Original Article

Comparing the diagnostic value of ^{18}F-FDG-PET/CT versus CT for differentiating benign and malignant solitary pulmonary nodules: a meta-analysis

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Background: This quantitative meta-analysis was conducted to provide an indirect comparison of the diagnostic value of computed tomography (CT) with positron emission tomography (PET)/CT for differentiating benign and malignant solitary pulmonary nodules (SPNs).

Methods: PubMed, Embase, and the Cochrane Library were searched to identify eligible studies throughout November 2018, which differentiated benign and malignant SPNs using CT or PET/CT. The summary sensitivity, specificity, positive and negative likelihood ratio (PLR and NLR), diagnostic odds ratio (DOR), and area under the receiver operating characteristic curve (AUC) were calculated using bivariate generalized linear mixed model and random-effects model. The diagnostic value of CT with PET/CT was indirectly evaluated using the ratio for diagnostic parameters.

Results: The sensitivity, specificity, PLR, NLR, DOR, and AUC for CT were 0.94 [95% confidence interval (CI): 0.87–0.97], 0.73 (95% CI: 0.64–0.80), 3.45 (95% CI: 2.60–4.58), 0.09 (95% CI: 0.04–0.17), 32.01 (95% CI: 15.10–67.86), and 0.89 (95% CI: 0.86–0.91), respectively. The pooled sensitivity, specificity, PLR, NLR, DOR, and AUC for PET/CT were 0.89 (95% CI: 0.85–0.92), 0.78 (95% CI: 0.66–0.86), 3.97 (95% CI: 2.57–6.13), 0.15 (95% CI: 0.10–0.20), 24.04 (95% CI: 12.71–45.48), and 0.91 (95% CI: 0.89–0.94), respectively. No significant differences were observed between CT and PET/CT for sensitivity, specificity, PLR, NLR, DOR, and AUC.

Conclusions: This study used both CT and PET/CT with a moderate-to-high diagnostic value for differentiating benign and malignant SPNs and showed no significant differences in diagnostic parameters between CT and PET/CT.

Keywords: ^{18}F-FDG-PET/CT; benign solitary pulmonary nodules (benign SPNs); malignant solitary pulmonary nodules (malignant SPNs); diagnosis

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Introduction

Lung cancer has been the leading cause of cancer incidence and mortality worldwide for several decades, accounting for nearly 13% of the total cancer cases (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, and 15% of cases are small cell lung cancer (SCLC) (2). Although the treatment strategies, including surgery, chemotherapy, radiotherapy, and targeted therapy, have developed rapidly, the prognosis of lung cancer remains poor; the 5-year survival rate

of NSCLC and SCLC is less than 15% and 1–3%, respectively (3,4). Therefore, choosing an appropriate diagnostic tool is essential to early detect and hence decrease the mortality rate of lung cancer.

Solitary pulmonary nodule (SPN) is an intraparenchymal lung lesion less than 3 cm, which is fully surrounded by lung tissue and does not correlate with lymph nodes, atelectasis, adenopathy, and pneumonia (5-7). The incidence of malignancies for SPNs ranged from 0.5% to 3.5%. It depended on patient characteristics and radiological features of nodules (8). These characteristics included age of patients, smoking status, history of cancer, nodule diameter, nodule volume, spiculated margins, and upper lobe location (9, 10). Currently, computed tomography (CT) is widely used for detecting and differentiating pulmonary nodules based on the difference in intensity against the background (11-13). However, the traditional CT for measuring tumor size may produce a large number of false positives and lead to unnecessary treatments (14-17). Moreover, the guidelines of the American College of Chest Physicians recommend that ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is a more sensitive and specific imaging technique for differentiating benign and malignant SPNs, while the costs and availability are limited (6). A previous study showed that the combination of CT and PET with an excellent performance in differentiating benign and malignant SPNs due to the combined sensitivity for CT and specificity for PET could provide improved diagnostic value (18). However, whether the diagnostic value of PET/CT was superior than CT remains controversial CT was conducted under breath hold and maximum inspiration, while the PET/CT was conducted under continuous shallow breathing of the patient. This difference causes differing diagnostic value between PET/CT and CT for detecting benign and malignant SPNs, especially for smaller SPNs (up to 8 mm).

Several systematic reviews and meta-analyses investigated the diagnostic value of CT or PET/CT for classifying benign or malignant SPNs. However, these studies just provided the pooled diagnostic parameters; the comparisons of the two diagnostic methods were not illustrated (19-21). Therefore, this comprehensive quantitative meta-analysis was conducted to indirect compare the diagnostic value of CT with PET/CT for differentiating benign and malignant SPNs. Moreover, whether the diagnostic value differed according to country, study design, and sample size of included studies was also examined.

Methods

Data sources, search strategy, and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (22). Studies published in English and investigating the diagnostic value of CT or PET/CT for classifying benign and malignant SPNs were eligible for inclusion in this study. The electronic databases, including PubMed, Embase, and the Cochrane Library, were systematically searched for studies from their inception up to November 2018. The Medical Subject Headings and free words of the following terms were used: ("solitary pulmonary nodules" OR "SPNs" OR "pulmonary coin lesion" OR "lung nodules") AND ("computed tomography" OR "CT" OR "PET/CT"). The reference lists from relevant review and studies were also reviewed to identify any potential eligible study.

The literature search and study selection process were conducted by two independent authors. Inconsistencies were settled through discussion between these two authors, and an additional author made the final decision. The inclusion criteria of this meta-analysis were as follows: (I) study design: prospective or retrospective; (II) patients: patients with benign and malignant SPNs; (III) diagnostic tool: CT or PET/CT; (IV) gold reference: histology or biopsy; and (V) outcomes: true and false positive, true and false negative, or data transformed into the aforementioned information.

Data collection and quality assessment

Two authors independently abstracted data and performed quality assessment. Any disagreement was resolved by these two authors referring to the original study. The collected information included first author's surname, publication year, country, study design, sample size, size of nodules, percentage male, mean age or age range, diagnostic tool, gold standard, true and false positive, and true and false negative. The quality of included studies was assessed using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) based on 14 items, and yes, no, or unclear were answered for each item (23).

Statistical analysis

The summary sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic

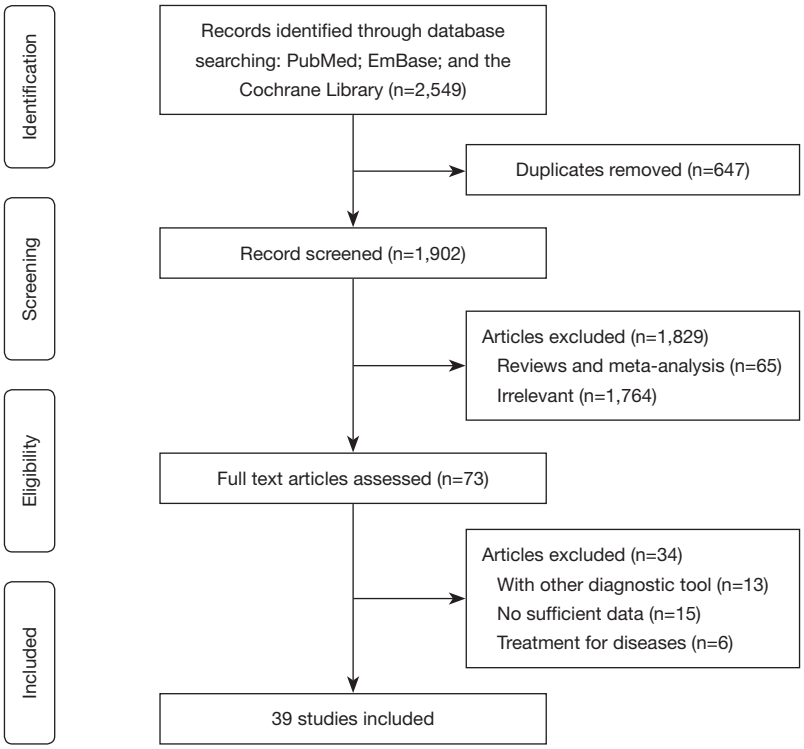

Figure 1 Flow diagram of study selection process.

odds ratio (DOR), and the area under the receiver operating characteristic curve (AUC) with corresponding 95% confidence intervals (CIs) were calculated based on true positive, false positive, false negative, and true negative in each individual study. The methods for calculating sensitivity, specificity, PLR, NLR, and DOR used bivariate generalized linear mixed and random-effects modes (24). The AUC for CT and PET/CT for differentiating benign and malignant SPNs was calculated using hierarchical regression (25). The Q statistic was employed to calculate heterogeneity among included studies, and a P value less than 0.10 was regarded as significant heterogeneity (26,27). Subgroup analyses for DOR were conducted based on country, study design, and sample size. Moreover, the ratio of diagnostic parameters between CT and PET/CT or subgroups was also calculated to indirect compare the diagnostic value of CT with PET/CT (28). The publication biases for CT and PET/CT were also evaluated using funnel plots and Deeks' asymmetry tests (29). The P value for all pooled analyses was two-sided, and a P value less than 0.05 was regarded as statistically significant. Stata software (version 10.0; Stata Corporation, TX, USA) was employed to conduct all statistical analyses.

Results

Literature search

The initial electronic searches produced 2,549 records, and 647 articles were excluded due to duplicate topics. The titles and abstracts were reviewed in the remaining 1,902 studies, and 1,829 studies were excluded due to irrelevant topics or design as review or meta-analyses. The full-text was assessed for the remaining 73 studies, and finally, 39 studies were selected (30-50) for this meta-analysis (51-68). The reasons for excluding 34 studies were as follows: patients diagnosed with other diagnostic tools (n=13), lack of sufficient data (n=15), and studies evaluating treatment effectiveness (n=6). The details of study selection process are presented in *Figure 1*. Moreover, manual searches of references in the aforementioned studies did not yield any new eligible study.

Study characteristics

The baseline characteristics of included studies and patients are shown in *Table 1*. Overall, 16 studies evaluated the

Table 1 Baseline characteristics of studies included in the systematic review and meta-analysis

Study	Publication year	Country	Study design	Sample size	Size of nodules (mm)	Percentage male (%)	Age (year)	Diagnostic tool	Gold standard	True positive	False positive	False negative	True negative
Swensen (30)	1992	USA	Retro	30	6–30	53.8	41–79	CECT	Histology or cytology	21	1	1	6
Swensen (31)	1995	USA	Retro	163	6–40	57.7	22–78	CECT	Histology	110	12	0	41
Yamashita (32)	1995	Japan	Retro	32	6-–30	65.6	27–78	CECT	Biopsy	16	9	2	5
Swensen (33)	1996	USA	Retro	107	7-–30	53.3	29–85	CECT	Histology	51	15	1	40
Potente (34)	1997	Italy	Retro	25	6–40	62.5	39–82	CECT	Histology	17	2	0	6
Swensen (35)	2000	USA	Pro	356	5–40	49.2	21–89	CECT	Histology	168	78	3	107
Yi (36)	2004	Korea	Retro	131	8–30	62.6	24–82	CECT	Histopathology	69	28	1	33
Kim (37)	2004	Korea	Pro	40	NA	NA	NA	CECT	Histology	17	10	2	21
Jeong (38)	2005	Korea	Retro	107	<30	57.9	22–81	CECT	Histology	46	6	3	52
Iwano (39)	2008	Japan	Retro	107	5–30	54.7	60.9	CT	Histology	40	12	12	43
da Silva (40)	2008	Brazil	Pro	39	NA	NA	NA	CT	Histology	7	0	3	29
Bai (41)	2009	China	Retro	68	8–30	55.9	28–79	CECT	Immunohistochemistry	34	16	2	16
Fan (42)	2012	China	Retro	82	<40	42.7	40–84	CECT	Biopsy	57	4	7	14
Shu (43)	2013	China	Retro	144	8–30	52.8	28–79	CECT	Immunohistochemistry	60	16	12	56
Ye (44)	2014	China	Pro	87	5–30	67.8	21–84	CECT	Histology	27	12	25	23
Chen (45)	2018	China	Retro	72	NA	56.9	14–85	CT	Histology	39	9	3	24
Herder (46)	2004	The Netherlands	Retro	36	<30	43.0	61.0	PET/CT	Histopathology	13	5	1	17
Yi (47)	2006	Korea	Pro	119	<30	52.1	31–81	PET/CT	Histopathology	76	5	3	35
Orlacchio (48)	2007	Italy	Retro	56	6–30	64.3	63.0	PET/CT	Histology	20	0	6	100
Tsushima (49)	2008	Japan	Retro	53	8–30	54.9	49–85	PET/CT	Histochemical	28	1	0	24
Degirmenci (50)	2008	Turkey	Retro	46	<30	50.0	34–83	PET/CT	Histopathology	16	4	10	19
Jeong (51)	2008	Korea	Retro	100	9–30	56.0	58.0	PET/CT	Histology	35	14	5	46
Kagna (52)	2009	Israel	Retro	93	3–30	75.3	46–90	PET/CT	Histology	27	10	8	48
Schillaci (53)	2009	Italy	Pro	30	9.5–30	56.7	36–80	PET/CT	Histology	14	1	4	11
Sathekge (54)	2010	Belgium	Pro	30	1.4–30	73.3	37–84	PET/CT	Histology	12	12	2	4
Divisi (55)	2010	Italy	Retro	124	5–15	73.4	40–72	PET/CT	Histology	89	7	4	24
Nguyen (56)	2011	USA	Retro	42	10–30	71.4	48–82	PET/CT	Histology	21	1	5	15
Li (57)	2011	China	Pro	96	4–30	64.6	57.5	PET/CT	Histology	58	9	2	27

Table 1 (*continued*)

Table 1 (*continued*)

Study	Publication year	Country	Study design	Sample size	Size of nodules (mm)	Percentage male (%)	Age (year)	Diagnostic tool	Gold standard	True positive	False positive	False negative	True negative
Sebro (58)	2013	USA	Retro	72	<30	97.2	69.9	PET/CT	Histology	58	6	3	5
Sim (59)	2013	UK	Retro	186	8–30	41.4	NA	PET/CT	Histology	137	14	21	14
Zhang (60)	2014	China	Pro	113	NA	59.3	26–81	PET/CT	Histology	68	6	9	30
Demir (61)	2014	Turkey	Retro	48	9–30	47.9	56.2	PET/CT	Histology	17	7	1	23
Li (62)	2014	China	Retro	298	<30	55.0	59.1	PET/CT	Histology	199	31	49	19
van Gómez López (63)	2015	Spain	Retro	55	<30	81.8	62.0	PET/CT	Histology	32	7	8	8
Dabrowska (64)	2015	Poland	Pro	71	8–30	36.6	45–88	PET/CT	Histology	37	1	12	21
Ohno (65)	2015	Japan	Pro	198	9–29	56.1	75.4	PET/CT	Histology	119	59	14	26
Wang (66)	2016	China	Retro	62	<30	NA	NA	PET/CT	Histology	15	15	2	30
Sahin (67)	2016	Turkey	Retro	41	<30	68.3	41–78	PET/CT	Histology	20	6	2	13
Lee (68)	2018	Korea	Retro	55	8–30	98.2	67.8	PET/CT	Histology	40	2	1	12

CECT, contrast enhanced computed tomography; CT, computed tomography; NA, not available; PET, positron emission tomography; Pro, prospective; Retro, retrospective.

diagnostic value of CT, and the remaining 23 studies investigated the diagnostic value of PET/CT for classifying benign and malignant SPNs. Thirteen studies investigated the diagnostic value of contrast enhanced CT, and the remaining 3 studies evaluated the diagnostic value of CT. These studies involved a total of 3,614 patients with SPNs. Eleven studies had a prospective design, and the remaining 28 studies had a retrospective design. Seventeen studies were conducted in Western countries and the remaining 22 in Eastern countries. The quality assessment of included studies is listed in *Table 2*; nearly all the studies had moderate or high quality.

Sensitivity and specificity

Figures 2 and *3* show the pooled sensitivity and specificity of CT and PET/CT for differentiating benign and malignant SPNs, respectively. The pooled sensitivity and specificity for CT were 0.94 (95% CI: 0.87–0.97), and 0.73 (95% CI: 0.64–0.80), respectively. Moreover, the pooled sensitivity and specificity for PET/CT were 0.89 (95% CI: 0.85–0.92), and 0.78 (95% CI: 0.66–0.86), respectively. The diagnostic value of sensitivity (ratio: 1.06: 95% CI: 0.99–1.13; P=0.111) and specificity (ratio: 0.94; 95% CI: 0.79–1.11; P=0.453) between CT and PET/CT was not statistically significant.

PLR and NLR

Figures 4 and *5* present the summary PLR and NLR of CT and PET/CT for differentiating benign and malignant SPNs, respectively. The summary PLR and NLR for CT were 3.45 (95% CI: 2.60–4.58), and 0.09 (95% CI: 0.04–0.17), respectively. Furthermore, the summary PLR and NLR for PET/CT were 3.97 (95% CI: 2.57–6.13), 0.15 (95% CI: 0.10–0.20), respectively. No significant differences were observed between CT and PET/CT for PLR (ratio: 0.87; 95% CI: 0.52–1.46; P=0.596), and NLR (ratio: 0.60; 95% CI: 0.27–1.34; P=0.212).

DOR and AUC

The pooled DOR for CT was 32.01 (95% CI: 15.10–67.86; *Figure 6*) with significant heterogeneity observed among included studies (P<0.001), while the summary DOR for PET/CT was 24.04 (95% CI: 12.71–45.48; *Figure 7*) with significant heterogeneity. The DOR between CT and PET/CT was not statistically significant (ratio: 1.33; 95% CI: 0.50–3.57; P=0.569). Moreover, the AUC for CT and

Table 2 Quality assessment of the included studies using the QUADAS tool

Study	Question about study design characteristic													
	Representative patient spectrum	Reporting of selection criteria	Reference standard	Absence of disease progression bias	Absence of partial verification bias	Absence of differential verification bias	Absence of incorporation bias	Description of index text execution	Description of reference standard execution	Reference standard blinded	Index test blinded	Absence of clinical review bias	Reporting of uninterpretable/ intermediate results	Withdrawal
Swensen	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Swensen	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Yamashita	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Swensen	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Potente	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Yes
Swensen	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Yi	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Yes
Kim	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Jeong	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Iwano	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
da Silva	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Bai	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes
Fan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Shu	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Ye	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Chen	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Herder	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Yi	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Yes
Orlacchio	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Tsushima	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Degirmenci	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Jeong	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Kagna	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Schillaci	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
Sathekge	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Divisi	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Nguyen	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Li	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes

Table 2 (*continued*)

Table 2 (*continued*)

Study	Question about study design characteristic													
	Representative patient spectrum	Reporting of selection criteria	Reference standard	Absence of disease progression bias	Absence of partial verification bias	Absence of differential verification bias	Absence of incorporation bias	Description of index text execution	Description of reference standard execution	Reference standard blinded	Index test blinded	Absence of clinical review bias	Reporting of uninterpretable/ intermediate results	Withdrawal
Sebro	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Sim	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Zhang	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Demir	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Li	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
van Gómez López	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Dabrowska	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Ohno	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Wang	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Sahin	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Lee	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Yes

PET/CT was 0.89 (95% CI: 0.86–0.91; *Figure 8*) and 0.91 (95% CI: 0.89–0.94; *Figure 9*), respectively. No significant difference was found between CT and PET/CT for AUC (ratio: 0.98; 95% CI: 0.94–1.02; P=0.268).

Subgroup analysis

The results of subgroup analyses for DOR are presented in *Table 3*. CT had high DOR than PET/CT for pooled studies conducted in Western countries (ratio: 5.37; 95% CI: 1.65–17.54). Furthermore, CT had lower DOR for studies conducted in Eastern countries than in Western countries (ratio: 0.16; 95% CI: 0.05–0.50). No other significant differences between CT and PET/CT or subgroups were observed.

Publication bias

Publication bias was assessed for CT and PET/CT and is presented in *Figure 10*. No significant publication bias was found for CT (P=0.34) and PET/CT (P=0.15).

Discussion

Numerous studies reported the diagnostic value of CT or PET/CT for differentiating benign and malignant SPNs. The present quantitative meta-analysis based on 39 studies was conducted to determine the diagnostic value of CT and PET/CT for classifying benign and malignant SPNs and provide the indirect comparison results for the better diagnostic tool. The findings of this meta-analysis indicated that both CT and PET/CT had a moderate-to-high diagnostic value for differentiating benign and malignant SPNs, with no significant differences between these two diagnostic tools. Moreover, CT should be recommended in Western countries due to high DOR compared with PET/CT. Finally, the DOR of CT was lower in Eastern countries than in Western countries.

Several meta-analyses have already investigated the diagnostic value of CT and PET/CT in classifying benign and malignant SPNs (19-21). Li *et al.* conducted a meta-analysis of 20 studies using ^{18}F-FDG-PET and reported the sensitivity of 0.89 (95% CI: 0.87–0.91), specificity of 0.70 (95% CI: 0.66–0.73), PLR of 3.33 (95% CI: 2.35–4.71), NLR of 0.18 (95% CI: 0.13–0.25), and DOR of 22.43 (95% CI: 12.55–40.07) (19). Ruilong *et al.* conducted a meta-analysis of 12 studies and suggested that the pooled sensitivity, specificity, PLR, and NLR of ^{18}F-FDG-PET

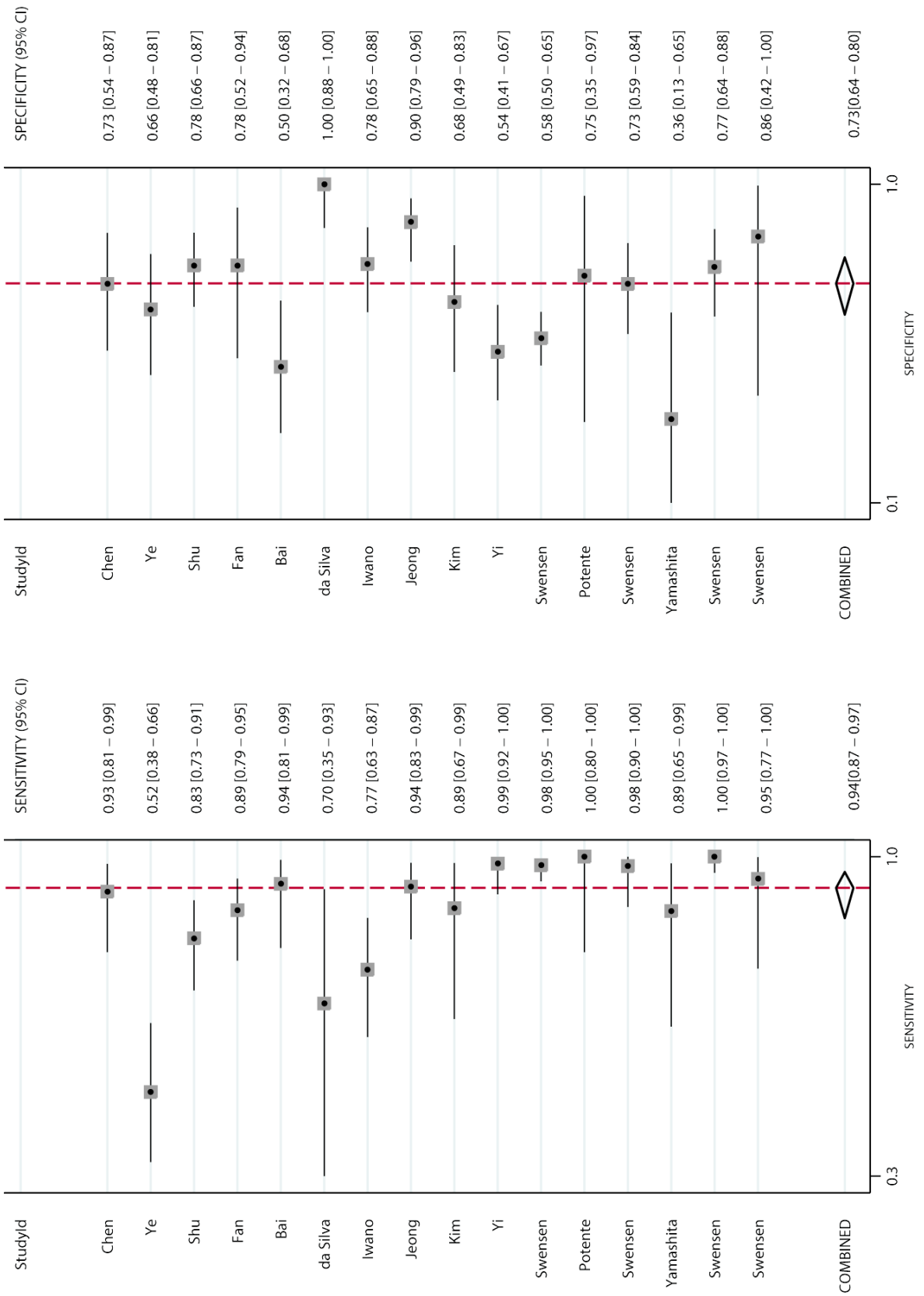

Figure 2 Pooled sensitivity and specificity of CT. CT, computed tomography.

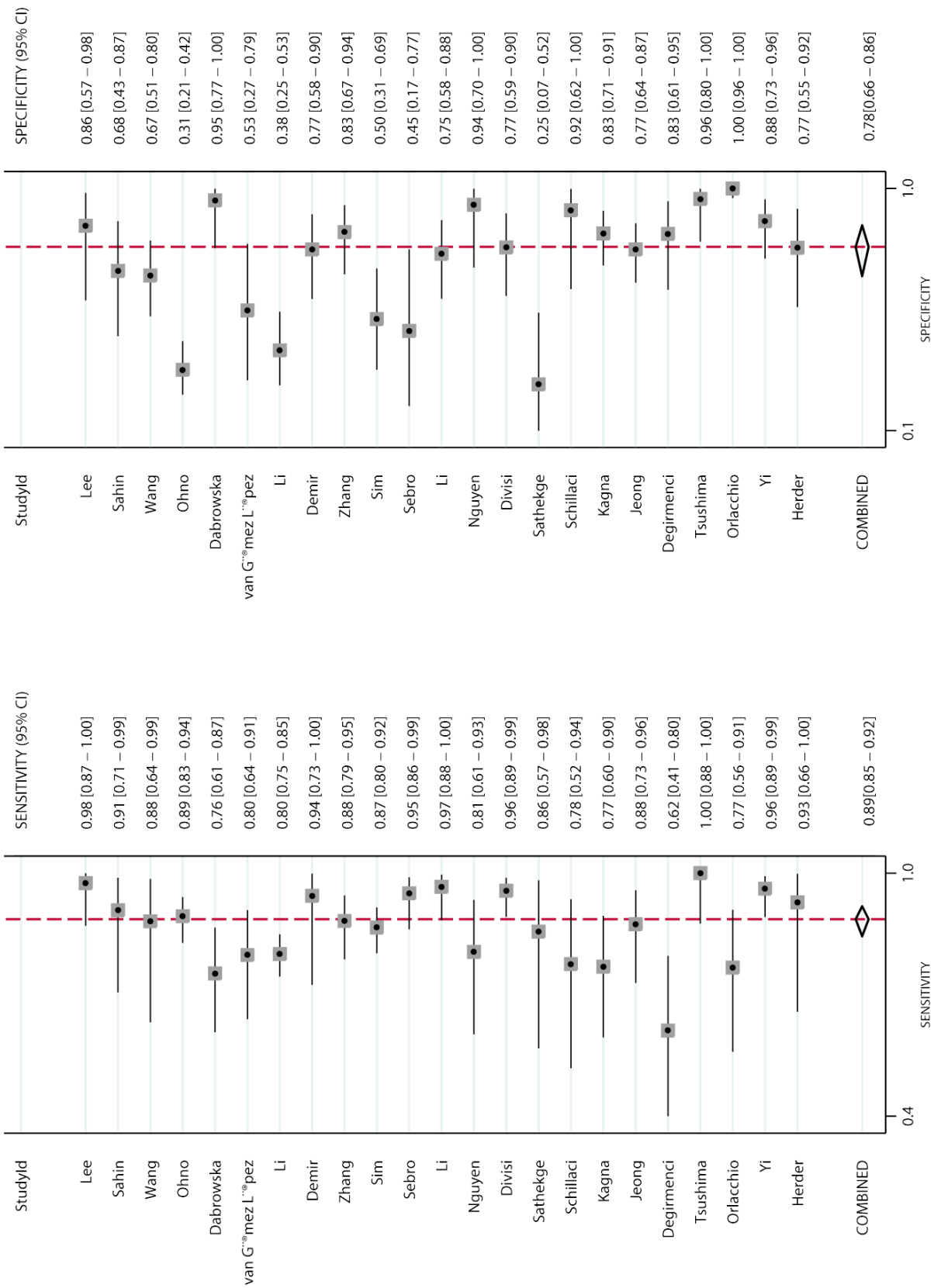

Figure 3 Pooled sensitivity and specificity of PET/CT. CT, computed tomography; PET, positron emission tomography.

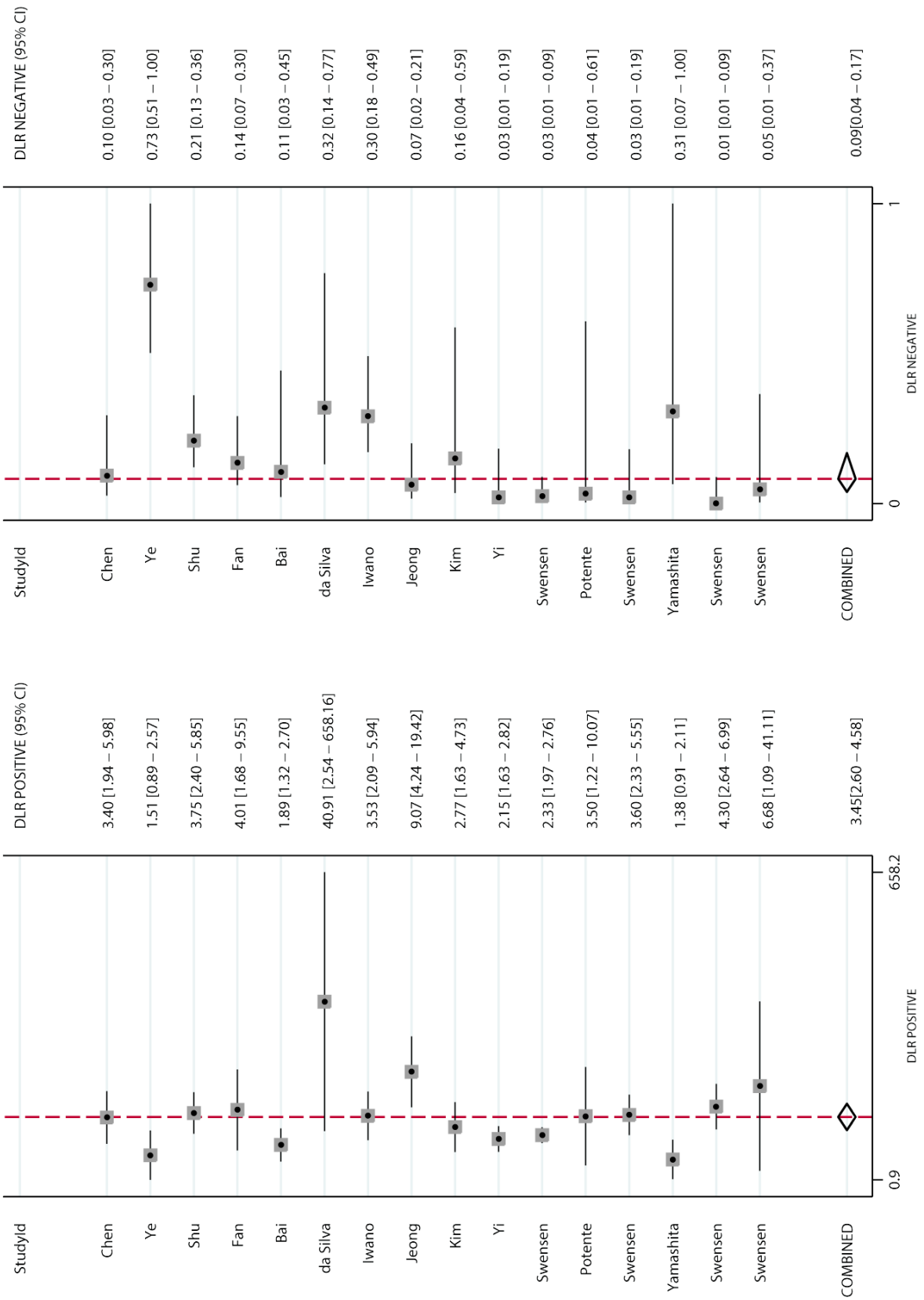

Figure 4 Pooled PLR and NLR of CT. PLR, positive likelihood ratio; NLR, negative likelihood ratio; CT, computed tomography.

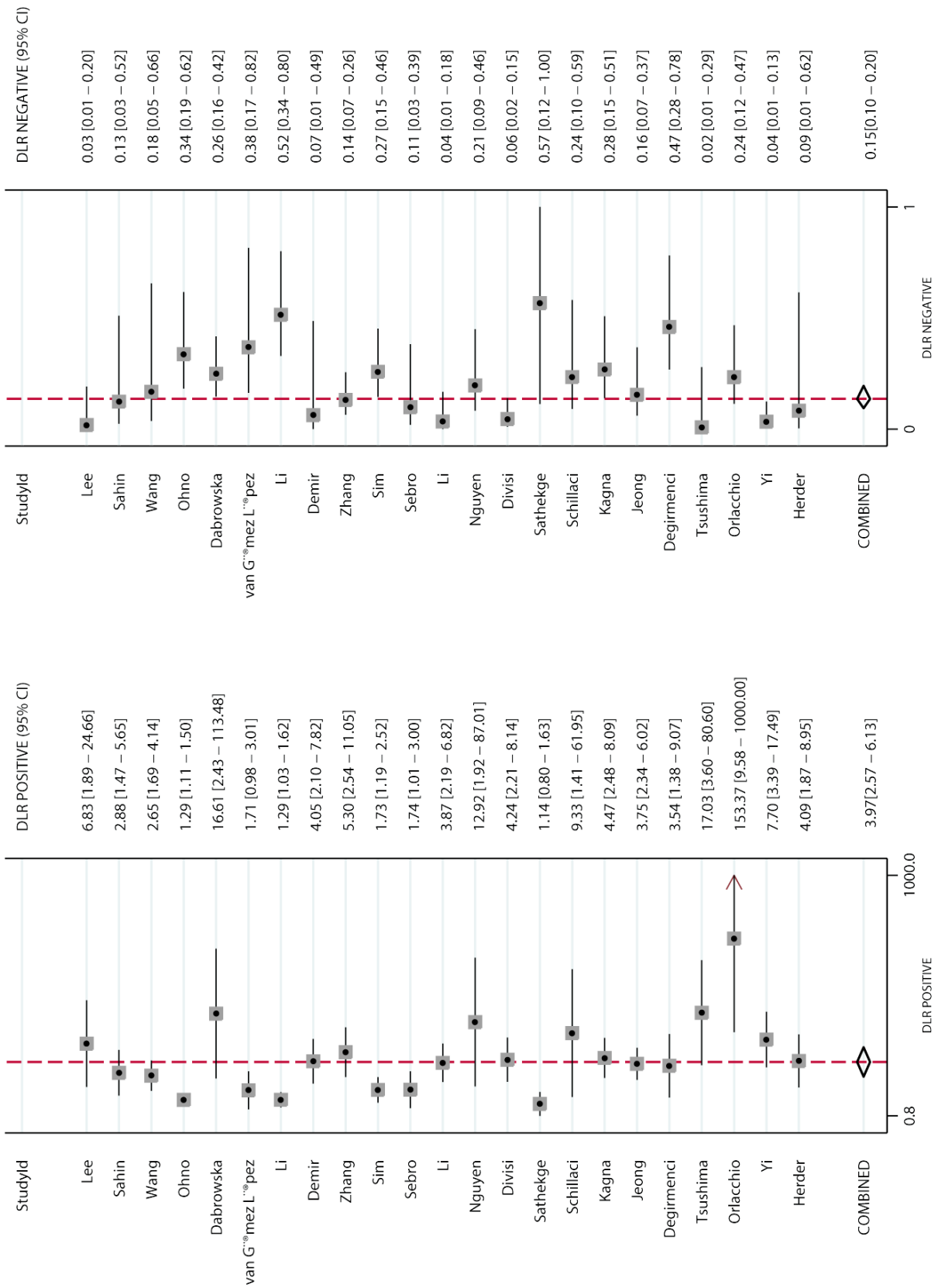

Figure 5 Pooled PLR and NLR of PET/CT. PLR, positive likelihood ratio; NLR, negative likelihood ratio; CT, computed tomography; PET, positron emission tomography.

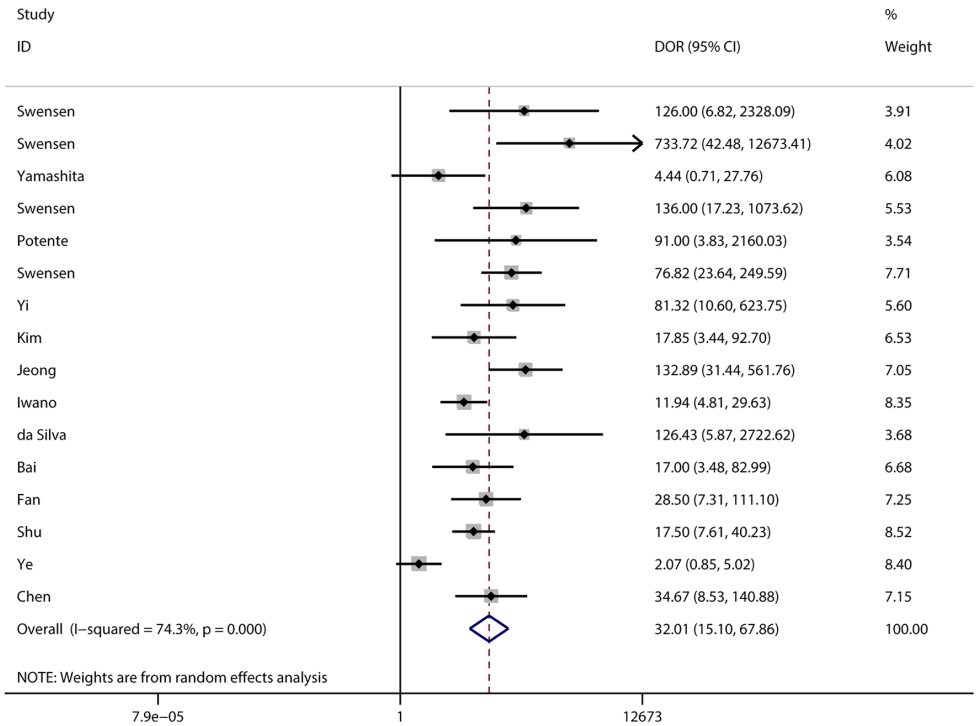

Figure 6 Pooled DOR of CT. DOR, diagnostic odds ratio; CT, computed tomography.

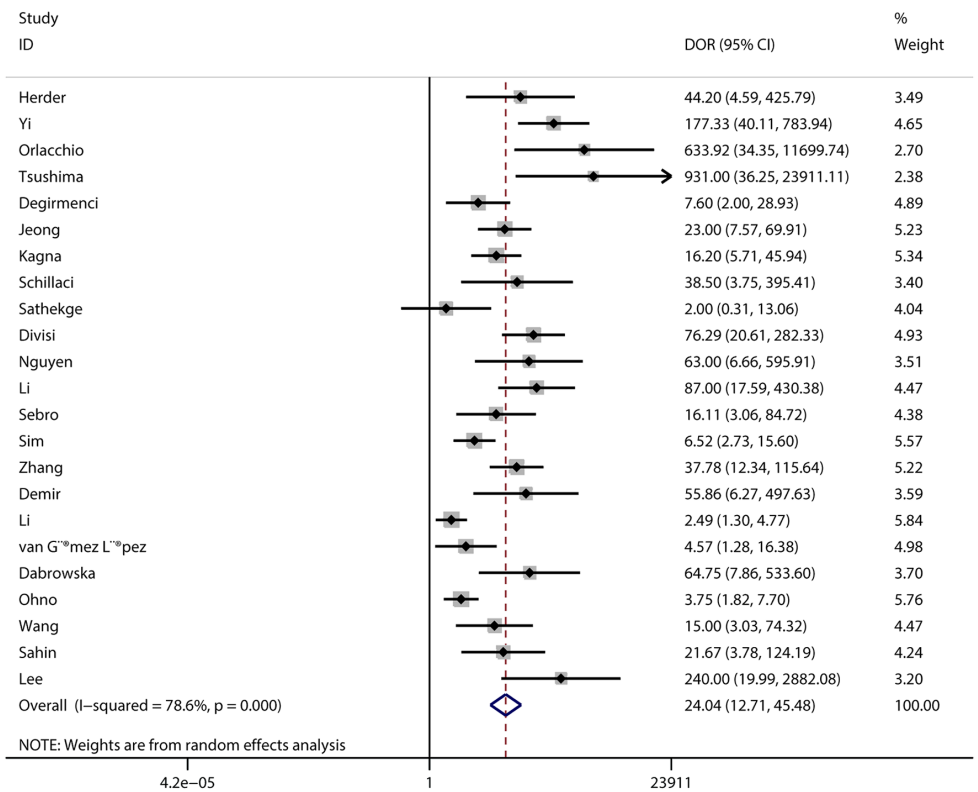

Figure 7 Pooled DOR of PET/CT. DOR, diagnostic odds ratio; CT, computed tomography; PET, positron emission tomography.

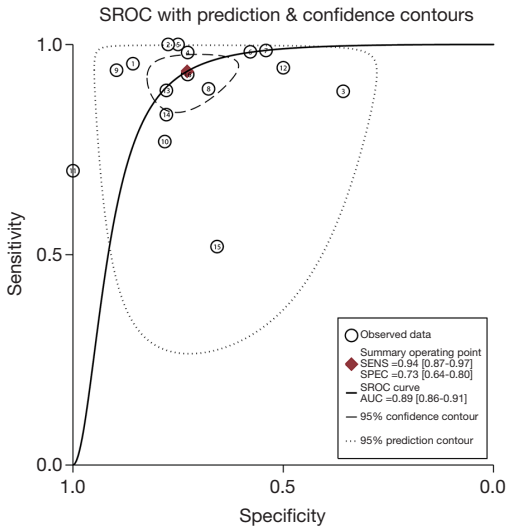

Figure 8 The summary ROC curve and AUC for CT. ROC, receiver operating characteristic; AUC, area under the ROC curve; CT, computed tomography.

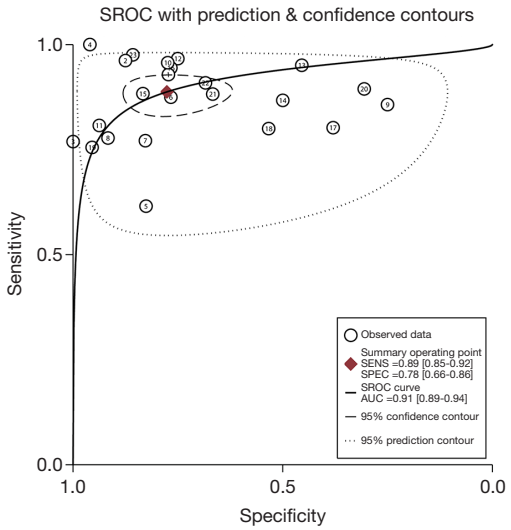

Figure 9 Summary ROC curve and AUC for PET/CT. ROC, receiver operating characteristic; AUC, area under the ROC curve; CT, computed tomography; PET, positron emission tomography.

Table 3 Subgroup analyses for the diagnostic odds ratio of CT and PET/CT for differentiating benign and malignant solitary pulmonary nodules

Variable	Subgroups	Diagnostic tool	Number of studies	DOR and 95% CI	P value for heterogeneity	Ratio between CT and PET/CT	Ratio between subgroups for CT	Ratio between subgroups for PET/CT
Country	Eastern	CT	10	17.68 (7.96–39.28)	<0.001	0.65 (0.19–2.27)	0.16 (0.05–0.50)	0.70 (0.19–2.54)
		PET/CT	12	27.22 (10.38–71.36)	<0.001			
	Western	CT	6	112.92 (48.51–262.84)	0.831	5.37 (1.65–17.54)		
		PET/CT	11	21.02 (9.18–48.12)	0.001			
Study design	Prospective	CT	4	20.95 (2.27–193.50)	<0.001	0.80 (0.06–10.96)	0.59 (0.06–6.03)	1.14 (0.24–5.44)
		PET/CT	7	26.12 (6.59–103.50)	<0.001			
	Retrospective	CT	12	35.58 (17.89–70.77)	0.012	1.55 (0.56–4.27)		
		PET/CT	16	22.93 (10.92–48.15)	<0.001			
Sample size	≥100	CT	7	56.88 (21.18–152.74)	0.002	3.00 (0.70–12.82)	3.06 (0.73–12.86)	1.00 (0.46–2.19)
		PET/CT	8	18.93 (6.54–54.79)	<0.001			
	<100	CT	9	18.58 (6.56–-52.67)	0.001	0.68 (0.19–2.45)		
		PET/CT	15	27.14 (12.99–56.70)	0.002			

CT, computed tomography; DOR, diagnostic odds ratio; PET, positron emission tomography.

were 0.82 (95% CI: 0.76–0.87), 0.81 (95% CI: 0.66–0.90), 4.30 (95% CI: 2.30–7.90), and 0.22 (95% CI: 0.16–0.30), respectively (20). Moreover, Zhang *et al.* indicated that the pooled sensitivity, specificity, PLR, NLR, DOR of CT were 0.89 (95% CI: 0.88–0.91), 0.70 (95% CI: 0.68–0.73), 2.88 (95% CI: 2.46–3.37), 0.16 (95% CI: 0.12–0.21), and 23.83 (95% CI: 16.18–35.11), respectively (21). The aforementioned results indicated that both CT and PET/CT had high sensitivity and moderate specificity for evaluating SPNs, while the comparison results of these

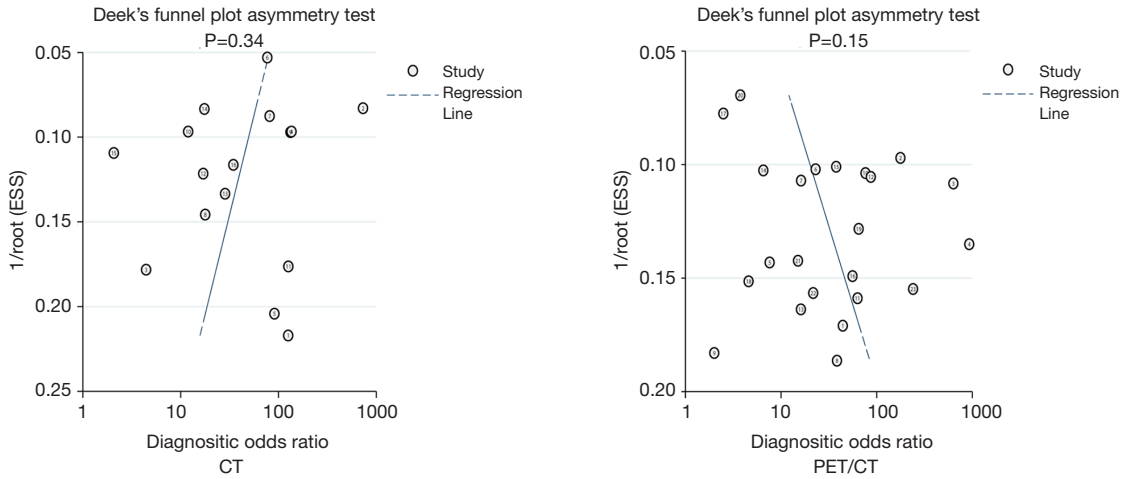

Figure 10 Publication biases for CT and PET/CT. CT, computed tomography; PET, positron emission tomography.

two diagnostic tools were not evaluated. Therefore, this quantitative meta-analysis was conducted to obtain the comprehensive diagnostic value of CT and PET/CT for classifying benign and malignant SPNs.

Although most included studies indicated high sensitivity (>0.80) and moderate specificity (>0.70) of CT, several studies reported inconsistent results. Ye *et al.* indicated patients with 12.4 HU or lower washout as a cutoff value; the sensitivity and specificity for malignancy were 52.5% and 65.0%, respectively (44). Bai *et al.* found that the sensitivity of CT was higher while the specificity of CT was lower than expected (41). da Silva *et al.* indicated that CT had a sensitivity of 70.0% and a specificity of 100.0% (40). Iwano *et al.* suggested CT differentiating malignant from benign SPNs with a sensitivity of 76.9% and a specificity of 80% (39). The other four studies reported CT with moderate or high sensitivity, while the specificity was lower than expected (32,35-37). The potential reasons for these results could be several studies without contrast injection, which were associated with a high incidence of false positive and negative. Moreover, the experience of radiologists could affect the accuracy of CT for evaluating SPNs. Similarly, five included studies indicated PET/CT with low or moderate sensitivity (48,50,52,53,64), and eight studies reported PET/CT with low specificity for classifying benign and malignant SPNs (54,58,59,62,63,65-67). The reason for this could be that ^{18}F-FDG was not a tumor-specific tracer, and false-positive results might be obtained in patients with inflammatory lesions (69,70).

No significant differences were found in sensitivity, specificity, PLR, NLR, DOR, and AUC between CT and PET/CT. However, the results of subgroup analyses indicated that the DOR of CT was higher than that of PET/CT in Western countries. Moreover, the DOR of CT might differ between Eastern and Western countries. However, these results might vary because of the imbalance in the number of included studies in corresponding subsets. Moreover, patient characteristics across included studies could affect the diagnostic accuracy of CT and PET/CT. Therefore, the results of subgroup analyses just provided relative results. Hence, further studies are needed to verify the diagnostic value of CT and PET/CT in classifying benign and malignant SPNs.

This study had several limitations. (I) The included studies had prospective and retrospective designs, thereby introducing potential uncontrolled selection and recall biases. (II) The size of nodules was variable across included studies, affecting the diagnostic accuracy of CT and PET/CT. (III) The skills of radiologists differed among included studies, resulting in a potential observer bias. (IV) The indirect comparison results of CT with PET/CT were based on different populations, and the results might vary due to uncontrolled heterogeneity among participants. (V) The analysis based on published studies and publication bias was inevitable.

The results of this meta-analysis indicated that both CT and PET/CT had a moderate-to-high diagnostic value for evaluating SPNs. Moreover, no significant differences in all diagnostic parameters were found between CT and PET/CT. Moreover, we noted CT was associated with high diagnostic value than PET/CT in Western countries, whereas the DOR of PET/CT in Eastern countries was

non-significant high than CT. Considering the high cost and limited availability of PET/CT, CT should be recommended for differentiating benign and malignant SPNs. Future prospective studies should be conducted to directly compare the diagnostic value of CT and PET/CT in detecting benign and malignant SPNs.

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Footnote

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

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