Are ^{18}F-FDG PET/CT based radiomics features useful for prediction of PD-L1 expression in non-small cell lung cancer?

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Keywords: ^{18}F-FDG -PET/CT
- Radiomics
- Non-small cell lung cancer
- PD-L1

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Received:
19 December 2024
Accepted revised:
14 September 2025

Abstract

Objective: This study investigated the diagnostic test accuracy of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) based radiomics features for prediction of programmed cell death protein 1 and its ligand (PD-L1) expression in non-small cell lung cancer (NSCLC). **Materials and Methods:** A systematic search was performed in PubMed and EMBASE (last updated in 31 August 2024). Studies evaluating diagnostic performance of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC. The sensitivities, specificities, positive and negative likelihood ratios (LR+ and LR-), and pooled area under curve (AUC) were estimated. **Results:** The pooled sensitivity of ^{18}F-FDG PET/CT was 0.75 (95% CI; 0.64-0.83) and a pooled specificity of 0.66 (95% CI; 0.52-0.78) for prediction of >1% expression of PD-L1. For prediction of >50% expression of PD-L1, the pooled sensitivity of ^{18}F-FDG PET/CT was 0.77 (95% CI; 0.67-0.85) and a pooled specificity of 0.61 (95% CI; 0.55-0.66). For >1% expression of PD-L1, the pooled AUC of fixed effects was 0.791 (95% CI; 0.771-0.811) and of random effects was 0.783 (95% CI; 0.722-0.845). For >50% expression of PD-L1, the pooled AUC of fixed effects was 0.735 (95% CI; 0.718-0.751) and of random effects was 0.766 (95% CI; 0.706-0.825). **Conclusion:** Analysis of the available studies indicated that ^{18}F-FDG PET/CT based radiomics features showed a moderate diagnostic performance for prediction of PD-L1 expression in NSCLC. However, future studies would be necessary for standardization of the method for prediction of PD-L1 expression in NSCLC using ^{18}F-FDG PET/CT based radiomics features.

Hell J Nucl Med 2025; 28(3): 260-270 *Epub ahead of print: 15 December 2025* *Published online: 30 December 2025*

Introduction

Non-small cell lung cancer (NSCLC) is the second most common cancer and the third leading cause of cancer-related death in men and women in the United States [1]. In 2023, an estimated 117,550 men and 120,790 women were diagnosed with NSCLC, and 67,160 men and 59,910 women died of the disease [1]. Based on cell origin, the majority of lung cancers (about 85%) are NSCLC [2]. Recently, with the introduction of immune checkpoint inhibitors (ICI), targeting the programmed cell death protein 1 (PD 1) and its ligand (PD-L1) axis, significantly impacted on the management of patients with NSCLC [3].

Even though ICI have dramatically changed the clinical outcomes of advanced NSCLC, only a subset of patients with NSCLC respond to ICI [4-8]. Thus substantial efforts are ongoing to identify a biomarker of response to anti-PD-1/PD-L1 immunotherapy. Although as a predictive biomarker PD-L1 expression in NSCLC has limitations, PD-L1 expression in NSCLC is the only FDA approved biomarker linked to specific PD-1/PD-L1 pathway blockade and expected to predict a response to anti-PD-1/PD-L1 antibodies [9]. Programmed cell death protein 1 and PD-L1 expression is usually determined by immunohistochemistry (IHC), which is time consuming and obtaining adequate tumor tissue for PD-L1 staining is not available in some patients.

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has become a standard modality for the diagnosis, staging, and evaluation of treatment response in NSCLC [10]. An association between glucose metabolism and epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement in NSCLC have also been previously reported [11, 12]. Recently, some studies have attempted to investigate PD-L1 expression from ^{18}F-FDG PET/CT images with promising results in NSCLC patients [13, 14]. However, the precise relationship between glucose metabolism and PD-L1 expression in NSCLC is not well known.

Radiomics is a unique and evolutional tool that converts imaging information to various quantifiable features reflecting genotypic and phenotypic characteristics of the tissue [15]. Fluorine-18-FDG PET/CT based radiomics features can be broadly grouped into shape or morphology features, namely, histogram-based features, texture-based features, edges features, and shape features [16]. Recently, radiomics have been adapted for cancer diagnosis, for differentiation of malignant lesions, and for assessment of treatment response [17, 18].

The purpose of the current study is to meta-analyze the published data on the diagnostic performance of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC, in order to provide more evidence-based data and to address further studies in the evaluation of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC.

Background concepts: Machine learning techniques for PET/CT analysis

The preferred reporting items for systematic reviews and meta-analyses statement was used to improve the reporting of our research [19].

Data sources and search strategy

A structured approach was followed to identify the patient population, interventions, comparators, outcomes, and study design (PICOS criteria) [19]. The electronic English-language literature searches of PubMed, Cochrane database, and Embase from the earliest available date of indexing through August 31, 2024 was used and hand-searched the reference lists of identified publications for additional studies was performed. The search strategy included both subject headings (MeSH terms) and keywords for the target condition (NSCLC), the imaging techniques under investigation (^{18}F-FDG PET/CT), and the interventions (positive PD-L1 expression). We used a search algorithm based on a combination of terms: (1) "PET" OR "positron emission tomography" OR "positron emission tomography/computed tomography" OR "PET/CT" OR "positron emission tomography-computed tomography" OR "PET-CT" OR "FDG" AND (2) "Radiomics" (3) "Lung Neoplasms" OR "Lung cancer" OR "Lung carcinoma" OR "NSCLC" (4) "PD-L1".

Criteria for inclusion in the current study

Studies were eligible if the following PICOS criteria were met. (a) Patient population consisted of NSCLC confirmed histologically; (b) the imaging of with ^{18}F-FDG PET/CT; (c) Histopathologic analysis of PD-L1 expression was available as a reference standard; (d) the study outcome described positive PD-L1 expression.

Exclusion criteria of studies was as follows; if a 2×2 table could not be extracted from the data, if there were fewer than 5 patients, and if multiple reports were published for the same study population. In the latter case, the most detailed or recent publication was extracted. Duplicate publications were excluded, as were publications such as review articles, case reports, conference papers, and letters, which do not contain the original data. Two researchers independently reviewed titles and abstracts of the retrieved articles, applying the above-mentioned selection criteria. Articles were rejected if clearly ineligible. The same two researchers then independently evaluated the full-text version of the included articles to determine their eligibility for inclusion.

Data extraction and quality assessment

Information about basic study (authors, year of publication, and country of origin), study design (prospective or retrospective), patients' characteristics and technical aspects were collected. Each study was analyzed to retrieve the number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) findings of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC according to the reference standard. Only studies providing such complete information were finally included in the meta-analysis. Quality of the included studies was assessed based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2) [20]. Two reviewers independently assessed each potentially eligible study and assigned them as a quality rating of "good," "fair," or "poor". Quality assessment was conducted based on following criteria: study design and presence of bias including selection, performance, recording, and reporting bias. Studies with high risk of bias were defined as poor quality, presence of moderate risk (did not affect the results) as fair quality, and those with minimal risk as good quality. The Radiomics Quality Score (RQS) was used to evaluate the methodological quality [21]. Disagreements were settled with consensus decision. Disagreement between the 2 authors was resolved by discussion.

Data synthesis and analysis

All data from each eligible study were extracted. Categorical variables are presented as frequencies or percentages, and continuous variables are presented as mean values unless stated otherwise. Measures of the diagnostic performance, including sensitivity, specificity, and diagnostic odds ratios (DOR), are reported as point estimates with 95% confidence intervals (CI). A DOR can be calculated as the ratio of the odds of positivity in a disease state relative to the odds of positivity in the non-disease state, with higher values indicating better discriminatory test performance [22]. Between-study statistical heterogeneity was assessed using I^2 and the Cochrane Q test on the basis of the random-effects analysis [23]. Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks and colleagues [24]. The bivariate random-effects model for analysis and pooling of the diagnostic performance measures across studies, as well as comparisons between different index tests were used [25, 26]. The bivariate model estimates pairs of logit transformed sensitivity and specificity from studies, incorporating the correlation that might exist between sensitivity and specificity. The bivariate model was used to create hierarchical summary receiver operating characteristic curves and to estimate the area under the curve [27]. When statistical heterogeneity was

substantial, meta-regression was performed to identify potential sources of bias [28]. Two-sided P≤0.05 was considered statistically significant. Statistical analyses were performed with commercial software programs (STATA, version 13.1; StataCorp LP, 4905 Lakeway Drive, College Station, TX, 77845, USA) and Meta-disc (version 1.4) downloadable freely from URL: http://www.hrc.es/investigacion/metadisc_en.htm.

Results

Literature search and selection of studies

After the comprehensive computerized search was performed and references lists were extensively cross-checked, our research yielded 41 records, of which 15 records of duplicated abstracts were excluded after reviewing the title and abstract. Also, 7 non-relevant studies, 3 conference abstracts, and 6 review articles were excluded. Remaining 10 full text articles were assessed for eligibility and 2 articles were excluded due to insufficient data for the calculation of sensitivity and specificity of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC. Finally, 8 studies were selected and were eligible for the systematic review and meta-analysis and no additional studies were found screening the references of these articles [29-36]. The characteristics of the included studies are presented in Table 1. The detailed procedure of study selection in the current meta-analysis is shown in Figure 1.

Study description, quality, and publication bias

The patient-based analysis was conducted in the current study. There were a total of 2,110 patients in the included studies, and the age ranged from 15 to 87 years. A total 1,296 patients were male and 814 patients were female. All 8 studies enrolled patients retrospectively [29-36]. Only one study performed external and cross validations of radiomics features [33]. Radiomics features were extracted using LIFEx software in 5 studies [30, 31, 34-36], ITK snap software in 2 studies [29, 33] and IBSI in one study [32]. Four studies [29-32] used the cut-off value of both of >1% and >50% of PD-L1 expression in IHC. Programmed cell death protein 1 and its ligand expression status was defined as positive and negative according to the cut-off 1% in other 4 studies [33-36]. The diagnostic accu-

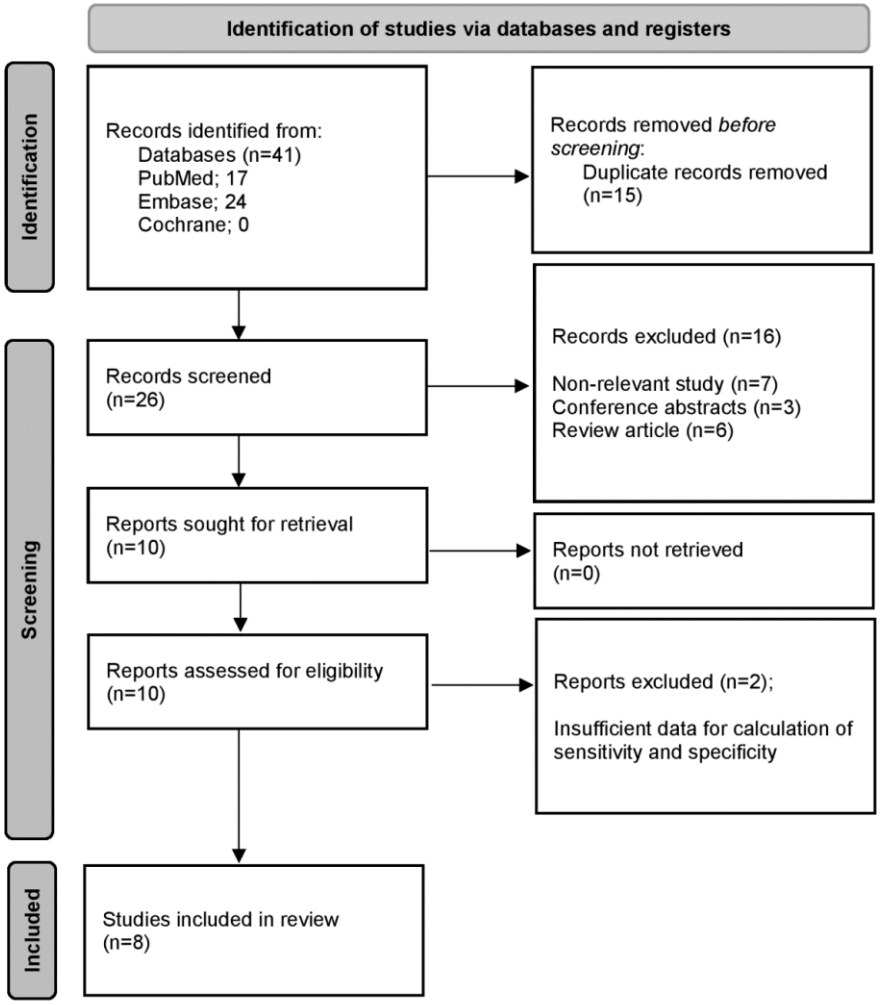

Figure 1. Flow diagram of the search for eligible studies on the diagnostic performances of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC.

Table 1. *Characteristics of the included studies.*

Authors	Year	Country	Study design	Cut-off value of PD-L1	Pt (n)	M/F	Age (Range)	Radiomics						GS
								Type of features	Software	Model algorithm	Features (n)	EV	CV	
Jiang M	2020	China	R	>1%, >50%	399	253/146	62 (39-75)	Shape, Histogram, First-order, Second-order, Texture analysis	ITK-snap	LASSO	1744	No	No	IHC
Li J	2021	China	R	>1%, >50%	255	170/85	64.2	Shape, Histogram, First-order, Second-order, Texture analysis	LIFEx	LASSO	80	No	Yes	IHC
Lim CH	2022	Korea	R	>1%, >50%	312	228/84	66.2	Shape, Histogram, First-order, Second-order, Texture analysis	LIFEx, Orange 3.25	LR	94	No	No	IHC
Monaco L	2022	Italy	R	>1%, >50%	86	77/29	74 (62-77)	Shape, Histogram, First-order, Second-order, Texture analysis	IBSI	LR	527	No	No	IHC
Mu W	2021	China	R	>1%	400	236/164	63.2	Shape, Histogram, First-order, Texture analysis	ITK-snap	LASSO	NA	Yes	Yes	IHC

(continued)

Zhang R	2022	Germany	R	>1%	221	72/149	69 (44-87)	Shape, Histogram, First-order, Second-order	LIFEx	LR, LASSO	86	No	No	IHC
Zhao X	2023	China	R	>1%	334	203/131	62.1 (15-87)	Shape, Histogram, First-order, Second-order	LIFEx	LASSO	75	No	No	IHC
Zhou J	2021	China	R	>1%	103	57/46	59 (33-78)	Shape, Histogram, First-order, Second-order, Texture analysis	LIFEx	LASSO	103	No	No	IHC

CV; Cross validation, EV; External validation, GS; Gold standard, HP; Histopathology, IBSI; Image biomarker standardization initiative, IHC; Immunohistochemistry, LASSO; Least absolute shrinkage and selection operator, LR; Logistic regression, n; Number, NA; Not available, Pt; Patients, Study design; R, Retrospective

racies could be obtained in 5 studies [32-36]. The AUC data were available in all 8 studies. The principal characteristics of 8 studies included in the meta-analysis are included in Table 1. To assess a possible publication bias, Deeks's funnel plot asymmetry tests were designed. The non-significant slope indicates that no significant bias was found. The P value was 0.18 (Figure 2).

Methodological quality assessment

According to the QUADAS-2 tool, overall risk of bias in patient selection was high in five studies (62.5%), unclear in two (25%) studies, and low in one (12.5%). Risk of bias in the index test was high in one study (12.5%) and unclear in seven studies (87.5%). Risk of bias in the reference standard test was unclear in two (25%) study and low in six studies (75%). Flow and timing had low in all studies (100%). Applicability concerns in patient selection were unclear in four (50%) studies and low in four (50%) studies. Applicability concerns in the index test were low in five (62.5%) studies and unclear in three studies (37.5%). Applicability concerns in reference standard were unclear in two studies (25%) and low in six (75%) studies. Figure 3 shows methodological quality summary of included studies.

A detailed report of RQS item score is shown in Table 2. The RQS ranged from 3 to 13 in the included studies. The RQS total and percentage scores were 8.3±3.85 and 23.2±10.7%, respectively. The highest possible score was 13 points, and the highest-rated study received a percentage score of 36.1%. None of the selected studies performed a phantom study, a clinical utility analysis, a cost-effectiveness analysis, discussed biological correlates, or conducted the research prospectively.

Diagnostic accuracy of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression

The results of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC of 8 included studies are presented in Table 3. For prediction of >1% expression of PD-L1, the pooled sensitivity of was 0.75 (95% CI; 0.64-0.83) with heterogeneity (I2=54.7, P=0.04) and a pooled specificity of 0.66 (95% CI; 0.52-0.78) with heterogeneity (I^2=82.2, P<0.001). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 2.2 (95% CI; 1.6-3.2) and negative likelihood ratio (LR-) of 0.38 (95% CI; 0.27-0.53). The pooled DOR was 6 (95% CI; 3-11).

For prediction of >50% expression of PD-L1, the pooled sensitivity of was 0.77 (95% CI; 0.67-0.85) with heterogeneity (I^2=0, P=0.525) and a pooled specificity of 0.61 (95% CI; 0.55-0.66) with heterogeneity (I^2=71.5, P=0.061). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 2.1 (95% CI; 1.3-3.3) and negative likelihood ratio (LR-) of 0.37 (95% CI; 0.24-0.56). The pooled DOR was 6 (95% CI; 2-15).

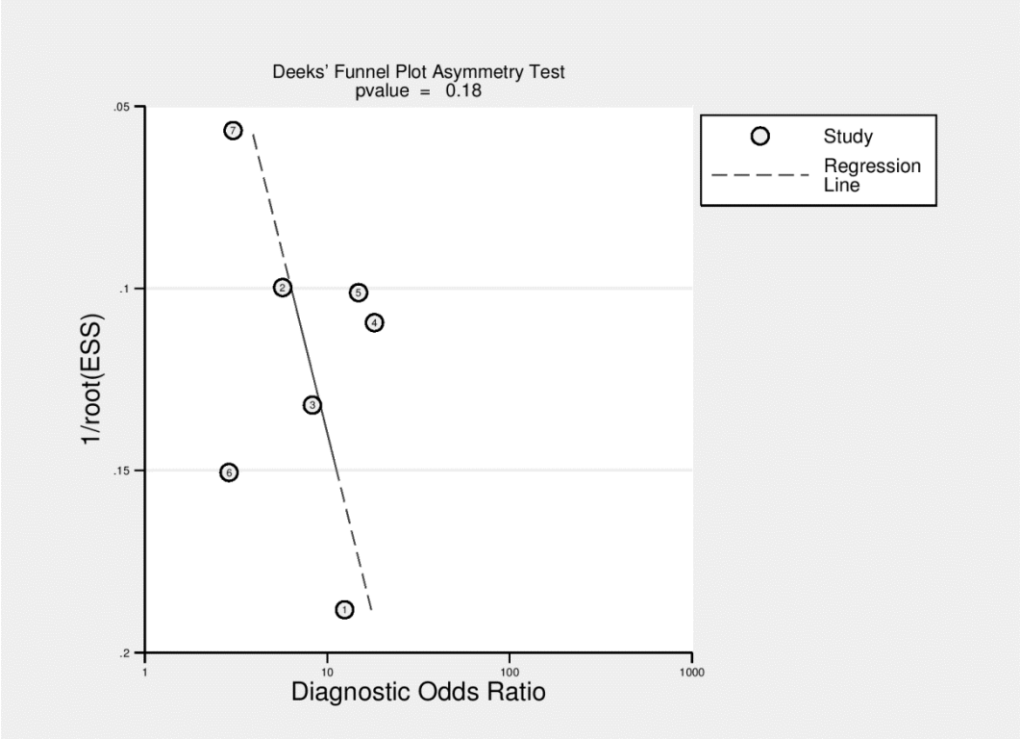

Figure 2. Results of Deeks`s funnel plot of asymmetry test for publication bias. Non-significant slope indicates that no significant bias was found. (ESS; Effective sample size)

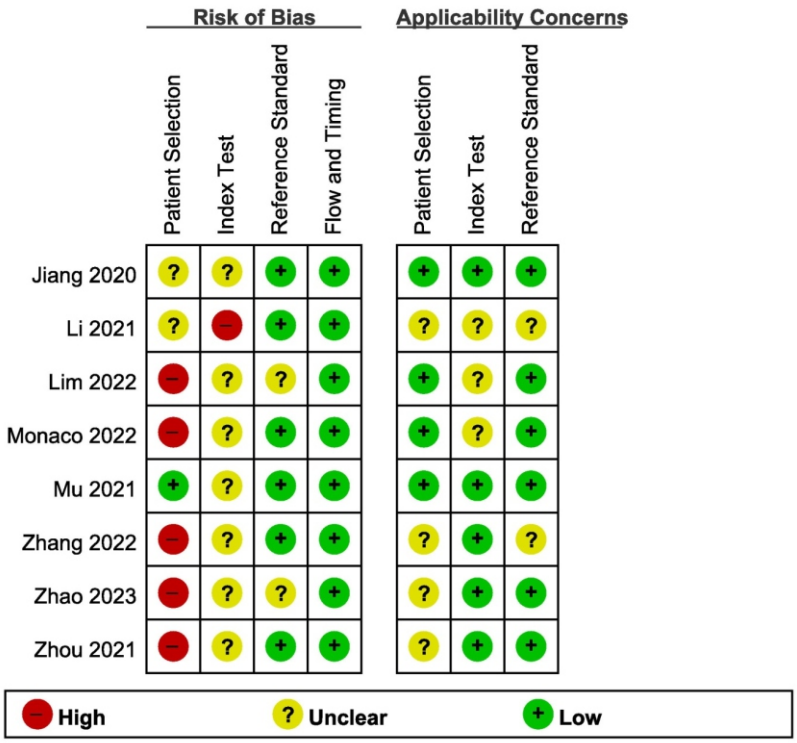

Figure 3. Risk of bias and applicability concerns summary.

Table 2. *Radiomics quality scores of the included studies.*

Study criteria	Jiang M	Li J	Lim CH	Monaco L	Mu W	Zhang R	Zhao X	Zhou J
Image protocol	1	1	1	1	1	1	1	1
Multiple segmentations	1	1	1	1	1	1	1	1
Phantom study	0	0	0	0	0	0	0	0
Multiple time points	0	0	0	0	0	0	0	0
Feature reduction	3	3	3	3	3	3	3	3
Non-radiomics	1	1	0	1	1	0	0	0
Biological correlates	0	0	0	0	0	0	0	0
Cut-off	0	0	0	0	0	0	0	0
Discrimination & Resampling	1	1	1	1	1	1	1	1
Calibration	0	0	0	0	0	0	0	0
Prospective	0	0	0	0	0	0	0	0
Validation	-5	2	-5	2	2	-5	2	2
Gold standard	0	0	0	0	0	0	0	0
Clinical utility	0	0	0	0	0	0	0	0
Cost effectiveness	0	0	0	0	0	0	0	0
Open science and date	3	4	3	2	3	2	2	3
Total score	5	13	4	11	12	3	10	9
Individual rating	13.8%	36.1%	11.1%	30.5%	33.3%	8.3%	27.7%	25%

Pooled estimates of AUC of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression

Figure 4 shows the results of forest plot of AUC of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC. For prediction of >1% expression of PD-L1, the pooled AUC of fixed effects was 0.791 (95% CI; 0.771-0.811) and of random effects was 0.783 (95% CI; 0.722-0.845) with heterogeneity (I^2=93.1, 95% CI; 89.4-95.5, P<0.001) (Figure 4A).

For prediction of >50% expression of PD-L1, the pooled AUC of fixed effects was 0.735 (95% CI; 0.718-0.751) and of random effects was 0.766 (95% CI; 0.706-0.825) with heterogeneity (I^2=90.1, 95% CI; 79.7-95.1, P<0.001) (Figure 4B).

Clinical utility

Using an ^{18}F-FDG PET/CT based radiomics features model would increase the post-test probability to 28% from 15% with a PLR of 2 when the pretest was positive and would reduce the post-test probability to 6% with an NLR of 0.38 when the pretest was negative. The clinical application is shown in Figure 5.

Likelihood ratio scatter-gram

Figure 6 shows the likelihood ratio scatter-gram which displays the summary point of likelihood ratios obtained as functions of mean sensitivity and specificity in the right lower quadrant suggesting that ^{18}F-FDG PET/CT based radiomics features might not be useful for exclusion and confirmation for prediction of PD-L1 expression in NSCLC.

Discussion

Recently, molecular targeted therapies have dramatically improved the prognosis of selected advanced-stage NSCLC patients with driver mutations such as EGFR-mutant, ALK-re-arranged NSCLC. However, these therapies are ineffective in the majority of patients whose tumors lack genetic alterations [37]. Immune checkpoint inhibitors, such as PD-1 or PD-L1, have become one of the most promising approaches in the treatment for advanced NSCLC patients whose tumor does not contain a driver mutation [38].

The current meta-analysis is the first to explore ^{18}F-FDG PET/CT based radiomics features for prediction of expression of PD-L1 in NSCLC on a per-patient basis. The prediction performance was good with sensitivity and specificity for both of cut-off value of >1% and >50% expression of PD-L1. Also, the pooled AUC was good for prediction of PD-L1 expression for both of cut-off value of >1% and >50%. For clinical utility, using ^{18}F-FDG PET/CT based radiomics features would increase the post-test probability to 28% from 15% with a PLR of 2 when the pretest was positive and would reduce the post-test probability to 6% with an NLR of 0.38 when the pretest was negative. This shows that using ^{18}F-FDG PET/CT based radiomics features could help improve the accuracy of predicting the PD-L1 expression in NSCLC. However, according to scatter gram, ^{18}F-FDG PET/CT based radiomics features should be cautiously used for exclusion and confirmation for prediction of PD-L1 expression in NSCLC.

The ^{18}F-FDG PET/CT based radiomics feature extraction

Table 3. *Diagnostic performances of ^{18}F-FDG PET/CT based radiomics features prediction of PD-L1 expression in NSCLC.*

Cut-off of PD-L1 expression	Sensitivity	I^2	P value	Specificity	I^2	P value	+LR	I^2	P value	-LR	I^2	P value
>1%	75 %	54.7 %	0.04	66 %	82.2 %	<0.001	2.2	72.7 %	<0.001	0.38	36.3 %	0.151
>50%	77 %	0 %	0.525	61 %	71.5 %	0.061	2.1	70.8 %	0.064	0.37	5.9 %	0.303

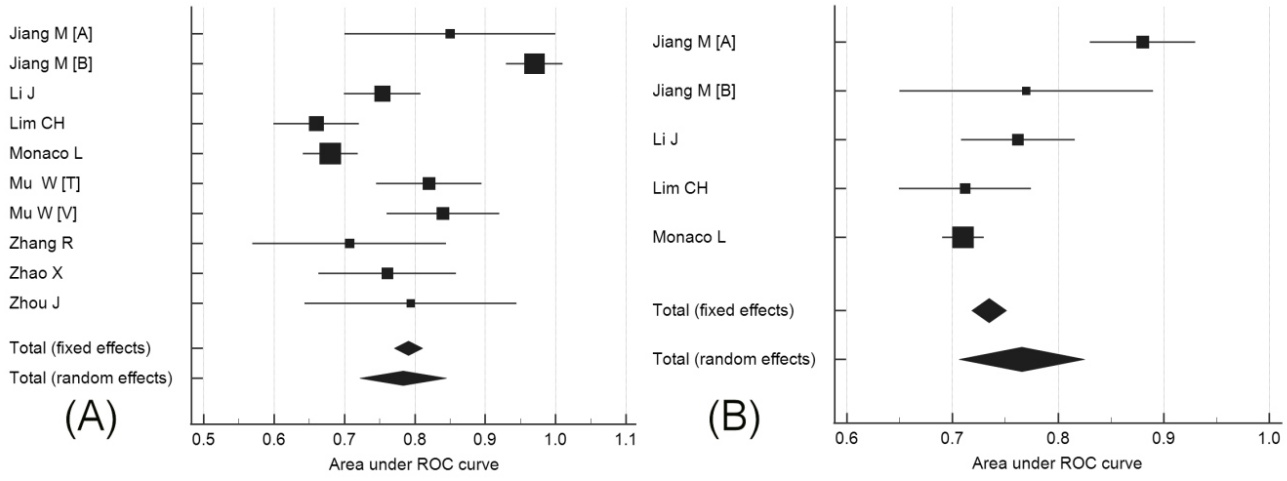

Figure 4. Forest plot of pooled AUC of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC.

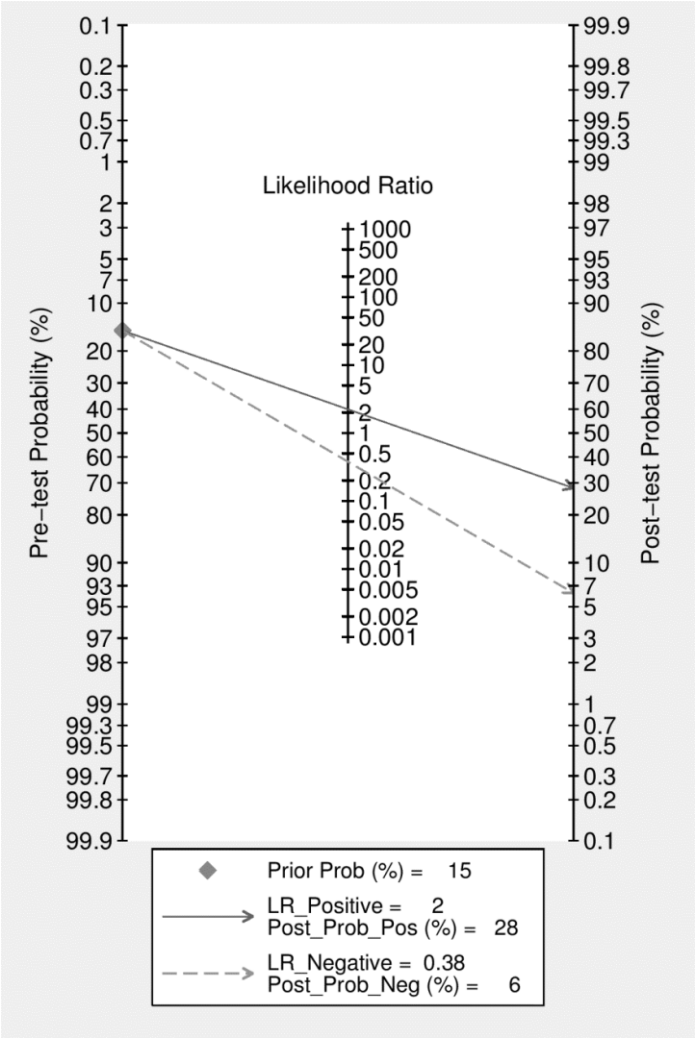

Figure 5. Fagan nomogram of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC.

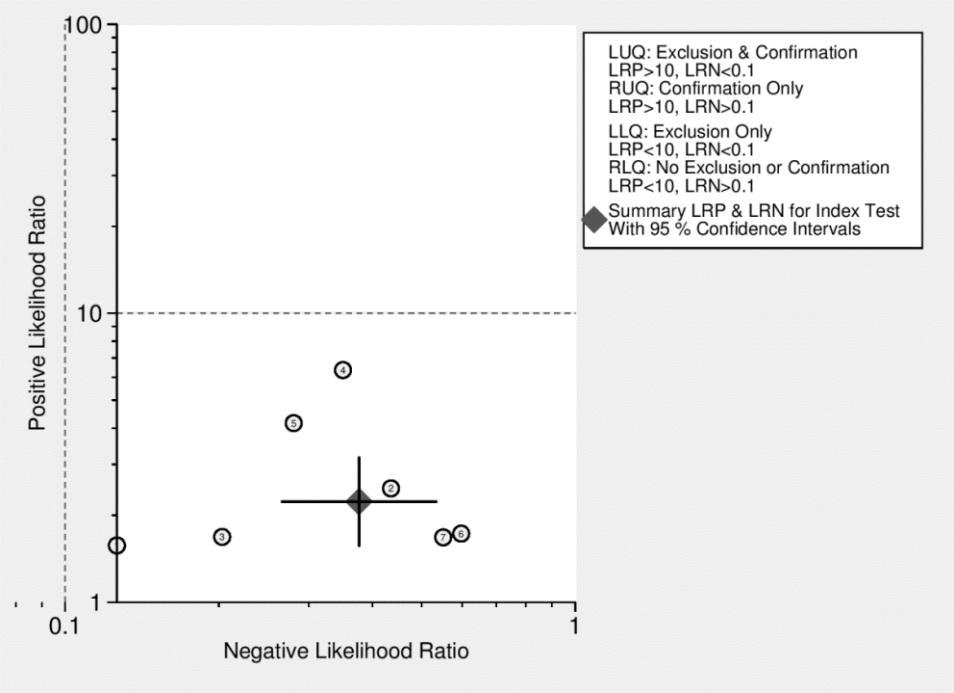

Figure 6. Likelihood ratio scatter-gram of ^{18}F-FDG PET/CT based radiomics features for prediction of PD-L1 expression in NSCLC.

and selection methods are diverse among included in the current metaanalysis and algorithm methods (LASSO, random forest, logistic regression). The present meta-analysis could not recommend the proper radiomics feature selection method or radiomics model method. The present meta-analysis showed that ^{18}F-FDG PET/CT based radiomics features had heterogeneity between included studies for prediction of PD-L1 expression in NSCLC in terms of sensitivity and specificity. The source of heterogeneity may be related to differences in feature extraction methods, types and number of features, and modelling methods in the included studies. Also, studies included in this meta-analysis used different definition for positivity of PD-L1 protein expression. Four studies used the cutoff value of both of >1% and >50% for defining PD-L1 positivity [29-32] and other 4 studies used >1% for positivity [33-36].

Despite the good predictive power of ^{18}F-FDG PET/CT based radiomics features, the overall quality of the included studies ranged from poor to moderate. The RQS ranged from 3 to 13 (out of the highest possible score of 36 points). Although RQS is widely used to assess the quality of radiomics research, RQS is a relatively recent and a purely methodological scoring system and does not consider differences in the current study because of difficulties to achieve. None of included study in the current meta-analysis had been externally verified. No study conducted a phantom study and a cost effectiveness analysis.

A recent study investigated the association between PD-L1 expression and IHC biomarkers or textural features of ^{18}F-FDG PET in 53 oropharyngeal or hypopharyngeal cancer patients who were ready to undergo radiotherapy-based treatment [39]. They reported the sensitivity, specificity, and accuracy for predicting PD-L1 expression of ≥5% were 78%, 46%, and 57%, respectively [39]. If the cutoff for PD-L1 expression was 1%, the corresponding values were 77%, 57%, and 68%, respectively [39]. According to this study, ^{18}F-FDG PET/CT derived textural features can provide supplemental information to determine tumor PD-L1 expression and the PD-L1 expressions were positively correlated with p16 and Ki-67, whereas the textural index of correlation was a negative predictor for PD-L1 expression of ≥5% [39].

The current study had some limitations. First, all studies included in the meta-analysis conducted a retrospective study design and were subject to selection bias and prone to data loss. Second, a relatively small number of articles are available for selection criteria. Third, radiomics features might be affected by imaging equipment technology, tumor delineation method, and used radiomics software. Third, the most studies included in the current analysis came from China, which could cause selection bias and heterogeneity. Finally, external validation of radiomics models was performed in only one study; therefore, further prospective studies using a larger and more blanced population from multiple centers and a subset of the data as a validation set are required. In the current meta-analysis, to minimize bias in the selection of studies and in the data extraction, reviewers who were blinded to the journal, author, institution, and date of publication independently selected articles based on the inclusion criteria, and scores were assigned to study design characteristics and examination results by using a standardized form that was based on the QUADAS-2 tool.

In conclusion, ^{18}F-FDG PET/CT based radiomics features showed a good diagnostic performance for prediction of PD-L1 expression in NSCLC. However, future studies are necessary for standardization of the method for prediction of PD-L1 expression in NSCLC using ^{18}F-FDG PET/CT based radiomics features.

The authors declare that they have no conflicts of interest.

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