Published in final edited form as:
JAMA. 2014 September 24; 312(12): 1227–1236. doi:10.1001/jama.2014.11488.

Accuracy of FDG-PET to diagnose lung cancer in areas with infectious lung disease: A meta-analysis

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Abstract

Importance—Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) is recommended for the non-invasive diagnosis of pulmonary nodules suspicious for lung cancer. In populations with endemic infectious lung disease, FDG-PET may not accurately identify malignant lesions.

Objective—To estimate the diagnostic accuracy of FDG-PET for pulmonary nodules suspicious for lung cancer in regions where infectious lung disease is endemic and compare the test accuracy in regions where infectious lung disease is rare.

Data Sources and Study Selection—Databases of MEDLINE, EMBASE and the Web of Science were searched from October 1, 2000, through April 28, 2014. Articles reporting

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information sufficient to calculate sensitivity and specificity of FDG-PET to diagnose lung cancer were included. Only studies that enrolled more than 10 participants with benign and malignant lesions were included. Database searches yielded 1923 articles, of which 257 were assessed for eligibility. Seventy studies were included in the analysis. Studies reported on a total of 8511 nodules; 5105 (60%) were malignant.

Data Extraction and Synthesis—Abstracts meeting eligibility criteria were collected by a research librarian and reviewed by 2 independent reviewers. Hierarchical summary receiver operating characteristic curves were constructed. A random-effects logistic regression model was used to summarize and assess the effect of endemic infectious lung disease on test performance.

Main Outcome and Measures—The sensitivity and specificity for FDG-PET test performance.

Results—Heterogeneity for sensitivity (I^2=87%) and specificity (I^2=82%) was observed across studies. The pooled (unadjusted) sensitivity was 89% (95% CI, 86%-91%) and specificity was 75% (95% CI, 71%-79%). There was a 16% lower average adjusted specificity in regions with endemic infectious lung disease (61% [95% CI, 49%-72%]) compared with nonendemic regions (77% [95% CI, 73%-80%]). Lower specificity was observed when the analysis was limited to rigorously conducted and well-controlled studies. In general, sensitivity did not change appreciably by endemic infection status, even after adjusting for relevant factors.

Conclusions and Relevance—The accuracy of FDG-PET for diagnosing lung nodules was extremely heterogeneous. Use of FDG-PET combined with computed tomography was less specific in diagnosing malignancy in populations with endemic infectious lung disease compared with nonendemic regions. These data do not support use of FDG-PET to diagnose lung cancer in endemic areas unless an institution achieves test performance accuracy similar to that found in nonendemic regions.

Keywords

Lung cancer; diagnosis; FDG-PET; meta-analysis

Clinicians rely heavily on radiographic imaging to identify and noninvasively diagnose lung nodules between 3 and 30mm in diameter. The advent of lung cancer screening in high risk populations using low dose computed tomography (CT) scans will increase the number of lung nodules detected, requiring clinical evaluation and diagnosis.[1] Depending on the risk for cancer, diagnostic guidelines suggest or recommend fluorodeoxyglucose F18 (FDG) combined with positron emission tomography (PET) as a noninvasive test to assess the risk of cancer or benign disease.[2-4]

In previously published meta-analyses.[5,6] FDG-PET was reported to be 90% to 94% accurate in the characterization of malignant or benign lung nodules, with a sensitivity of 94% to 96% and specificity of 78% to 86%. Furthermore, combined FDG-PET and CT (FDG-PET/CT) scans have demonstrated a reduction in nontherapeutic resections (e.g. resection for benign lesions or metastatic disease) by 17% to 20%.[7,8] For these reasons, FDG-PET/CT is widely accepted for the clinical diagnosis and staging of lung cancer in patients with suspicious lung nodules.[2,9]

Recent studies examining FDG-PET accuracy in diagnosing lung cancer in patients with lung lesions who reside in regions where fungal and other infectious lung diseases are endemic have shown mixed results.[10,11] Histoplasmosis, coccidioidomycosis and blastomycosis are the most prevalent fungal lung diseases in the United States,[12,13] and are common etiologies of lung granulomas.[12] Histoplasmosis and blastomycosis are endemic across much of the Mississippi, Ohio and Missouri river valley regions through southern Ontario, Canada, whereas coccidioidomycosis is prevalent in the southwestern United States.[12] Two international studies in areas with endemic tuberculosis found reduced FDG-PET/CT specificity of 25%[14] and 21%.[15]

We undertook a systematic review and meta-analysis of the literature published after the 2001 meta-analysis by Gould et al[6] describing FDG-PET accuracy to diagnose lung cancer among patients being evaluated with lung nodules or masses. This updated meta-analysis investigates the accuracy of FDG-PET to diagnose lung lesions in regions with locally endemic infectious lung diseases.

Methods

Studies evaluating individuals for possible lung cancer using FDG-PET, FDG-PET/CT or FDG-PET combined with another imaging modality were reviewed. We searched MEDLINE using the PubMed interface, EMBASE and the Web of Science for studies published between October 1, 2000 and April 28, 2014 (Appendix Table 1). The guidelines for Preferred Reporting Items for Systemic Reviews and Meta-Analyses were followed.[16] Reasons for study exclusion are detailed in the statistical abstract and visually displayed in Figure 1.

A study was classified as being from an endemic infectious region or population when the study reported presence of infectious lung diseases in the population from which participants were recruited or if granulomas arising from infectious lung diseases comprised at least 50% of reported benign etiologies. PET scan results were described by method of measuring FDG-PET avidity, the levels of risk or avidity, and the standardized uptake value threshold used to differentiate benign and cancerous diagnosis of disease. Details of study selection, data extraction, and synthesis are described in the statistical supplement.

Data Synthesis and Analysis

The sensitivity and specificity for FDG-PET test performance (pooled across studies) are displayed using forest plots. Study heterogeneity was assessed with an I^2 statistic. Test performance in the presence of heterogeneity[17] was summarized using hierarchical summary receiver operator curves (HSROC). Stability of test accuracy over time was assessed with diagnostic odds ratios and in the context of a random effects model.

Publication bias was visually inspected using a funnel plot and quantitatively measured (see statistical appendix).[18] Study quality was measured using a modified Quality Assessment of Diagnostic Accuracy Studies questionnaire (see statistical appendix for methodology).[19,20] Verification bias was defined as occurring when all diagnoses were determined

pathologically or when a pathological diagnosis was coupled with a period of radiographic surveillance shorter than 12 months.[21,22]

A large I^2 value indicates the data are not consistent with a simple pooling model; a more sophisticated model is needed to properly combine the data. Accordingly, a random-effects logistic regression was used to model test performance and account for heterogeneity among studies not attributable to observed study characteristics.

Study characteristics included in the model were endemic infectious lung disease in the study population, mean or median lesion diameter of less than 2 cm, scanner type as either PET only, combined PET and CT, or PET and another scanning modality (eg, time delayed PET, magnetic resonance imaging, volumetric CT), study quality score, and whether the study relied on only pathological determination of diagnosis. In studies with multiple imaging modalities, only the FDG-PET/CT portion of results were used (see Appendix Table 3).

Quality score was dichotomized with higher-quality studies (defined as those having at least 70% [≥11] affirmative quality questions).[23] The final model equations, procedures used for model selection, methods of assessing model fit, and details on numerical fitting appear in the statistical appendix. Missing data were handled with multiple imputation performed using chained equations (10 imputations were used; details appear in the statistical appendix).

The regression model provides an estimate of sensitivity (or specificity) adjusted to a particular set of study characteristics (ie, a particular study profile). These adjusted estimates are then averaged together to yield a single, average estimate of sensitivity (or specificity). This estimate, which we refer to as the average adjusted estimate, is similar to a simple pooled unadjusted estimate of sensitivity or specificity, except that the average adjusted estimate now properly accounts for the various study profiles observed in our sample.

To maintain generalizability, the averaging of adjusted estimates occurs with respect to the observed frequency of study profiles in our sample. We report the average adjusted estimates of sensitivity and specificity because of the ease of their interpretation and general applicability. We also calculated certain adjusted estimates of sensitivity and specificity as a sensitivity analysis to ensure result robustness. We defined rigorously conducted and well-controlled studies as studies with high quality, lesion size of less than 2 cm, use of adiagnostic method that minimizes the likelihood of verification bias, and use of combined PET and CT.

In addition to using 95% confidence intervals to estimate population parameters, we used 95% prediction intervals (PIs) to estimate the anticipated performance of a single study randomly chosen from this population of studies. The PIs describe the population heterogeneity of test performance. All statistical tests were 2-sided with a type I error of .05. All analyses were performed with Stata version 12 (StataCorp) and R 2.15.3 (R Foundation for Statistical Computing).

Results

A total of 1923 articles were found; 16 articles were added from bibliography reviews along with an unpublished abstract. Forty-six articles were removed as duplicates and 1893 studies were screened. Upon initial abstract review, 1636 articles were excluded. An article could be excluded for multiple reasons, but the most common reason for exclusion during either portion of the review was inclusion of participants with 100% cancer prevalence (n=1025).

Two hundred and fifty-seven studies received full review, of which 187 were excluded upon secondary review. The remaining 70 studies met all inclusion criteria and were used for the final analysis (Appendix Table 2). The total number of reported nodules being evaluated by FDG-PET among the 70 studies was 8511 and median number of nodules per study was 83 (interquartile range, 56-140 nodules/study). Pooled cancer prevalence among nodules was 60% (n=5105 nodules). Individual study cancer prevalence varied from 21% to 86% across studies. Ten of 70 studies documented endemic infectious lung disease.[10,11,14,15,24-29]

The overall agreement for study eligibility between reviewers was 94.8%, and the K was 0.72 (using the method by Cohen), showing moderate agreement between reviewers. Consensus was used when reviewers disagreed; agreement was not reviewed quantitatively. Despite contacting corresponding authors, missing data on mean or median nodule size remained in 12 studies. Among the 49 studies reporting a mean or median lesion size, the median lesion size across studies was 2 cm (interquartile range, 1.7-2.8 cm) (Appendix Table 2).

Meta-analysis

An unadjusted pooled analysis of the 70 studies showed evidence of significant heterogeneity among studies in sensitivity, (I^2 of 87% [95% CI, 85%-90%]) and specificity (I^2 of 82% [95% CI, 78%-86%]). Pooled sensitivity of FDG-PET for diagnosing lung cancer was 89% (95% CI, 86%-91%) and pooled specificity was 75% (95% CI, 71%-79%).

Ten studies reporting endemic disease had an unadjusted pooled specificity of 54% (95% CI, 37%-69%)[10,11,14,15,24-29] compared with 78% (95% CI, 74%-81%) in the remaining 60 studies. The asymmetry test (using the method by Deeks et al[18]) did not show evidence of publication bias ($P = .14$). No trend over time or between periods in diagnostic accuracy was observed (supplemental appendix).

A random-effects model that included a random intercept for each study and various fixed effects for the study characteristics (see statistical appendix for details) was used to account for the observed heterogeneity. The model yielded an average adjusted estimate of sensitivity of 89% (95% CI, 87%-91%) and specificity of 75% (95% CI, 71%-78%) (Figure 2)[30-89].

The area under the HSROC curve (Figure 3) was 0.90 (95% CI, 0.87-0.92). The PIs show the extreme amount of heterogeneity among studies that remains after adjusting for study characteristics. The sensitivity of a randomly chosen study was predicted as 89% (95% PI, 70%-97%) and specificity was 75% (95% PI, 45%-91%). Similar increases in PI length were

observed for all analyses. The results presented in the following sections are adjusted results from the random-effects model using multiple imputation.

Infectious Lung Disease

Ten studies reporting infectious lung disease endemic to the local population comprised 1431 individuals, of whom 1082 had cancer (76%). Granulomas as a percentage of benign diagnoses ranged from 45%[26] to 75%.[14] Studies of populations in China,[27] South Africa[14] and Japan[15] reported tuberculosis as the common etiology for granulomatous disease.

The remaining North American studies found histoplasmosis, coccidioidomycosis, inflammation and unspecified granuloma as common etiologies for pathologically diagnosed benign disease. Four of the ten studies were retrospective[10,25,28,29] and 7 studies[10,11,14,15,25,26,29] determined diagnosis with pathology only.

The specificity was estimated to be 16% lower in populations with endemic infectious lung disease. This lower specificity persisted at 14% even for rigorously conducted and well-controlled studies. The average adjusted estimate of specificity in regions with endemic disease was 61% (95% CI, 49%-72%) compared with 77% (95% CI, 73%-80%) for nonendemic populations (Figure 3). For rigorously conducted and well-controlled studies, the estimates of specificity in endemic and nonendemic regions were 66% (95% CI, 51%-78%) and 80% (95% CI, 74%-85%), respectively.

The average adjusted sensitivity did not significantly differ by endemic status (94% [95% CI, 90%-96%] vs 88% [95% CI, 85%-90%] in nonendemic regions). The adjusted estimate of sensitivity in rigorously conducted and well-controlled studies was slightly higher in endemic regions (96% [95% CI, 92%-98%] vs 90% [95% CI, 86%-93%] in nonendemic regions).

Size of Lesion

Among the 34 studies reporting average or median lesion diameters of less than or equal to 2 cm, the average adjusted sensitivity was 87% (95% CI, 84%-90%).[14,24,26-29,32,39,45,46,48,50,52-54,58,60,62,64,67-69,72,74,75,77,80-83,85-88] In comparison, 23 studies with an average or median diameter greater than 2 cm had a slightly higher average adjusted sensitivity (91% [95% CI, 89%-93%]).[10,11,15,25,30,31,34,35,37,41,43,44,55-57,61,63,73,76,78,79,84,86] Specificity of FDG-PET to diagnose lung cancer was not significantly influenced by lesion size (74% for studies with lesions ≤2 cm and 75% for studies with larger average lesion size).

Type of FDG-PET Scan

The 40 studies using FDG-PET/CT demonstrated slightly better average adjusted sensitivity (90% [95% CI, 88%-92%]) compared with the 19 studies using only FDG-PET (89% [95% CI, 84%-92%]) or the studies combining FDG-PET with another method of imaging (82% [95% CI, 75%-89%]).[11,15,25,30,32-37,39,40,47,49-51,54,57,75,90] Scanner type had little association with specificity. The average adjusted specificity for studies that used a FDG-

PET or FDG-PET/CT in combination with another imaging modality (75%) was similar to studies using only FDG-PET/CT (76%).[38,41-43,53,62,75,79,80,87]

PET not combined with CT or with other imaging modalities had a slightly worse average adjusted specificity of 70% (95% CI, 62%-77%) compared with FDG-PET/CT or FDG-PET plus another imaging modality. Among the other imaging modalities reported, 2 studies used single-photon emission CT as the alternative secondary scanning modality.[41,43] Two studies used dynamic, 3-dimensional CT scanning.[53,87] Two studies reported using F18-fluorothyminidine in conjunction with FDG.[42,79] One study used a sodium iodide detector[38] and 3 studies created algorithms of staggered PET scans and changes in standard uptake values (dual-time point).[28,62,80]

Study Quality

Study quality scores ranged from 3 to 14 (median score was 10 of 15 possible points). The quality metric that most studies failed to meet was patients receiving the same reference standard regardless of index test result (67%). Studies often lacked sufficient numbers of benign cases (29 studies had <25 benign cases). Most studies (81%) emulated the use of the FDG-PET scan in current clinical practice.

Lower-quality studies had reduced average adjusted sensitivity (87%[95% CI, 85%-90%]) compared with higher-quality studies (91%[95% CI, 88%-93%]) after controlling for other study characteristics in the regression model. Average adjusted specificity was similar across lower-quality studies (75%) compared with higher-quality studies (74%). Studies that relied on either pathological diagnosis or less than 1 year of follow-up had similar average adjusted sensitivity (87% [95% CI, 83%-90%) compared with those that did not (90% [95% CI, 88%-92%]).

The average adjusted specificity among studies that relied on a combination of prolonged surveillance and pathological diagnosis had higher average adjusted specificity (77% [95% CI, 73%-81%]) than those that exhibited possible verification bias (69% [95% CI, 61%-75%]). Additional study quality results are provided in the statistical supplement.

Sensitivity Analysis for the Effect of Individual Studies on Pooled Estmates

Removal of the largest study by Bryant and Cerfolio[26] (n=585), which reported endemic infectious lung disease, reduced the average adjusted specificity from 61% to 56% in studies with endemic infectious lung disease. Its removal had little influence on the sensitivity of the test in either average adjusted results or in the endemic infectious lung disease populations. A sensitivity analysis using the distance method by Cook identified 1 study (Garcia Vicente et al[80]) as potentially over influential. However, its exclusion did not noticeably change results. No individual study unduly influenced the estimated sensitivity or specificity of FDG-PET.

Discussion

For the last decade, molecular imaging with FDG-PET has become part of the diagnostic arsenal of tests considered for the evaluation of suspicious lung nodules. This method of

imaging is suggested based on low-quality evidence (grade 2C) for the diagnosis of solid nodules larger than 8mm.[2] The limitation of FDG-PET in the diagnosis of smaller lesions is well documented and this meta-analysis also found studies reporting lesions smaller than 2 cm had lower sensitivity compared with studies reporting on larger nodules.[3,91,92] Previous meta-analyses found FDG-PET to be highly sensitive (94% to 96%) and reasonably specific (78% to 86%) in the diagnosis of lung cancer.[5,6] Compared to prior studies, the sensitivity and specificity in our meta-analysis was lower. The HSROC was 0.9, which is similar to that reported by Gould et al[6], and our study also exhibited heterogeneity across studies.

In the 2001 meta-analysis,[6] 727 of the 1474 (49%) lesions were from Japanese or European populations.[6] Also, a portion of the studies in the meta-analysis were populations from the northeast or other areas of the United States where granulomatous disease is less common. Similarly in the study by Cronin et al,[5] 860 of the 1190 lesions (72%) reported in the 22 studies reviewed were from geographic areas where infectious lung disease is rare.

In regions where infectious lung disease is highly prevalent, the specificity of FDG-PET scans to diagnose lung nodules suspicious for lung cancer in our study was approximately 61%. However, the best specificity in endemic regions (from either the average adjusted or adjusted results) was 66%. Therefore, in individuals being evaluated for a suspicious lung lesion, and who reside in a region with significant endemic infectious lung disease, FDG-PET/CT scan does not reliably distinguish benign disease from lung cancer.

We have shown that the specificity of FDG-PET/CT for the diagnosis of lung cancer was overstated in regions with endemic infectious lung disease and could lead to unnecessary biopsies or thoracotomies for indeterminate lung nodules. Knowledge of this limitation in such regions is especially important should low-dose CT screening for lung cancer is widely adopted and should be reflected in current nodule management guidelines.[2,3]

Our review included more studies and had greater heterogeneity in both sensitivity and specificity when compared to earlier meta-analyses by Gould et al[6] and Cronin et al.[5] Some heterogeneity across studies arises from the scanning method, the size of the lesion examined, whether the study relied only on pathological verification of cancer, and the prevalence of endemic infectious lung disease in the study population. However, there remained substantial variability among studies in test performance that was not accounted for by these factors.

We observed a transition in the literature from scanners using FDG-PET only to FDG-PET/CT since their introduction into clinical practice in 2001.[93,94] Recently, radiologists have undertaken significant efforts to find a complement or replacement for the FDG radionuclide or the positron emission image-generating scanner.[42,95-98]

We attempted to include the breadth of research in PET for lung nodule diagnosis by searching for studies that compared new modalities or radio nuclides to existing FDG-PET or PET plus CT. Multimodality studies collectively had a higher specificity (80%) compared to studies using either FDG-PET or CT alone, but as a group they may be susceptible to publication bias that potentially decreases the accuracy of FDG-PET compared with the newer imaging methods.

To date, no replacement for FDG has been suggested for the diagnosis of lung nodules suspicious for lung cancer.[91,99] In addition, a majority of participants (n=4615) were in studies in which the mean or median lesion size was less than or equal to 2 cm. The lower sensitivity observed in this analysis arises, in part, from the application of this diagnostic modality to a broader clinical population with both smaller lesions and a greater likelihood of infectious disease.

After adjusting for study characteristics in our model, the precision of estimated sensitivity and specificity is quite good (shown by the narrow 95% CIs in Figure 3). However, variability remains even after adjusting for known study characteristics as shown in the distribution of individual study sensitivity and specificity estimates and combined PIs.

The range of test performance observed in practice is quite large (shown by the wide PIs in Figure 3). These reflect a lack of consistency in the application of FDG-PET diagnosis for lung nodules that is concerning and this meta-analysis suggests significant variability in practice patterns. Accordingly, technical standards and consistent adherence to imaging protocols and image interpretation should be strictly followed to reduce these inconsistencies. This is especially important in smaller lesions (<2cm) and in regions with endemic infectious lung disease to prevent false-positive and negative test results that could cause harm to patients.

The limitations of this analysis are those common to meta-analyses (eg, publication bias, selection bias, limited information from study reports, and potential for ecological fallacy). Even though we did not find evidence of significant publication bias, this does not exclude its possibility. Because FDG-PET was recommended for the diagnosis of lung cancer, a publication bias to report poor FDG-PET accuracy or negative results may exist.

Studies reporting results from scanners with FDG-PET only may no longer reflect clinical practice and arguably should not be included in this analysis. However, we controlled for the shortcomings of scanners with FDG-PET only in the regression model so that additional studies reporting results from smaller lesions and from regions with endemic infectious lung disease could be explored.

Although the accuracy of FDG-PET/CT is superior to the accuracy of FDG-PET only, we included both modalities because they are still in use in the United States and elsewhere, and, as previously stated, we did not find a significant difference in specificity based on these 2scanner types. To avoid selection bias, this meta-analysis attempted to broadly review studies reporting use of FDG-PET to characterize lung nodules and examined studies in which FDG-PET/CT was compared with other imaging modalities for the diagnosis and staging of lung cancer. We controlled for study heterogeneity using a random-effects regression model with a number of clinically important covariates; however, residual confounding may still be present.

In this large meta-analysis, the observed association between lower specificity and endemic infectious lung disease appeared robust across sensitivity analyses. We found that studies that fully used the metabolic and anatomic information from a FDG-PET/CT scan in a semiquantitative interpretation (rather than a simplified dichotomizing of a standard uptake

value) demonstrated improved test accuracy. Even in areas of endemic disease, robust reading methods by experienced readers generated accurate scans.[26,27]

Until this expertise and method is more uniformly applied among scan readers, FDG-PET for the diagnosis of lung cancer in patients who reside in a region with significant endemic infectious lung disease should be recognized as having lower specificity (approximately 61%) than previously reported. Knowledge of this reduction in specificity should limit the use of FDG-PET to diagnose lung cancer unless substantial institutional expertise in FDG-PET interpretation has been proven. Should low-dose CT screening for lung cancer become the diagnostic standard, knowledge of FDG-PET/CT performance is even more critical because the vast majority of indeterminate lung nodules detected through screening are benign.[100]

Conclusions

The accuracy of FDG-PET for diagnosing lung nodules was extremely heterogeneous. Use of FDG-PET/CT was less specific in diagnosing malignancy in populations with endemic infectious lung disease compared with nonendemic regions. These data do not support the use of FDG-PET to diagnose lung cancer in endemic regions unless an institution achieves test performance accuracy similar to that found in nonendemic regions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Authors wish to thank Rebecca Jerome, MLS, MPH research librarian Vanderbilt University Medical Center, for her uncompensated assistance in the literature review. We also wish to thank the reviewers for their insight and assistance in making our manuscript stronger. Drs. Grogan and Deppen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

This work has been supported by R03HS021554-01 from AHRQ (E.L.G.). This work was also supported by: Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service Career Development Award 10-024 (E.L.G.), NIH/NCI K07 CA172294 (M.C.A.), Vanderbilt Institute for Clinical and Translational Research grant, UL1TR000011 from NCATS/NIH (REDCap database), the lung SPORE CA90949 (P.P.M.), and a EDRNU01 CA152662 (P.P.M.).

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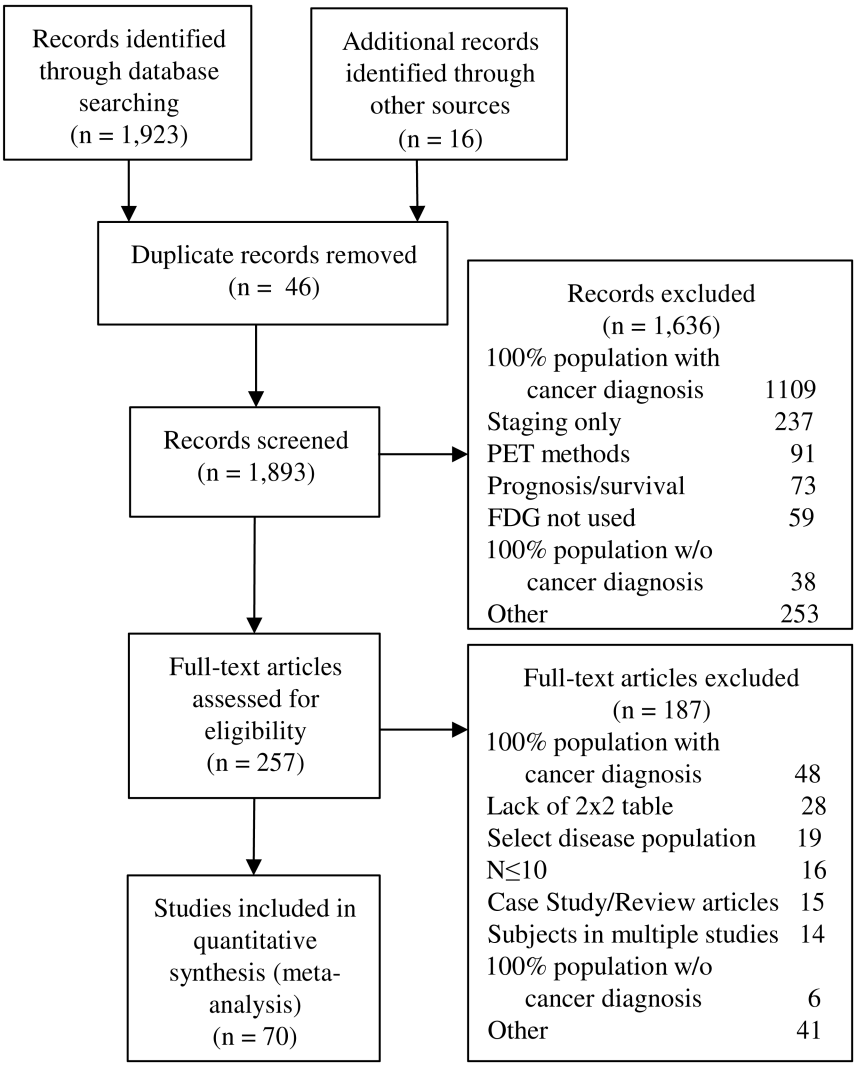

Figure 1. Literature search PRISMA consort diagram

PRISMA diagram of systematic review of eligible studies (Preferred Reporting Items for Systematic reviews and Meta-Analyses). The same study could be excluded for multiple reasons.

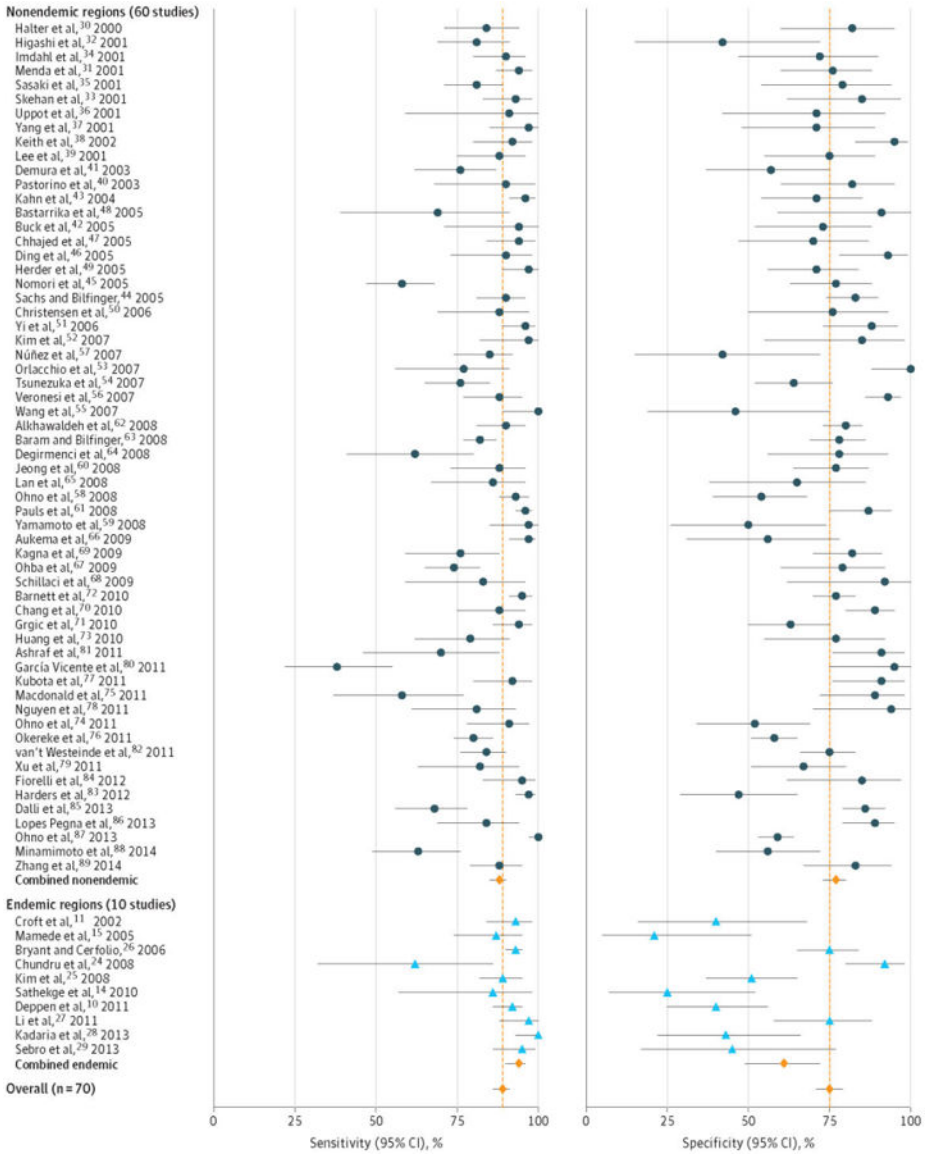

Figure 2. Individual study estimates of sensitivity and specificity with average adjusted results

Forest plot reporting individual study sensitivity and specificity. Endemic infectious lung disease with are in blue and nonendemic studies are in black. Average adjusted results for endemic studies (n=10), non-endemic studies (n=60) and all studies combined (n=70) sensitivity and specificity are in red. Error bars are 95% confidence intervals for each study's corresponding test characteristic.

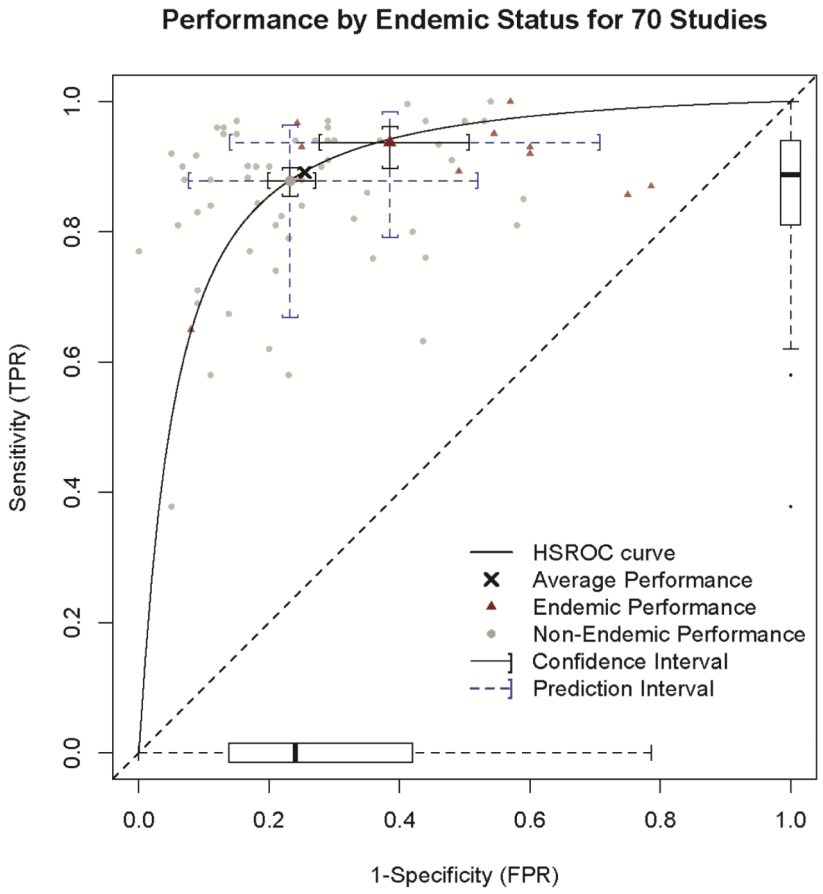

Figure 3. Performance by endemic status for 70 studies

Hierarchical Summary Receiver Operator (HSROC) Curve with operating points for endemic and nonendemic infectious lung disease studies and 95% Confidence and Prediction Intervals for those operating points. The horizontal box and whiskers plot represents the distribution of study specificity, and the vertical box and whiskers plot represents the distribution of study sensitivity. The box limits are the closest data point to the interquartile range of 25 and 75% with the bar being the median (50%). Error bar whiskers represent the data point closest to 1.5 times the interquartile range and the dots outside the whiskers represent outlier study values.