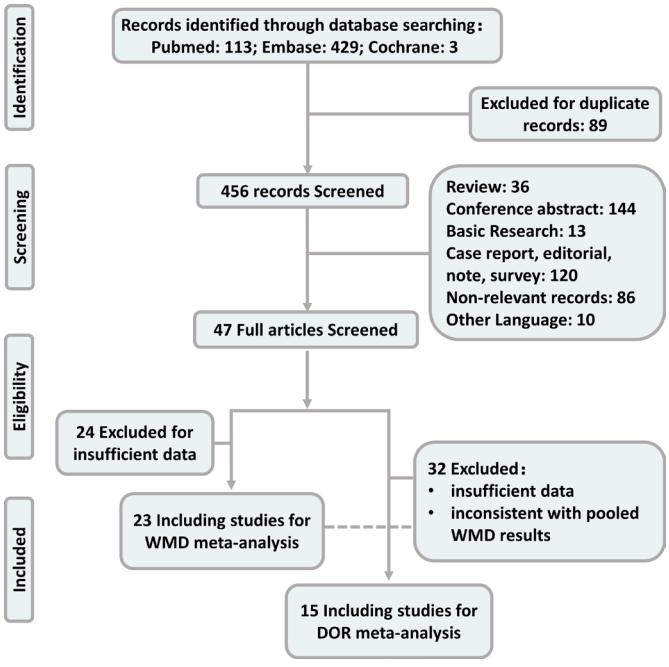

Figure 1 Publication screening flowchart. DOR, diagnostic OR; WMD, weighted mean difference.

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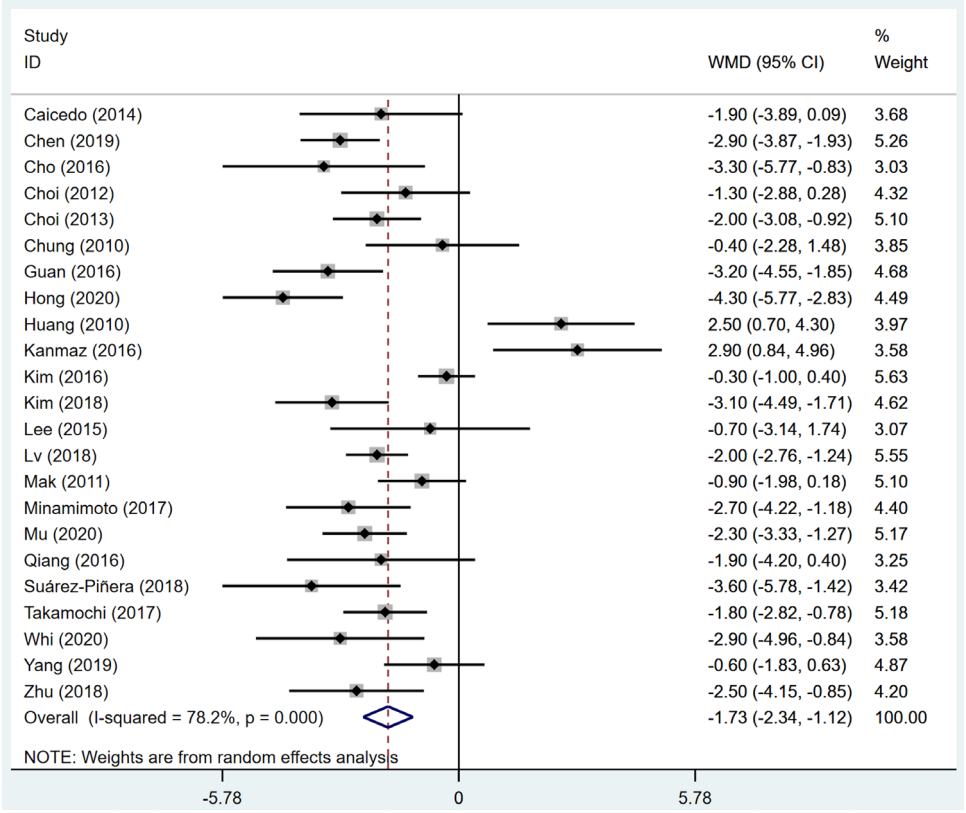

Figure 2 Forest plot for analysis of ^{18}F-fluorodeoxyglucose uptake in epidermal growth factor receptor mutant versus wild-type in patients with non-small cell lung cancer. WMD, weighted mean difference.

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% CIs. 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 OR (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 V.15.1 (StataCorp LP) and RevMan V.5.3 (Cochrane Collaboration, Copenhagen, Denmark). P≤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 three studies). The remaining 15 studies were included in the meta-analysis. The detailed procedure of study selection is shown in figure 1.

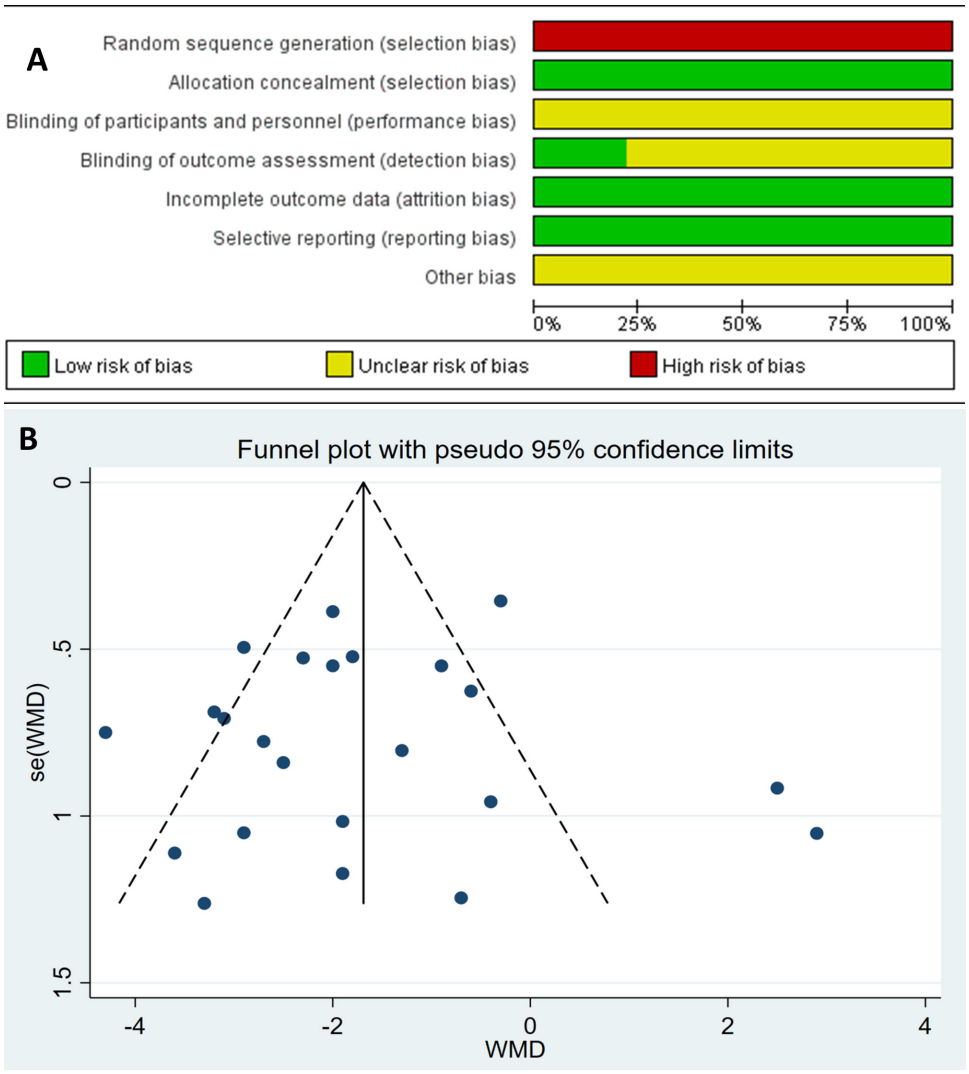

Figure 3 (A) Risk of bias of included studies.(B) Funnel plot of maximum of standard uptake value in epidermal growth factor receptor mutant versus wild-type in patients with non-small cell lung cancer. WMD, weighted mean difference.

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 to −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 the presence of *EGFR* mutations in patients with NSCLC, 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 the 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).

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

The diagnostic effectiveness of ^{18}F-FDG PET/CT in predicting *EGFR* mutation in patients with NSCLC was meta-analysed across 15 studies. The pooled sensitivity was 0.70 (95% CI 0.60 to 0.79) with heterogeneity (I^2=90.86, 95% CI 87.38 to 94.34, p<0.05). The pooled specificity was 0.59 (95% CI 0.52 to 0.66) with heterogeneity (I^2=91.43, 95% CI 88.23 to 94.63, p<0.05; figure 5). DLR syntheses

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*[33]	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*[19]	2016	Korea	R	61	61	33/28	29	58	PCR	30/31	5.5 MBq/kg	9.6	WMD/DOR
Choi *et al*[34]	2012	Korea	R	163	60	99/64	73	130	PCR	57/106	5.18 MBq/kg	NA	WMD
Choi *et al*[35]	2013	Korea	R	331	62	158/173	145	331	PCR	156/175	5.18 MBq/kg	NA	WMD
Chung *et al*[25]	2010	Korea	R	106	64	63/43	60	97	PCR	42/64	4.8 MBq/kg	NA	WMD
Gao *et al*[36]	2020	China	R	167	58	87/80	67	162	PCR	72/94	370 MBq	11.5	DOR
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
Hong *et al*[37]	2020	Korea	R	134	69	89/45	76	134	PCR	62/72	52/7 MBq/kg	9.6	WMD/DOR
Huang *et al*[11]	2010	China	R	77	62	44/33	16	77	PCR	49/28	370 MBq	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*[38]	2016	Korea	R	198	62	113/85	68	183	PCR	101/97	5.18 MBq/kg	NA	WMD
Kim *et al*[39]	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*[40]	2015	China	R	71	65	33/38	19	71	PCR	48/23	370 MBq	NA	WMD
Liao *et al*[26]	2020	China	R	191	63	101/90	65	191	PCR	63/128	3.7 MBq/kg	7.78	DOR
Lv *et al*[22]	2018	China	R	808	59	468/340	310	731	PCR	371/437	5.5 MBq/kg	7	WMD/DOR
Liu *et al*[41]	2017	China	R	87	60	49/38	32	78	PCR	41/46	NA	10.4	DOR
Mak *et al*[24]	2011	USA	R	100	65	39/61	73	90	PCR	24/76	5.55–7.4 MBq	NA	WMD
Minamimoto *et al*[42]	2017	USA	R	127	67	NA	NA	127	PCR	32/95	12~17 mCi	NA	WMD
Mu *et al*[30]	2020	China, USA	R	681	63	378/303	315	567	PCR	312/369	NA	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*[43]	2016	China	R	97	65	50/47	51	97	PCR	44/53	7.4 MBq/kg	NA	WMD
Suárez-Piñera *et al*[44]	2018	Spain	R	106	71	NA	NA	106	PCR	24/82	5.29 MBq/kg	NA	WMD
Takamochi *et al*[23]	2017	Japan	R	734	68	367/367	363	734	PCR	334/400	3.5 MBq/kg	2.69	WMD/DOR
Whi *et al*[45]	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

DOR, diagnostic OR; EGFR, epidermal growth factor receptor; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; LUAD, lung adenocarcinoma; WMD, weighted mean difference.

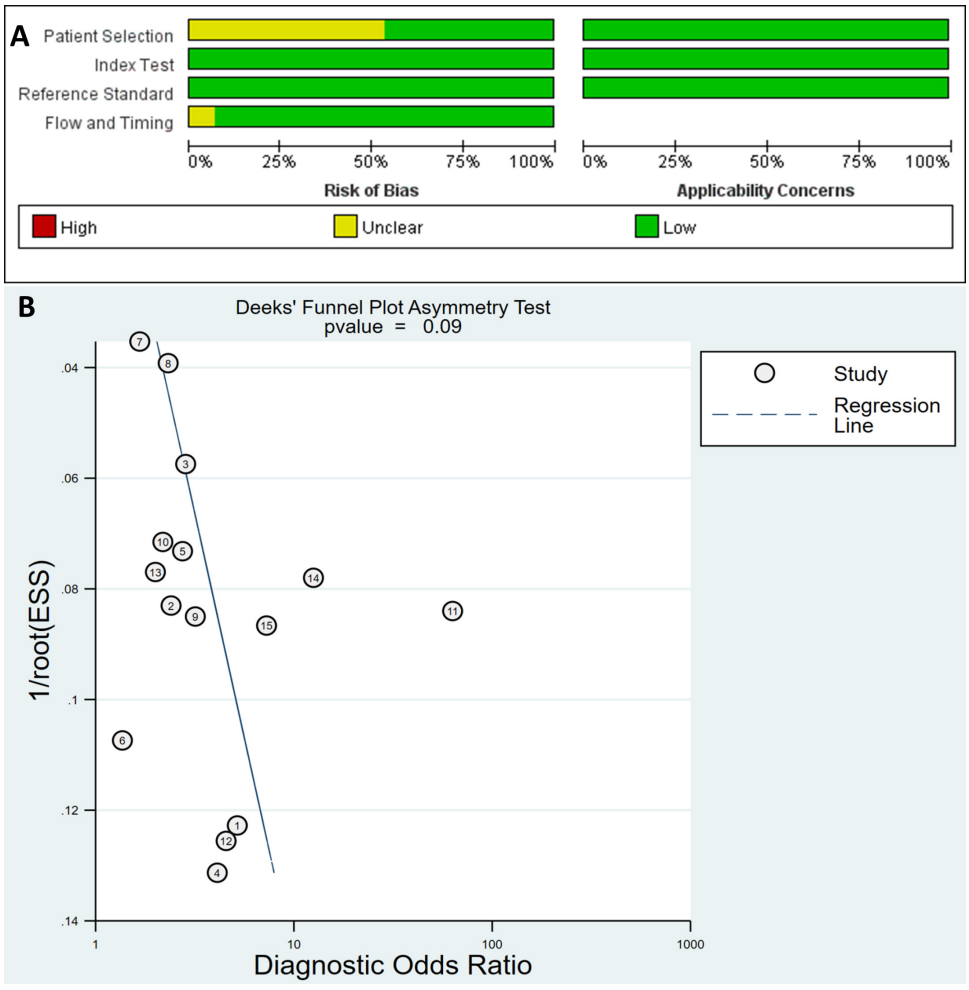

Figure 4 (A) Assessment of risk of bias of the included studies using QUADAS-2 tool. (B) Deeks's funnel plot of asymmetry test for publication bias showed no significant bias was found. ESS, effective sample size; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; WMD, weighted mean difference.

gave an overall DLR+ of 1.74 (95% CI 1.49 to 2.03) and DLR− of 0.50 (95% CI 0.38 to 0.65; figure 6). The pooled DOR was 3.50 (95% CI 2.37 to 5.17; figure 6). The area under curve (AUC) obtained from SROC was 0.68 (95% CI 0.64 to 0.72; figure 7A). Lower pooled sensitivity, specificity and DOR were shown with the three studies included in the prediction of EGFR mutations in patients with NSCLC (see online supplementary 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 patients with NSCLC. A typical molecular imaging technique, ^{18}F-FDG PET/CT has been used in prediction of *EGFR* status in patients with NSCLC. However, various studies have published contradictory results. This is the first systematic review and meta-analysis to summarise current evidence for the use of ^{18}F-FDG PET/CT to predict EGFR status in patients with NSCLC. 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 patients with NSCLC, 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 that SUV_{max} was significantly correlated with

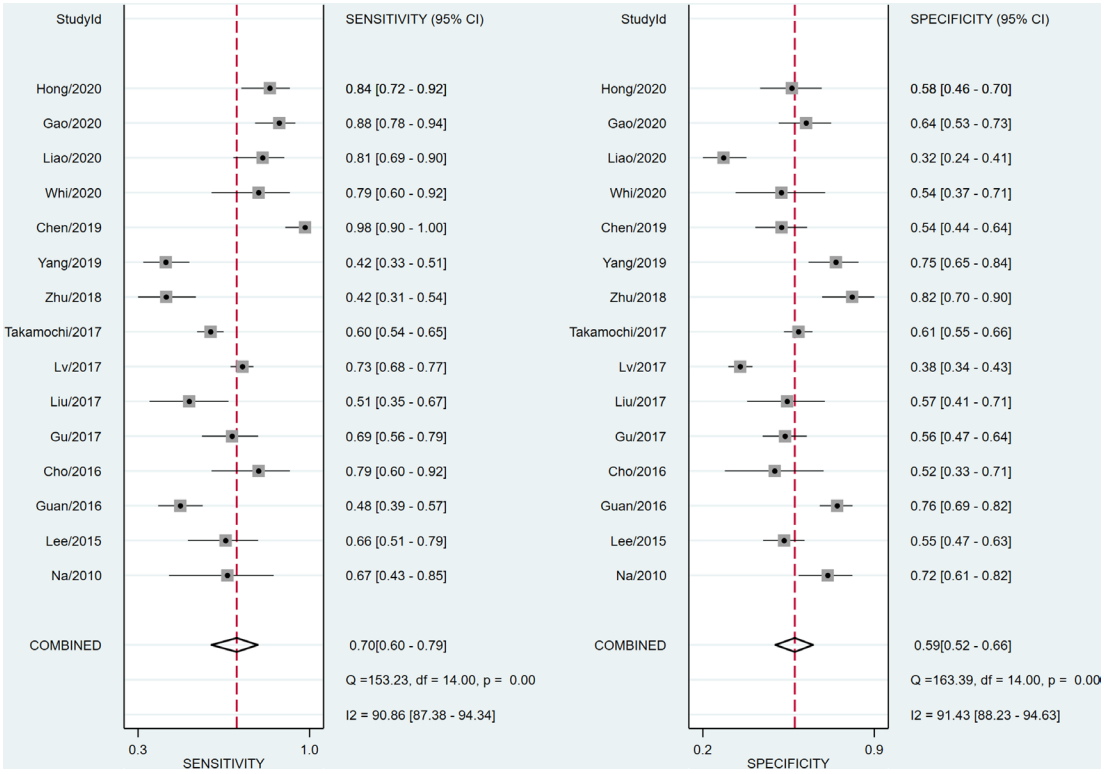

Figure 5 Forest plot of pooled sensitivity and specificity of ^{18}F-fluorodeoxyglucose positron emission tomography/CT for predicting epidermal growth factor receptor mutations in patients with non-small cell lung cancer.

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* mutations.[19] Research by Guan *et al* showed that ^{18}F-FDG uptake values could effectively predict the *EGFR* mutation status of patients with NSCLC. ROC curve analysis revealed the AUC was 0.65, with an 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

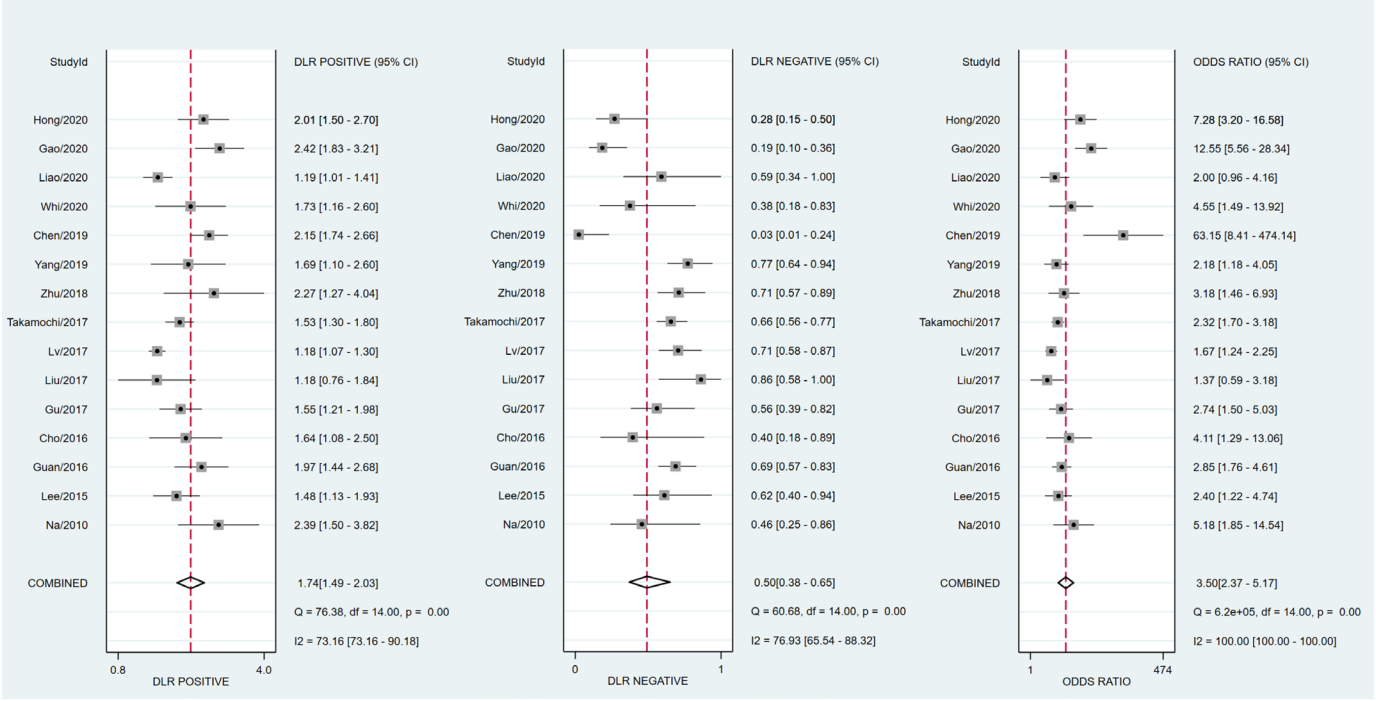

Figure 6 Forest plot of pooled positive, negative diagnostic likelihood ratio (DLR) and diagnostic OR of ^{18}F-fluorodeoxyglucose emission tomography/CT for predicting epidermal growth factor receptor mutations in patients with non-small cell lung cancer.

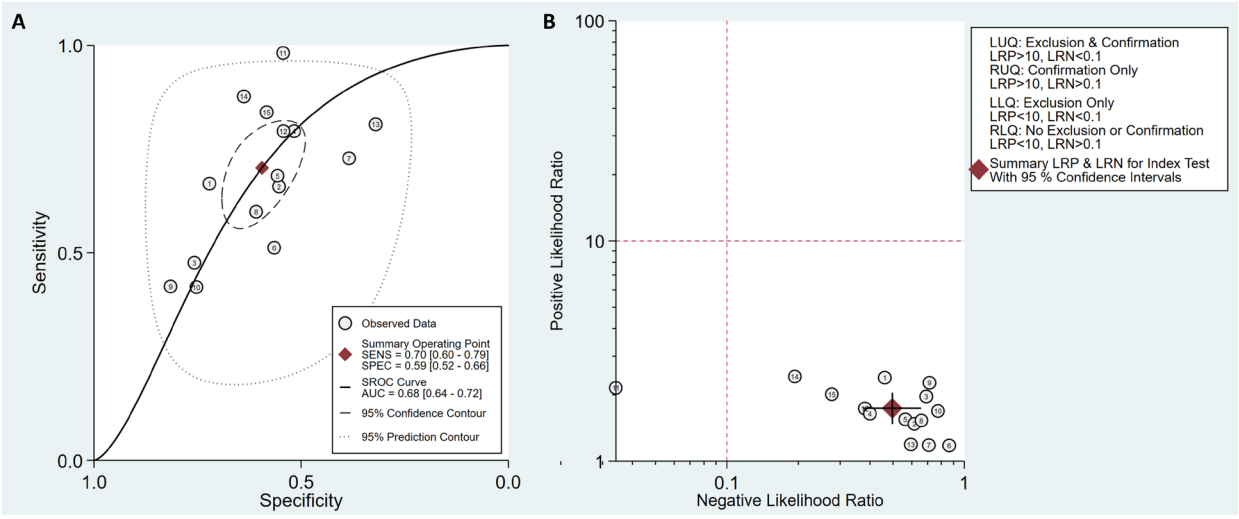

Figure 7 (A) Summary receiver operating characteristic (SROC) curves of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT for predicting epidermal growth factor receptor (*EGFR*) mutations in patients with non-small cell lung cancer (NSCLC). (B) Likelihood ratio scatter plot of ^{18}F-FDG PET/CT predicting *EGFR* mutations in patients with NSCLC. AUC, area under curve.

of *EGFR* mutations using different cut-off values.[8 9 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.[10] However, multiple groups have reported no association between SUV_{max} and *EGFR* status. Mak *et al* reported that high normalised 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.[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 patients with NSCLC 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 patients with NSCLC. 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 tumour volume and total glucose glycolysis were investigated to potentially predict EGFR mutations.[25 26] Recent studies also focused on ^{18}F-FDG PET/CT radiomics.[27 28] Radiomics refers to the extraction of quantitative characteristics from medical images.[29] The PET/CT-based radiomic characteristics showed good performance in the prediction of *EGFR* mutations in patients with NSCLC.[30 31] Although the predication efficacy improved, its clinical application requires additional studies to confirm and optimise. Beyond ^{18}F-FDG, novel radiotracers have also been investigated. ^{18}F-MPG PET/CT was demonstrated to be a valid strategy for stratifying patients with NSCLC with *EGFR*-activating mutations for *EGFR*-TKI treatment,[32] 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 patients with NSCLC.

Strengths and limitations

The strength of this study is that the conflicting results were first analysed 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 tumour 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 patients with NSCLC.

Contributors BD is the first author. BD and YL obtained funding. BD, XL and YL designed the study. BD, YC, GL and SW collected and analysed 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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Disclaimer This study was a systematic review and meta-analysis. Ethics committee approval was not necessary because all data were carefully extracted from existing literature.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No additional data are available.

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