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Accuracy of baseline low-dose computed tomography lung cancer screening: a systematic review and meta-analysis

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Abstract

Background: Screening using low-dose computed tomography (LDCT) is a more effective approach and has the potential to detect lung cancer more accurately. We aimed to conduct a meta-analysis to estimate the accuracy of population-based screening studies primarily assessing baseline LDCT screening for lung cancer.

Methods: MEDLINE, Excerpta Medica Database, and Web of Science were searched for articles published up to April 10, 2022. According to the inclusion and exclusion criteria, the data of true positives, false-positives, false negatives, and true negatives in the screening test were extracted. Quality Assessment of Diagnostic Accuracy Studies-2 was used to evaluate the quality of the literature. A bivariate random effects model was used to estimate pooled sensitivity and specificity. The area under the curve (AUC) was calculated by using hierarchical summary receiver-operating characteristics analysis. Heterogeneity between studies was measured using the Higgins I^2 statistic, and publication bias was evaluated using a Deeks' funnel plot and linear regression test.

Results: A total of 49 studies with 157,762 individuals were identified for the final qualitative synthesis; most of them were from Europe and America (38 studies), ten were from Asia, and one was from Oceania. The recruitment period was 1992 to 2018, and most of the subjects were 40 to 75 years old. The analysis showed that the AUC of lung cancer screening by LDCT was 0.98 (95% CI: 0.96–0.99), and the overall sensitivity and specificity were 0.97 (95% CI: 0.94–0.98) and 0.87 (95% CI: 0.82–0.91), respectively. The funnel plot and test results showed that there was no significant publication bias among the included studies.

Conclusions: Baseline LDCT has high sensitivity and specificity as a screening technique for lung cancer. However, long-term follow-up of the whole study population (including those with a negative baseline screening result) should be performed to enhance the accuracy of LDCT screening.

Keywords: Lung cancer; Low-dose computed tomography; Screening; Sensitivity; Specificity; Meta-analysis

Introduction

Lung cancer resulted in the largest number of deaths and the second largest number of new cases around the world in 2020.[1] According to the Globocan 2020 released by the International Agency for Research on Cancer, the number of new cases and deaths due to lung cancer worldwide in 2020 were approximately 2.21 million and 1.80 million, respectively, accounting for 11.4% and 18.0% of all cancer cases and deaths, respectively.[1] Survival is highly dependent on early diagnosis; therefore, an effective screening program for the early detection of lung cancer could have a significant role in reducing this high mortality rate.[2]

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Previous clinical trials have found that screening methods, such as chest radiology and sputum cytology, do not provide a mortality advantage over standard practice.[3] In the early 1990s, low-dose computed tomography (LDCT) was introduced as a potential screening tool. High-quality images could be produced at much lower dose levels than with standard computed tomography (CT). The use of LDCT for lung cancer screening has now been shown to be an effective screening modality that can reduce mortality from lung cancer.[4,5] Therefore, LDCT can now be considered an acceptable form of early lung cancer screening.[6] Subsequently, more lung cancer screening studies with LDCT have been performed. However, to our knowledge, no meta-analysis has evaluated the diagnostic accuracy of LDCT testing for lung cancer.

Therefore, the present meta-analysis aimed to estimate the accuracy of population-based screening studies primarily assessing baseline LDCT screening for lung cancer. Our study will objectively and accurately evaluate the screening effect of LDCT for lung cancer and provide a reasonable reference basis for the selection of lung cancer screening technology in the future.

Methods

Literature search strategies

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Diagnostic Test Accuracy Statement.[7] Themes of "lung neoplasms" "mass screening" "early detection of cancer" and "tomography, X-ray computed" were used as Medical Subject Headings subject terms and "lung neoplasm" "pulmonary neoplasm" "bronchopulmonary neoplasm" "bronchial neoplasm" "lung cancer" "pulmonary cancer" "bronchopulmonary cancer" "broncho-pulmonary cancer" "bronchial cancer" "lung carcinoma" "pulmonary carcinoma" "bronchopulmonary carcinoma" "bronchial carcinoma" "bronchogenic carcinoma" "lung blastoma" "pulmonary blastoma" "bronchopulmonary blastoma" "broncho-pulmonary blastoma" "bronchial blastoma" "lung tumor" "pulmonary tumor" "bronchopulmonary tumor" "broncho-pulmonary tumor" "bronchial tumor" "screen" "test" "testing" "detection" "computed tomography" "LDCT" "CT" "low-dose computed tomography" "sensitivity" "specificity" "negative rate" "positive rate" "predictive value" "diagnostic accuracy", and "diagnostic performance" as free words in English language were used in combination to search. The retrieved databases included MEDLINE (via PubMed), Excerpta Medica Database (EMBASE), and Web of Science. The date of the literature was specified up to April 10, 2022. In addition, references to relevant systematic reviews and studies were manually searched as a supplement to the electronic search.

Inclusion and exclusion criteria

The literature included in this study met the following criteria: (1) prospective or retrospective studies evaluating patients in the context of screening; (2) LDCT as a screening method; (3) clear diagnostic criteria for lung cancer (biopsy, surgery, or follow-up results); and (4) number of cases for which true positives, false-positives, false negatives, and true negatives could be extracted or calculated.

The literature excluded in this study was mainly due to the following reasons: cellular or animal studies; studies on accuracy of computer-aided diagnostic techniques; reviews and case reports; sample sizes <200; necessary data could not be extracted or calculated directly from the original article; or studies with smaller sample sizes when subjects overlapped.

Data extraction

Data were extracted independently by two authors (FNY and YW) according to a predefined data collection form, and in case of inconsistency, a third senior researcher (LWG) made the judgment. The extracted data consisted of four parts: (1) literature characteristics, including first author and year of publication; (2) screening protocol information, including study site, study design, period of recruitment, project name, sample size, age and sex of study subjects, positive definition, and gold standard; (3) study result information, including the number of true-positive, false-positive, false-negative, and true-negative cases. In the case of incomplete data in the 2-by-2 contingency table, data were obtained by contacting the authors or were extrapolated from indicators, such as sensitivity, specificity, and positive predictive value as reported in the literature.

Quality assessment

In this study, two authors (YX and JD) independently reviewed each study for the bias assessment and applicability using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool and discrepancies were resolved by consensus. QUADAS-2 includes four domains: patient selection, index test, reference standard, and flow and timing, with a total of 18 signaling questions.[8] The risk of bias was assigned as high, low, or unclear for each domain. Studies with at least one domain at high risk of bias or with all four domains at unclear risk were assigned an overall assessment of "at risk" of bias.

Statistical analysis

A 2-by-2 contingency table was constructed. Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) of hierarchical summary receiver-operating characteristics (HSROC) were calculated. The pooled summary of sensitivity, specificity, PLR, NLR, and AUC was estimated based on the bivariate random effects meta-analysis. The summary DOR was computed using the Mantel–Haenszel method. Heterogeneity was assessed using the Higgins I^2 statistic, with $I^2 > 50\%$ indicating the presence of heterogeneity.[9] When there was substantial heterogeneity in diagnostic accuracy across studies, we investigated a threshold effect by (1) visual assessment of coupled forest plots of

sensitivity and specificity, and (2) a Spearman correlation coefficient between the sensitivity and false-positive rate (correlation coefficient >0.60 indicated a threshold effect).[10] We also visually assessed the differences between the 95% confidence region and the 95% prediction region in the HSROC curve to examine the presence of heterogeneity between studies.[11] Subgroup analyses for sensitivity, specificity, AUC, PLR, NLR, and DOR were subsequently carried out according to the geographical areas of the study origin, study design, year of publication, number of patients, population, multicenter or not, and positive definition. Deeks' funnel plot was generated to test for publication bias, with statistical significance being assessed based on Deeks' asymmetry test.

The statistical analyses were performed using STATA SE version 15.1 for Windows (StataCorp LP, College Station, TX, USA). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Systematic review and study characteristics

A total of 1707 relevant papers were searched in MEDLINE, Excerpta Medica Database (EMBASE), and Web of Science by the search formula, and 11 papers were added by manual search. Only 735 papers remained after duplicates were removed. With reference to the inclusion and exclusion criteria, the literature was initially screened, and 463 papers were eliminated by reading the titles and abstracts. Then, the remaining papers were read in full, 224 papers were excluded, and 48 papers[4,12-58] were finally included. The literature screening process is shown in Figure 1.

Two separate studies were reported in one paper,[20] so a total of 49 studies were included in this meta-analysis. Of these, 22 studies were conducted in Europe, 15 in North America, ten in Asia, one in South America, and one in Oceania. The years of publication of the included studies were 2001 to 2021 and the years of recruitment/screened were 1992 to 2018, with the earliest screening program from the USA[12] and the most recent screening program from China.[56] The scan parameters ranged from 100 to 140 kVp for tube voltage and 15 to 250 mAs for tube current. Of these, 14 studies (28.6%) used 140 kVp and 15 to 75 mAs, 7 (14.3%) used 120 kVp and <40 mAs, 7 (14.3%) used 120 kVp and ≥40 mAs, 6 (12.2%) achieved an effective radiation dose <2 mSv, 5 (10.2%) used 100 to 140 kVp and 20 to 100 mAs according to subject body weight and the other 10 (20.4%) did not provide scan parameters. A total of 157,762 cases were included in the study, with a sample size ranging from 224 to 26,722 cases

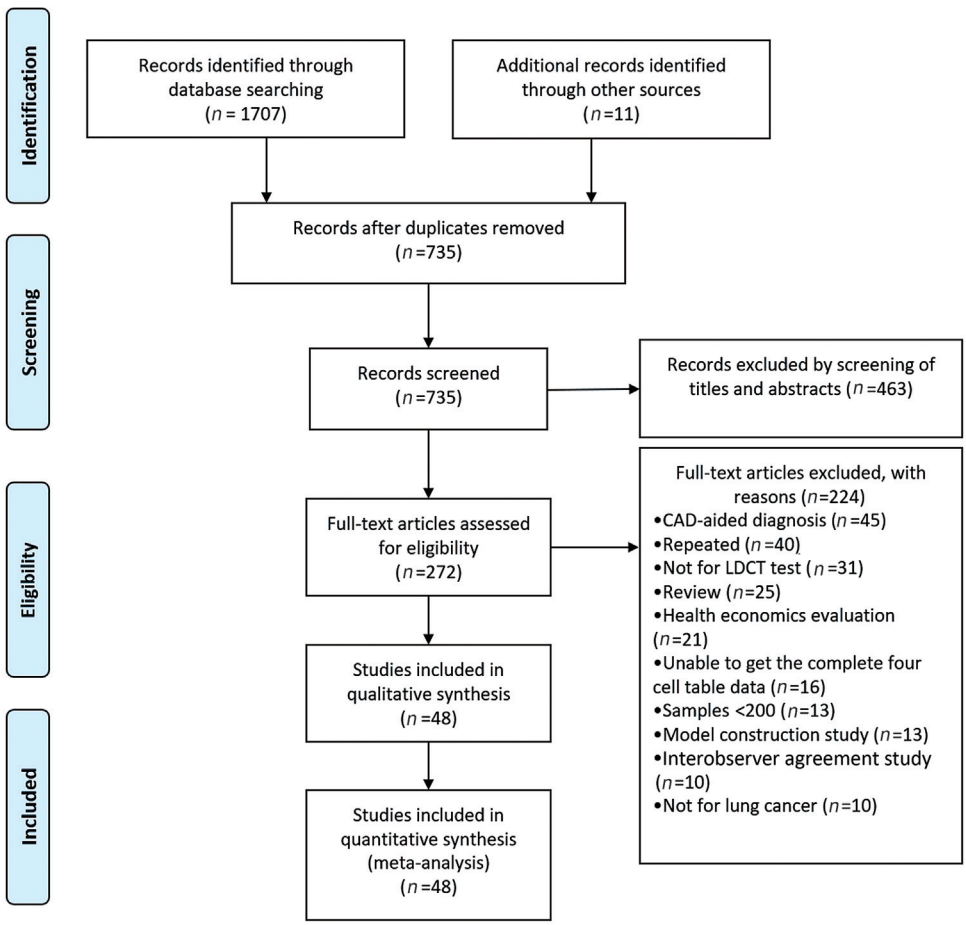

Figure 1: Flow diagram of the systematic literature search for studies of baseline low-dose CT lung cancer screening. CAD: Computer-aided diagnostic techniques; CT: Computed tomography; LDCT: Low-dose computed tomography.

Table 1: Studies included in the meta-analysis and their characteristics.

Author	Year	Country	Project name	Total number of participants screened (baseline)	Male (%)	Age (years)*	Positive definition
Aberle *et al*[4]	2011	USA	NLST	26,722	59	55–74	Lung-RADS ≥3
Henschke *et al*[12]	2001	USA	ELCAP	1000	54	≥60	NCN
Sone *et al*[13]	2001	Japan	Shinshu	5483	44	64 (40–74)	Non-cancerous lung lesion, non-cancerous but suspicious lung lesion, suspicion of lung cancer, indeterminate small lung nodule (<3 mm), and extrathoracic abnormality
Diederich *et al*[14]	2002	Germany	Münster	817	72	53 (40–78)	NCN ≥10 mm
Nawa *et al*[15]	2002	Japan	Hitachi	7956	79	55–59	NCN ≥8 mm
Sobue *et al*[16]	2002	Japan	ACLA	1611	88	40–79	Nodule ≥5 mm
Swensen *et al*[17]	2002	USA	Mayo	1520	52	59 (50–85)	NCN
Pastorino *et al*[18]	2003	Italy	Milan	1035	71	58 (50–84)	NCN ≥5 mm
Gohagan *et al*[19]	2004	USA	LSS	1586	58	55–74	NCN ≥3 mm, focal parenchymal opacification and endobronchial lesions
Henschke *et al*[20]	2004	USA	ELCAPs I and II	2968	NA	≥40	Solid or part-solid NCN ≥5 mm or non-solid NCN ≥8 mm
Henschke *et al*[20]	2004	USA	ELCAPs I and II	4538	NA	≥40	Solid or part-solid NCN ≥5 mm or non-solid NCN ≥8 mm
MacRedmond *et al*[21]	2004	Ireland	PALCAD	449	50	56†	NCN ≥10 mm
Bastarrika *et al*[22]	2005	Spain	Pamplona	911	74	55 (≥40)	One to six NCN, or more than six nodules with the largest one ≥5 mm
Chong *et al*[23]	2005	Korea	Seoul	6406	86	46–85	NCN
Novello *et al*[24]	2005	Italy	Turin	519	74	59 (54–79)	NCN ≥5 mm
Blanchon *et al*[25]	2007	France	Depiscan	336	71	56 (47–75)	NCN ≥5 mm
Infante *et al*[26]	2008	Italy	DANTE	1276	100	65 (60–74)	NCN ≥6 mm
Toyoda *et al*[27]	2008	Japan	Osaka	4689	59	≥40	Diagnosed with the need for further clinical examination
Veronesi *et al*[28]	2008	Italy	COSMOS	5201	66	57 (50–84)	NCN ≥5 mm
Wilson *et al*[29]	2008	USA	PLuSS	3642	51	59 (50–79)	NCN ≥4 mm
Lopes Pegna *et al*[30]	2009	Italy	ITALUNG	1406	64	55–69	NCN ≥5 mm or a non-solid nodule ≥10 mm or the presence of a part-solid nodule
Pedersen *et al*[31]	2009	Denmark	DLCST	2052	55	49–74	NCN ≥5 mm
van Klaveren *et al*[32]	2009	Netherlands and Belgium	NELSON	7557	84	59 ± 6	NCN ≥10 mm
Croswell *et al*[33]	2010	USA	PLCOS	1610	58	55–74	NCN >3 mm
Menezes *et al*[34]	2010	Canada	Toronto study	3352	46	60 (50–83)	NCN ≥5 mm or non-solid nodule ≥8 mm
Becker *et al*[35]	2012	Germany	LUSI	2029	50	50–69	NCN ≥5 mm
Pastorino *et al*[36]	2012	Italy	MILD	2303	69	58 (≥49)	NCN ≥60 mm^3
Rzyman *et al*[37]	2013	Poland	Pilot Pomeranian Lung Cancer Screening Program	8649	NA	50–75	NCN ≥10 mm or NCN <10 mm with typical radiological findings
Sozzi *et al*[38]	2014	Italy	MILD	643	NA	≥50	NCN ≥5 mm
Crucitti *et al*[39]	2015	Italy	Unrespiro per la vita	1500	62	62† (≥55)	NCN ≥4 mm
Milch *et al*[40]	2015	USA	New York	320	54	64 (55–74)	Lung-RADS ≥3
Sanchez-Salcedo *et al*[41]	2015	Spain	P-IELCAP	3061	73	55 (49–62)	Emphysema
dos Santos *et al*[42]	2016	Brazil	BRELT1	790	50	61.9 ± 4.6	NCN >4 mm
Field *et al*[43]	2016	UK	UKLS	1994	75	67 (50–75)	NCN ≥3 mm
Ritchie *et al*[44]	2016	Canada	PanCan	828	NA	50–75	Lung-RADS ≥3/NCN ≥4 mm
Jacobs *et al*[45]	2017	USA	Gundersen Health System	680	55	64 (55–77)	Lung-RADS ≥3
Marshall *et al*[46]	2017	Australia	QLCSS	256	67	65 (60–74)	Lung-RADS ≥3/NCN ≥4 mm
Hsu *et al*[47]	2018	China	Taiwan	1978	55	57 (40–80)	Lung-RADS ≥3/NCN ≥4 mm
Meier–Schroers *et al*[48]	2018	Germany	Bonn	224	NA	59 (50–70)	Lung-RADS ≥3
Bhandari *et al*[49]	2019	USA	Kentucky	4500	46	62	Lung-RADS ≥3
Crosbie *et al*[50]	2019	UK	LHC	1384	NA	65†	Solid nodule ≥8 mm with a risk of malignancy ≥10% or any other finding concerning for malignancy requiring immediate assessment
Fan *et al*[51]	2019	China	Shanghai	14,506	60	53 (35–96)	NCN
Kaminetzky *et al*[52]	2019	USA	ACR accredited lung cancer screening program	1181	48	64 ± 16	Lung-RADS ≥3
Spiro *et al*[53]	2019	UK	LungSEARCH	239	52	63	NCN ≥9 mm
Tremblay *et al*[54]	2019	Canada	Alberta	775	50	63†	Lung-RADS ≥3
Leleu *et al*[55]	2020	France	French prospective study	949	NA	55–74	NCN >10 mm
Wei *et al*[56]	2020	China	LungSPRC	2006	60	40–74	Solid or part-solid nodules ≥5 mm, or non-solid nodules ≥8 mm, or airway lesion, nodules and masses suspicious for lung cancer
Wu *et al*[57]	2021	China	BUILT study	1502	44	57 (51–64)	NCN ≥2 mm
Wang *et al*[58]	2021	China	Shandong	10,823	54	≥40	Lung-RADS ≥4

*Data are presented as median (range), range, median, mean ± standard deviation. †Mean. ACLA: Anti Lung Cancer Association; BRELT1: First Brazilian Lung Cancer Screening Trial; BUILT: Buddhist Tzu Chi Medical Foundation; COSMOS: Continuous Observation of Smoking Subjects; DANTE: Detection And screening of early lung cancer with Novel imaging TEchnology and molecular assays; DLCST: Danish Lung Cancer Screening Trial; ELCAP: Early Lung Cancer Action Project; ITALUNG: Italian Lung Trial; LHC: Lung health check; LSS: Lung screening study; Lung-RADS: Lung CT screening reporting and data system; LungSPRC: Lung Cancer Screening Program in Rural China; LUSI: Lung Cancer Screening Intervention Trial; MILD: Multicentric Italian Lung Detection; NA: Not available; NCN: Non-calcified nodule; NLST: National Lung Screening Trial; PALCAD: ProActive Lung Cancer Detection; PanCan: Pan-Canadian Early Detection of Lung Cancer Study; P-IELCAP: Pamplona International Early Lung Cancer Detection Program; PLCOS: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PLuSS: Pittsburgh Lung Screening Study; QLCSS: Queensland Lung Cancer Screening Study; UKLS: UK Lung Cancer Screening.

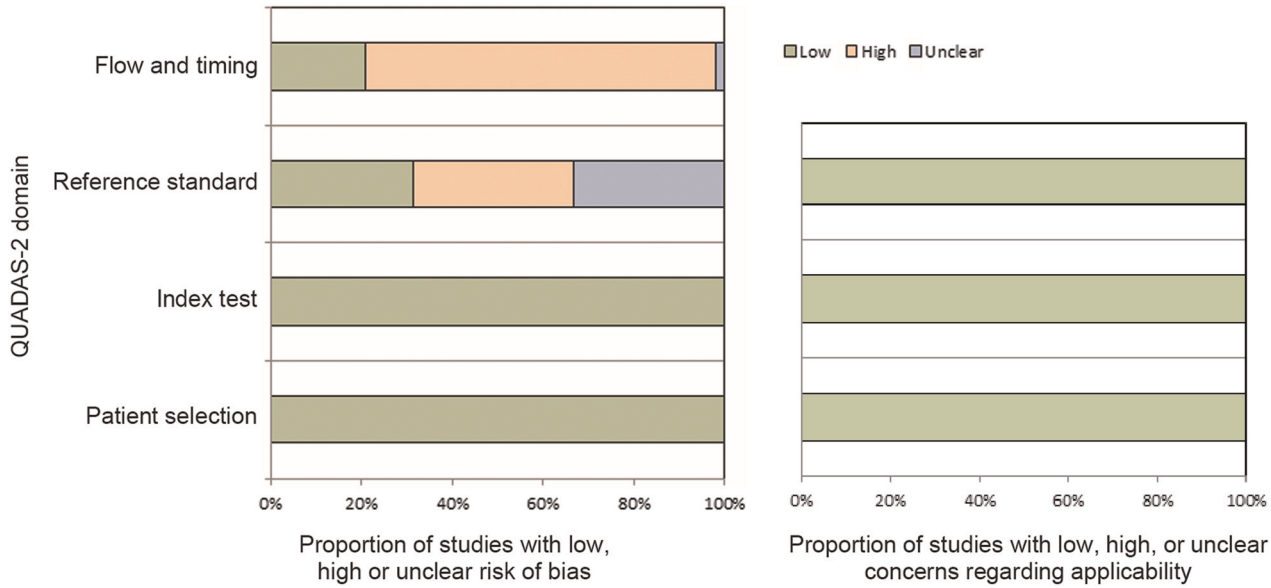

Figure 2: Risk of bias graph by the quality assessment of diagnostic accuracy studies version. QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2.

in each study, of which 18.4% (9/49) had a study sample size ≥5000. Subjects were screened at the starting and ending ages of 40 years and 96 years, respectively [Table 1].

Quality assessment

The results of quality assessments using the QUADAS-2 tool are summarized in Figure 2. With regard to patient selection and index tests, all studies had a low risk for bias. In the domain of bias in the reference standard, 17 studies were scored as "high risk" and 16 studies were scored as "unclear risk" because of no/unclear explanation of the blinding results of the index test. With regard to bias in the patient flow and timing, 37 studies were scored as "high risk" and one study was scored as "unclear risk", mainly because not all patients received the reference standard. With regard to applicability, all included studies were scored "low" in the three domains.

Threshold effect test

Figure 3 shows the HSROC curve illustrating the pooled AUC estimates derived from a bivariate random-effects model analysis. The distribution of sensitivity and specificity did not show a "shoulder shape," and the HSROC curve was symmetrical about the opposite diagonal, suggesting that there was no diagnostic threshold effect among the included studies. The correlation between sensitivity and 1-specificity was tested, and the Spearman coefficient was −0.09 ($P = 0.563 > 0.05$), suggesting that sensitivity and specificity were independent, further confirming that there was no diagnostic threshold effect between the two variables.

Meta-analysis of diagnostic accuracy

A bivariate random-effects model was used to quantify the diagnostic accuracy. The overall sensitivity, specificity,

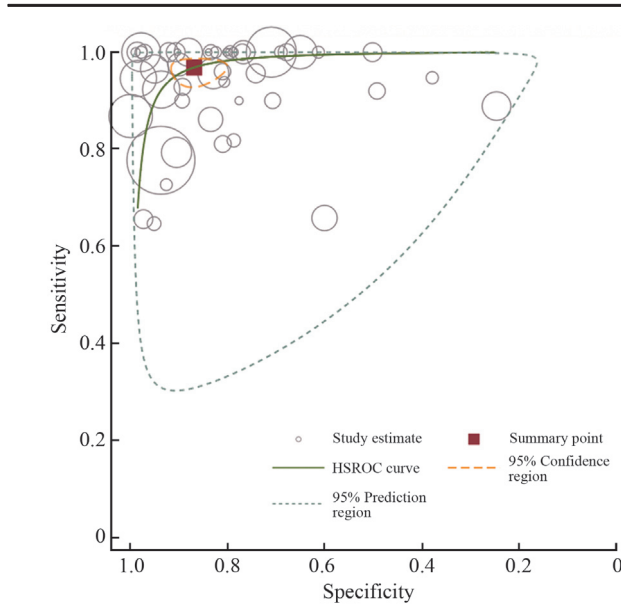

Figure 3: HSROC curves of LDCT for lung cancer diagnosis. HSROC: Hierarchical summary receiver-operating characteristics; LDCT: Low-dose computed tomography.

PLR, NLR, DOR, and AUC were 0.97 (95% CI: 0.94–0.98), 0.87 (95% CI: 0.82–0.91), 7.30 (95% CI: 5.20–10.30), 0.04 (95% CI: 0.02–0.07), 197 (95% CI: 93–415), and 0.98 (95% CI: 0.96–0.99), respectively. The results of the Higgins I^2 statistic [Figure 4] suggested that there was a large heterogeneity in both sensitivity ($I^2 = 89.16\%$) and specificity ($I^2 = 99.87\%$).

Subgroup analysis

To further explore the causes of study heterogeneity, we divided the participants into subgroups according to the geographical areas of the study origin, study design, year of publication, number of patients, population, multicen-

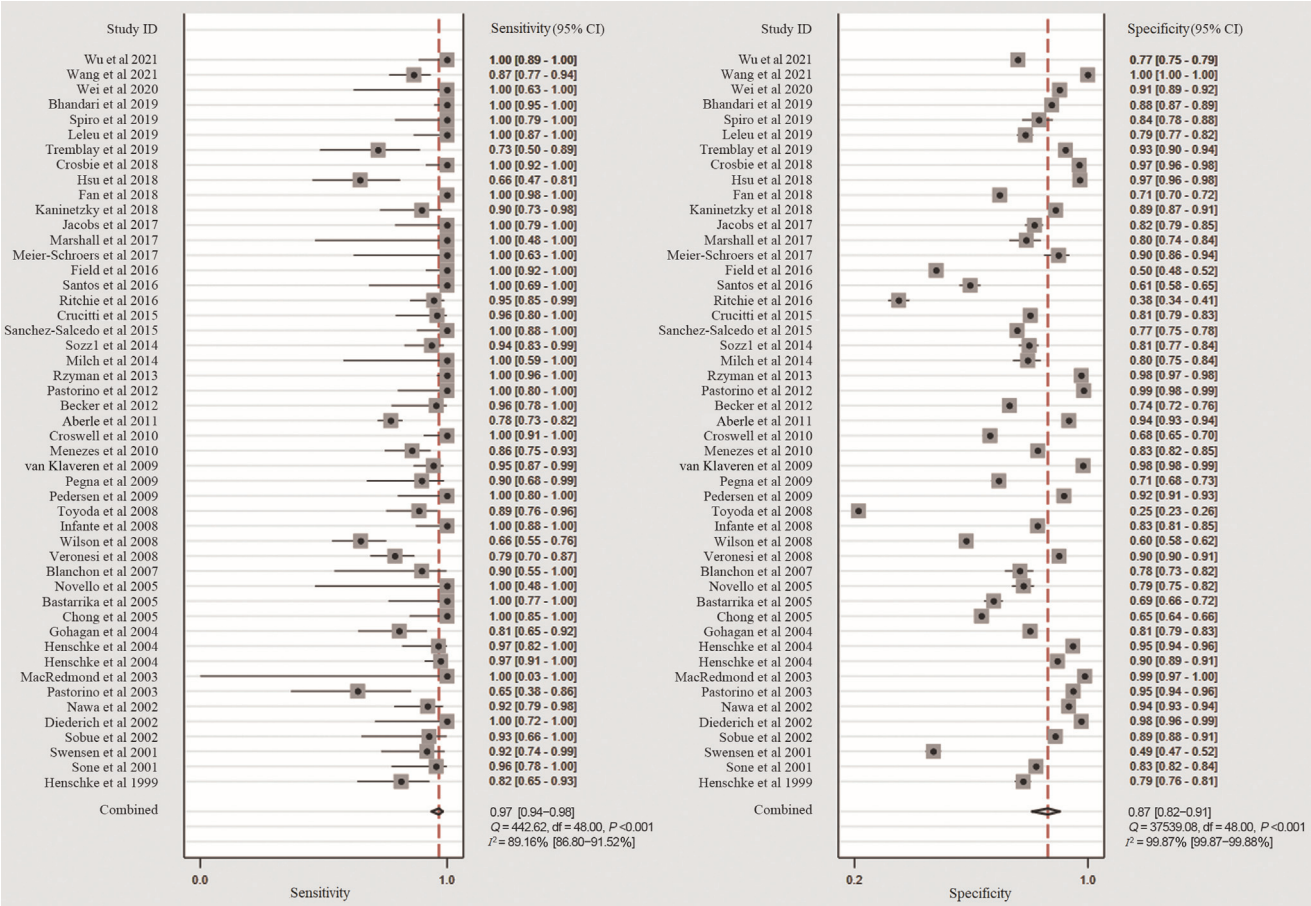

Figure 4: Coupled forest plots of the pooled sensitivity and specificity.

ter or not, and positive definition. As shown in Table 2, the results of the subgroup analysis showed a slight increase in pooled sensitivity (0.99) and specificity (0.90) in Europe but a slight decrease in North America (sensitivity = 0.93 and specificity = 0.82). Stratified analysis by positive definition showed that sensitivity was the highest with the detection of non-calcified nodules (NCNs) (0.99), which showed the lowest specificity (0.67). As the definition of positivity changes (NCN diameter increases), there is a tendency for sensitivity to decrease and specificity to increase. Subgroup analysis showed that the results did not change significantly with the study origin, study design, year, scanning parameters, sample size, population and number of participating centers. In short, the estimated heterogeneity for the included studies decreased to some degree but was not eliminated.

Publication bias

Weighted linear regression was used to test the symmetry of the funnel plot, with DOR as the dependent variable, 1/square root of the effective sample size (root [ESS]) as the independent variable and weight as the ESS [Figure 5]. The slope of the regression line was calculated to be −6.02 ($P = 0.485 > 0.05$) and the difference was not statistically significant, indicating that there was no publication bias among the included studies.

Discussion

Before this study, there were several meta-analyses of lung cancer screening by LDCT.[2,59,60] Different from our study, these meta-analyses focus on the efficacy of LDCT screening, such as lung cancer incidence, lung cancer mortality, and all-cause mortality. Although some of these meta-analyses have addressed the question of accuracy in subanalyses, they only described it and did not pool the results. This systematic review investigated the diagnostic performance of LDCT for lung cancer screening. Pooled effect estimates from the included studies demonstrated high accuracy of LDCT screening and robust study results with an overall sensitivity of 0.97 (95% CI: 0.94–0.98), overall specificity of 0.87 (95% CI: 0.82–0.91), and AUC of 0.98 (95% CI: 0.96–0.99).

The age and population of the screened subjects are important factors affecting the accuracy of LDCT screening. Among lung cancer screening guidelines, most recommend 50 years or 55 years of age as the starting age and 74 years as the upper age limit for lung cancer screening, although some guidelines recommend screening up to 77 years or 80 years of age.[61-65] For the studies included in this meta-analysis, the screening age range was 40 to 96 years old, and six of them chose the age range recommended by the guidelines. The benefit of lung cancer screening increases with the increasing risk of lung cancer

Table 2: Results of subgroup analyses for diagnostic accuracy.

Variables	Studies, *n*	Sensitivity	Specificity	AUC	PLR	NLR	DOR	Heterogeneity test	
								P for *Q* test	I^2 (%)
Overall	49	0.97	0.87	0.98	7.3	0.04	197	<0.001	100
Region									
Asia	10	0.97	0.89	0.98	8.5	0.04	217	<0.001	99
Europe	22	0.99	0.90	0.99	9.5	0.02	595	<0.001	98
North America	15	0.93	0.82	0.94	5.1	0.09	56	<0.001	99
Study design									
RCT	13	0.96	0.82	0.97	5.3	0.05	119	<0.001	94
Prospective cohort	32	0.96	0.88	0.98	8.3	0.04	191	<0.001	99
Year									
1999–2005	14	0.94	0.88	0.97	7.8	0.07	110	<0.001	93
2006–2010	10	0.92	0.80	0.94	4.7	0.10	49	<0.001	98
2011–2015	8	0.98	0.90	0.98	9.4	0.02	436	<0.001	98
2016–2021	17	0.99	0.87	0.99	7.9	0.01	1094	<0.001	99
Scan parameters									
140 kVp, 15–75 mAs	14	0.95	0.88	0.97	8.2	0.06	143	<0.001	99
120 kVp, <40 mAs	7	0.94	0.96	0.98	20.9	0.06	334	0.004	79
120 kVp, ≥40 mAs	7	0.99	0.87	0.97	7.8	0.01	573	<0.001	93
100–140 kVp, 20–100 mAs	5	0.95	0.81	0.95	5.1	0.06	90	0.500	100
Number of patients									
<5000	40	0.97	0.84	0.97	6.1	0.04	166	<0.001	99
≥5000	9	0.97	0.94	0.99	17.0	0.04	477	<0.001	99
Population									
High-risk	41	0.96	0.86	0.97	6.7	0.04	160	<0.001	99
Normal	8	0.98	0.91	0.99	11.5	0.02	591	<0.001	99
Multicenter									
No	25	0.94	0.89	0.97	8.5	0.06	137	<0.001	99
Yes	24	0.98	0.84	0.97	6.2	0.02	301	<0.001	99
Positive definition									
Lung-RADS ≥3	9	0.95	0.86	0.96	6.8	0.06	122	<0.001	98
NCN	4	0.99	0.67	0.81	3.0	0.02	149	<0.001	89
NCN ≥4 mm	7	0.95	0.64	0.89	2.7	0.07	36	<0.001	96
NCN ≥5 mm	9	0.92	0.86	0.94	6.5	0.09	70	<0.001	95
NCN ≥10 mm	4	0.98	0.98	0.99	47.2	0.02	2536	0.097	39

AUC: Area under the curve; CT: Computed tomography; DOR: Diagnostic odds ratio; Lung-RADS: Lung CT screening reporting and data system; NCN: Non-calcified nodule; NLR: Negative likelihood ratio; PLR: Positive likelihood ratio; RCT: Randomized controlled trial.

in the screening population. According to the National Lung Screening Trial (NLST) data, the number of lung cancer screening cases needed for each case of lung cancer death reduction in high-risk populations was significantly lower than that in low-risk populations. Among all the people who avoided dying of lung cancer due to screening, 88.0% were at high risk of lung cancer.[66] Therefore, across the lung cancer screening guidelines or consensuses published by countries around the world, lung cancer screening in high-risk populations is recommended.[61-64] Of the studies included in this meta-analysis, 83.7% (41/49) were conducted in high-risk populations.

Similar to our results, a systematic review showed that the sensitivity of LDCT for lung cancer screening ranged from 59.0% to 100.0%, and the specificity of LDCT ranged from 26.4% to 99.7%.[2] An important reason for the relatively large difference in sensitivity and specificity is the difference in the definition of positivity. Whether the screening is positive determines whether further diagnostic tests and invasive tests are needed. If the definition of positive screening is broad, it may lead to overdiagnosis and overtreatment.[67] However, if the definition is conservative, lung cancer may be missed. The NLST defines nodules >4 mm as screening positive to obtain a false-positive rate of 96.4%.[4] In a randomized controlled trial on lung cancer screening in China, the nodule determination criteria using those of the NLST study were found to have good sensitivity and specificity (98.1% and 78.2%) but a false-positive rate of 93.7% (753/804).[68] Gierda *et al*[69] compared lung cancer misses and false-positives with different nodule classification criteria based on NLST data. The results showed that, although the nodule classification criteria of 5, 6, 7, and 8 mm missed 1.5%, 2.7%, 6.5%, and 9.9% of cases, respectively, the number of false-positives was reduced by 14.2%, 35.5%, 52.7%, and 64.8%, respectively. In our study, the sensitivity and specificity with the nodule classification criteria of 4, 5, and 10 mm were 0.95 and 0.64, 0.92 and 0.86, and 0.98 and 0.98, respectively. The false-positive rates were 95.7%, 89.4%, and 62.5%, respectively.

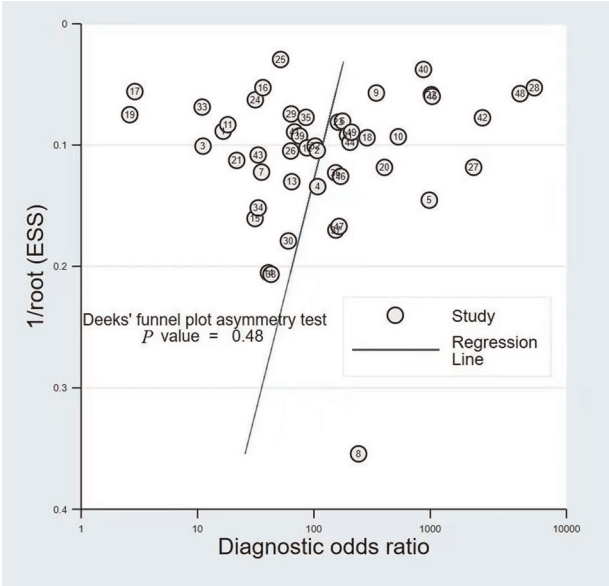

Figure 5: Deeks' funnel plot. ESS: Effective sample size.

The present study has several strengths. First, in contrast to published systematic reviews of LDCT screening,[2,59,60] the present analysis is one of the first systematic reviews investigating the diagnostic performance of LDCT for lung cancer screening. Second, we applied rigorous inclusion/exclusion criteria and advanced meta-analysis of diagnostic accuracy. Finally, subgroup analyses for sensitivity, specificity, AUC, PLR, NLR, and DOR stratified by the geographical areas of the study origin, study design, year of publication, number of patients, population, multicenter or not, and positive definition were conducted. Thus, the effect of potential confounders was minimized. In addition, no publication bias was observed in our analyses, indicating that our results are robust.

However, the meta-analysis has several limitations. First, false negative rates have not been generally well reported among the published studies, resulting in a possible overestimation of our findings (especially sensitivity). Second, substantial study heterogeneity was observed. To solve this issue, we examined the threshold effect between sensitivity and specificity using a coupled forest plot and Spearman correlation coefficient and performed subgroup analyses. Of course, we were not fully able to explain the heterogeneity. Including more prospective studies with a larger study population might help to validate the present conclusions with relatively less heterogeneity. Finally, in our study, the included studies were restricted to those published in English, which might introduce language bias as well.

In conclusion, the present study summarizes the accuracy data of LDCT for lung cancer screening worldwide, which provides basic data for policy-makers in developing prospective lung cancer screening programs on the one hand and helps the subjects weigh the advantages and disadvantages of screening more scientifically on the other hand. The evaluation of the accuracy of the scientific design of lung cancer screening technology is still very limited; therefore, a comprehensive evaluation of low-cost primary screening technology and protocols with a rigorous scientific design will be an important next step.

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Conflicts of interest

None.

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