



Diagnostic accuracy and safety of cone-beam computed tomography-guided percutaneous transthoracic lung biopsy: an updated systematic review and meta-analysis

Yoojin Nam^{1,2}

Hye Ree Cho¹

Eunji Kim¹

Pa Hong¹

¹Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Department of Radiology, Changwon, Republic of Korea

²University of Ulsan College of Medicine, Seoul, Republic of Korea

PURPOSE

To update the pooled diagnostic accuracy and safety of cone-beam computed tomography (CBCT)-guided percutaneous transthoracic needle biopsy (PTNB) for pulmonary lesions.

METHODS

PubMed, Embase, and Cochrane CENTRAL were searched through April 2026 for studies of CBCT-guided PTNB including ≥ 10 patients. Sensitivity and specificity were pooled using a bivariate random-effects model. Complication rates (pneumothorax and pulmonary hemorrhage, encompassing both clinically significant hemoptysis and radiographic perilesional change) were pooled using generalized linear mixed models. Heterogeneity and publication bias were assessed. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies, used the Quality Assessment of Diagnostic Accuracy Studies 2, and was prospectively registered in PROSPERO (CRD420261370382).

RESULTS

Twenty-four studies were eligible (k: 22 with extractable 2×2 data; n = 3,681; 2010–2026). Pooled sensitivity was 92.2% [95% confidence interval (CI): 90.4–93.7] and pooled specificity was 96.7% (95% CI: 94.3–98.2). The summary receiver operating characteristic area under the curve was 0.974. Pneumothorax incidence was 18.4% [95% CI: 15.5–21.7; prediction interval (PI) 8.3–35.8%]. Hemorrhage incidence (k: 19) pooled at 6.1% (95% CI: 3.5–10.6); high heterogeneity (I^2 : 90.9%) reflected variation in outcome definitions.

CONCLUSION

CBCT-guided PTNB demonstrates high diagnostic accuracy for pulmonary lesions. The pooled specificity should be interpreted as a plausible upper-bound estimate because of universal differential verification bias across the included studies.

CLINICAL SIGNIFICANCE

The wide pneumothorax PI (8–36%) indicates that complication rates may vary substantially across centers despite the precise pooled estimate.

KEYWORDS

Cone-beam computed tomography, percutaneous transthoracic needle biopsy, diagnostic accuracy, sensitivity, specificity, pneumothorax, meta-analysis

Handling editor: Onur Taydas

Corresponding author: Pa Hong

E-mail: honeia11@gmail.com

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Percutaneous transthoracic needle biopsy (PTNB) is a standard diagnostic procedure for pulmonary lesions suspicious for malignancy. Image guidance is critical for accurate needle placement and safe tissue acquisition. Conventional multi-detector computed tomography (CT) and CT fluoroscopy have long been the primary guidance modalities for PTNB. Over the past two decades, cone-beam CT (CBCT), also known as C-arm CT or flat-panel detector CT, has emerged as an alternative guidance modality for percutaneous lung biopsy performed in the interventional radiology suite.

CBCT systems, integrated into angiographic suites, generate intraprocedural volumetric images using a flat-panel detector mounted on a C-arm gantry. These systems offer several features relevant to percutaneous lung biopsy, including three-dimensional (3D) needle path planning with virtual trajectory overlay, augmented fluoroscopy with real-time needle tracking, respiratory phase matching, and the ability to perform the entire procedure within a single interventional suite without patient transfer. Advanced CBCT-based technologies, including positron emission tomography (PET)-CT

fusion guidance, laser-guided needle placement, and electromagnetic navigation, have become more widely adopted since the mid-2010s and have extended biopsy feasibility for small or peripheral lesions.

Yan et al.¹ published the only existing meta-analysis of CBCT-guided lung biopsy in 2017, synthesizing data from eight studies published through 2016. Since then, more than 20 additional primary studies have been published,²⁻²³ more than doubling the available evidence base and adding data on CBCT technologies that were not available at the time of the previous review. An updated systematic review is warranted to incorporate this expanded evidence, characterize the contemporary CBCT technology landscape represented in the literature, and provide more precise pooled estimates with narrower confidence intervals (CIs).

The purpose of this systematic review and meta-analysis was to update and extend the meta-analysis by Yan et al.¹ by determining the pooled diagnostic accuracy (sensitivity and specificity) and safety outcomes (pneumothorax and hemorrhage rates) of CBCT-guided PTNB for pulmonary lesions using all available evidence through 2026.

choscopic approaches, mediastinal targets without pulmonary parenchymal involvement, non-human subjects, or lacked diagnostic outcome data.

Reference standard

The reference standard for final diagnosis included surgical pathology, clinical and radiological follow-up of at least six months confirming benign stability or malignant progression, or repeat biopsy providing definitive tissue diagnosis.

Information sources and search strategy

PubMed and Embase were searched from inception through April 6, 2026, without language or date restrictions. Search strategies combined controlled vocabulary (MeSH/Emtree) with free-text synonyms for CBCT and lung biopsy. The Embase search applied the [embase]/lim filter to exclude MEDLINE duplicates. A confirmatory Cochrane Central Register of Controlled Trials (CENTRAL) search (Issue 3 of 12, March 2026) was conducted on April 22, 2026, using the same conceptual blocks and yielded seven records, none of which met eligibility criteria beyond the PubMed- and Embase-derived pool. Full search strategies, including the CENTRAL confirmatory search, are provided in Supplementary Material 1.

Study selection

Records were deduplicated using PubMed Identifier (PMID) matching, where available, and normalized-title matching otherwise. The full deduplication workflow, including sample size at each step, is provided in Supplementary Material 2.

Title and abstract screening was performed independently by Reviewer 1 and Reviewer 2 using predefined exclusion codes E1–E5. Inter-rater agreement was 93.9% (845 of 900 records; Cohen's κ : 0.572), calculated on the original 900-record PubMed and Embase pool before the post-hoc Cochrane CENTRAL augmentation. The six CENTRAL-derived records were subsequently classified by both reviewers with complete agreement and added without recomputation. Fifty-five disagreements were resolved by consensus following full-text review.

For inclusion in the qualitative synthesis, studies were required to report diagnostic accuracy or complication data from a CBCT-guided PTNB cohort of at least 10 patients. Inclusion in the bivariate meta-analysis

Main points

- Across 22 studies (3,681 patients; 2010–2026), cone-beam computed tomography (CBCT)-guided percutaneous transthoracic needle biopsy achieved a pooled sensitivity of 92.2% [95% confidence interval (CI): 90.4%–93.7%] and a pooled specificity of 96.7% (95% CI: 94.3%–98.2%) using a bivariate Reitsma random-effects model, with a summary receiver operating characteristic area under the curve of 0.974.
- Pooled procedural complication rates were 18.4% for pneumothorax (95% CI: 15.5–21.7) and 6.1% for pulmonary hemorrhage (95% CI: 3.5–10.6), consistent with established safety profiles for CT-guided biopsy.
- Because all included studies shared a universal differential verification design (Quality Assessment of Diagnostic Accuracy Studies-2 Domain 4 rated high-risk in 22 of 22 studies), pooled specificity should be interpreted as a plausible upper-bound estimate rather than an unbiased measure.
- Compared with the only prior meta-analysis (Yan et al. 2017, 8 studies), this review almost triples the primary evidence base and incorporates contemporary CBCT navigation technologies introduced after 2016, including augmented fluoroscopy, positron emission tomography-CT fusion, laser guidance, three-dimensional virtual navigation, and metabolic single-photon emission computed tomography/CT comparators.

Methods

Protocol and registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies guidelines. The review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD420261370382; registered April 15, 2026). Because this study was a systematic review and meta-analysis of previously published aggregate-level data from studies that had obtained their own ethical approvals, institutional review board approval and informed consent were not required, and no new human participants were involved.

Eligibility criteria

Studies were eligible if they reported diagnostic accuracy (sensitivity, specificity, diagnostic yield, or reconstructable 2 × 2 table data) or complication rates for PTNB performed under CBCT guidance in 10 or more patients with pulmonary lesions. Synonyms for CBCT included CBCT, C-arm CT, flat-panel detector CT, and proprietary names (DynaCT, XperCT, Innova CT, Artis zeego). Studies were excluded if they exclusively involved bron-

sis additionally required a reconstructable 2×2 contingency table. Of 78 full-text records, 24 met the criteria for qualitative synthesis, and 22 met the criteria for bivariate analysis. Two studies were retained for narrative synthesis only: Huang et al.,²⁴ a Chinese-language journal article not indexed in MEDLINE for which full-text retrieval was unsuccessful, and Floridi et al.,²⁵ which provided insufficient cell data for 2×2 reconstruction. The complete screening consensus record is provided in Supplementary Material 3.

Data extraction

For each study, the following data were extracted: 2×2 table data [true positives, false positives (FPs), false negatives, and true negatives (TNs)] using a three-level hierarchy: (1) directly reported values, (2) sensitivity and specificity with total sample size, and (3) diagnostic yield with sample size and prevalence. Studies for which none of these approaches permitted reconstruction of a 2×2 contingency table were retained for narrative synthesis rather than included in the bivariate meta-analysis.

Attempts to contact authors for missing cell data were not pursued because the two narrative-only studies (Huang et al.,²⁴ and Floridi et al.,²⁵) represented a small proportion of the available evidence relative to the primary bivariate analysis (k : 22; N : 3,681), and the primary pooled estimates remained robust following exclusion under the intention-to-diagnose (ITD)-only sensitivity analysis reported in the Results section. This decision is acknowledged as a limitation in the Discussion.

Additional variables included study design, country, sample size, lesion characteristics, needle type, CBCT system, and complication rates. Data extraction was performed independently by two reviewers (Reviewer 1 and Reviewer 2). Following consensus reconciliation of initial disagreements, a cell-level audit was performed against the source PDFs for all 88 cells (22 studies $\times$ 4 cells), yielding a post-consensus match rate of 100% (88 of 88).

Risk of bias assessment

Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool with signaling questions tailored to CBCT-guided biopsy. Two reviewers (Reviewer 1 and Reviewer 2) independently rated all four domains, with Reviewer 2 blinded to Reviewer 1's ratings until consensus. This independent, blinded

dual-review process was completed for all 22 included studies.

Aggregate item-level inter-reviewer agreement was 88.6% (78 of 88 ratings) with perfect agreement in Domains 2–4 (Cohen's κ : 1.000). All 10 disagreements occurred in Domain 1 (patient selection) and were resolved by consensus according to a prespecified rule requiring the explicit use of "consecutive" or "random sampling" terminology for a low-risk rating. Detailed inter-reviewer agreement metrics, including the comparison of Cohen's κ and Gwet's AC1 for Domain 1, are provided in Supplementary Material 4.

All studies were rated as having a high-risk of bias in Domain 4 because of universal differential verification bias and were retained in the primary analysis regardless of risk-of-bias rating. Study-level QUADAS-2 ratings and a supporting rationale are provided in Supplementary Material 5.

Statistical analysis

Non-diagnostic biopsy results were handled using an ITD approach whenever primary-study reporting permitted reclassification. Non-diagnostic specimens were classified as test-negative, with the final diagnosis (determined by repeat biopsy, surgery, or clinical follow-up) used as the reference-standard classification. This ITD approach was fully applied to Cho et al.²¹

In four studies (Zou et al.,²⁰ Rotolo et al.,¹¹ Lee et al.,¹² Floridi et al.⁸), only per-protocol 2×2 tables were reported, and final reference-standard outcomes for the indeterminate subset were unavailable. Consequently, per-protocol counts were used directly, and ITD reclassification could not be performed. A post-hoc sensitivity analysis restricted to the 18 studies for which a consistent ITD approach was applicable is reported in Sensitivity analyses section (full rationale and timing are provided in Supplementary Material 6).

Sensitivity and specificity were pooled using the bivariate random-effects model of Reitsma (mada package in R). Summary receiver operating characteristic (SROC) curves were generated. Threshold effects were assessed using the Spearman correlation between logit-transformed sensitivity and FP rate. A continuity correction of 0.5 was applied to cells with zero counts before logit transformation.

Complication-rate proportion outcomes (pneumothorax and pulmonary hemorrhage/hemoptysis) were pooled using generalized linear mixed models (GLMMs) with

logit transformation and Hartung–Knapp CI adjustment. Diagnostic yield was summarized only at the study level because primary-study denominators (technical-success-only vs. ITD) could not be standardized across studies.

Between-study heterogeneity was quantified for each pooled outcome using Cochran's Q test (with P value), the I^2 statistic, and the τ^2 variance estimate, with 95% prediction intervals (PIs) reported alongside the pooled estimates. I^2 and τ^2 were estimated using the restricted maximum likelihood (REML) estimator implemented in metafor 4.8-0. The REML-based I^2 may yield small non-zero values even when Cochran's Q is not statistically significant, reflecting differences between REML variance-component estimation and the closed-form DerSimonian–Laird estimator.

Random-effects models were used throughout because Cochran's Q was significant for sensitivity, pneumothorax, and hemorrhage. Although Cochran's Q was not significant for specificity, random-effects modeling was retained to avoid artificially narrow CIs from a fixed-effect model applied to data constrained by the specificity ceiling effect (zero FPs in 19 of 22 studies) and by universal differential verification bias.

Publication bias was assessed using the Deeks funnel plot asymmetry test. To complement this analysis, the Duval and Tweedie trim-and-fill procedure was applied on the univariate logit-transformed scale to sensitivity, specificity, pneumothorax, and hemorrhage outcomes. A univariate approach was used because trim-and-fill methods for bivariate Reitsma models are not well established. Diagnostic yield was excluded because of denominator heterogeneity. P values are reported to three decimal places, and values below 0.001 are reported as $P < 0.001$.

Subgroup analyses specified in the PROSPERO protocol included pre- vs. post-2017 publications and navigation-enhanced vs. conventional CBCT. Inferential pooled bivariate sensitivity and specificity subgroup comparisons were not performed because of sparse and clinically heterogeneous data. Specifically, patient-level information on needle-pass counts, targeting workflow, and lesion-size distributions required for stratified bivariate pooling was not consistently available, and temporal stratification would have confounded the technology era with the reporting-standard era. Consequently, subgroup descriptions presented in

the Results are exploratory and intended for hypothesis generation only.

Prespecified sensitivity analyses included exclusion of the single largest study (Lee et al.⁷) and restriction to publications from 2017 onward. A post-hoc sensitivity analysis restricted to the 18 studies for which a consistent ITD approach was applicable was added during manuscript revision. The post-hoc ITD-only analysis, Cochrane CENTRAL confirmatory search, and clarification of subgroup framing were each recorded in the PROSPERO amendment log (Supplementary Material 6), with timing and rationale documented for each amendment. All analyses were performed in R version 4.5.3 (R Foundation for Statistical Computing, Vienna, Austria) using mada (0.5.11), meta (8.2-1), and metafor (4.8-0).

Results

Study selection

The search identified 1,057 records (PubMed: 224; Embase: 826; Cochrane CENTRAL confirmatory search: 7). After removal of 151 duplicate records (11 intra-Embase duplicates silently collapsed during import, 139 PubMed–Embase cross-database overlaps identified by PMID matching and title comparison, and 1 CENTRAL–Embase overlap), 906 unique records proceeded to screening.

Title and abstract screening excluded 828 records: 252 for lacking CBCT guidance (E1), 296 for bronchoscopic approaches (E2, including 1 Cochrane CENTRAL electromagnetic-navigation bronchoscopy record), 137 for non-lung targets (E3), 69 for lacking diagnostic outcomes (E4, including 5 CENTRAL trial-registration records), and 74 for publication type (E5).

Seventy-eight records underwent full-text assessment. Of these, 54 were excluded under the predefined primary-reason-per-study convention (48 excluded during initial full-text screening and 6 additional exclusions confirmed during post-screening dual-reviewer consensus: IDs 2, 55, 88, 160, 165, 180). The most frequent primary reasons for exclusion were lack of extractable diagnostic accuracy data or complication-only reporting (F6), overlapping patient cohorts (F7), and inaccessible full text (F5). Per-record primary exclusion codes and rationales for all 54 excluded studies are provided in Supplementary Material 3, including records resolved through FLAG consensus adjudication (IDs 54, 188, 268, 458, 549).

Twenty-four studies met the eligibility criteria for qualitative synthesis. Of these, 22 provided extractable 2×2 contingency table data for the bivariate meta-analysis (Figure 1). The remaining two studies (Huang et al.²⁴ and Floridi et al.²⁵) reported procedural or complication data but lacked sufficient information to reconstruct a 2×2 contingency table; the per-patient final reference-standard outcomes required to populate the FP and TN cells could not be extracted from the available reports.

Study characteristics

Characteristics of the 22 studies²⁻²³ included in the bivariate analysis are summarized in Table 1. The studies were published between 2010 and 2026 and originated from Korea (n = 8), China (n = 5), Italy (n = 4), Taiwan (n = 2), Thailand (n = 1), Spain (n = 1), and the Netherlands (n = 1). Sample sizes ranged from 26 to 1,089 patients (total n = 3,681). Two studies were prospective, and 20 were retrospective.

CBCT systems included Siemens (Siemens Healthineers, Forchheim, Germany; Artis zeego/DynaCT/zee, n = 15), Philips (Philips Healthcare, Best, the Netherlands; Allura XperCT/XperGuide, n = 6), and both systems (n = 1). Core needle biopsy was used in 20 studies, fine-needle aspiration in 1 study, and mixed techniques in 1 study.

Advanced CBCT technologies represented in the included studies comprised PET-CT fusion guidance (n = 2), augmented fluoroscopy navigation (n = 1), laser-guided needle placement (n = 1), 3D virtual navigation overlay (n = 2), 3D polyline-guided targeting (n = 1), and metabolic single-photon emission CT/CT comparator (n = 1).

Diagnostic accuracy

The bivariate Reitsma model yielded a pooled sensitivity of 92.2% (95% CI: 90.4–93.7%; 95% PI: 85.7–95.9%) and a pooled specificity of 96.7% (95% CI: 94.3–98.2%; 95% PI: 91.0–98.9%, bivariate Reitsma) (Table 2, Figure 2); the corresponding univariate REML logit PI of 90.7–99.0% in Table 3). These wider PIs, which reflect the expected variability in a future study rather than uncertainty around the pooled estimate, indicate that a new single-center cohort could plausibly report sensitivity in the mid-80% range or specificity in the low-90% range despite the precise pooled estimates.

The SROC area under the curve (AUC) was 0.974 (Figure 3). Between-study heteroge-

neity was moderate for sensitivity (I^2 : 57.4%) and nominally absent for specificity (I^2 : 0.0%); the bivariate I^2 was low according to the Zhou and Dendukuri approach.

The absence of observed heterogeneity for specificity should not be interpreted as evidence of true cross-study homogeneity. Nineteen of 22 studies reported zero FP counts (total FP: 4 across all studies; per-study FP data are provided in Supplementary Material 7), and all 22 studies shared the same differential verification structure (QUADAS-2 Domain 4 rated high-risk in all studies). This verification bias operates uniformly and structurally compresses between-study variance at the specificity ceiling.

The Spearman threshold-effect test has limited power to detect modest threshold shifts with k: 22. In the present dataset, the highly concentrated FP distribution further reduces detectable variation. Accordingly, the observed Spearman rho of -0.002 ($P = 0.994$) is consistent with the absence of a detectable threshold effect but does not exclude small threshold-related effects.

Per-study sensitivity and specificity estimates with 95% Clopper–Pearson CIs are provided in Supplementary Material 7. Per-study QUADAS-2 ratings and a per-domain rationale are provided in Supplementary Material 5.

Diagnostic yield

Study-level diagnostic yield across the 24 studies included in the qualitative synthesis ranged from 71.9% to 99.3%. A pooled diagnostic-yield GLMM was not performed because yield denominators were reported inconsistently across studies (technical-success-only vs. ITD) and could not be standardized to a common definition based on the available data. Study-level yields for all 24 included studies, together with the yield-denominator convention used in each primary study, are provided in Supplementary Material 3.

Sensitivity analyses

Two sensitivity analyses were performed. The first, prespecified in the PROSPERO protocol, excluded the largest study (Lee et al.⁷ n = 1,089, representing 30% of the pooled sample). This analysis yielded a sensitivity of 91.8%, specificity of 96.3%, and AUC of 0.977 (k: 21; n = 2,592), demonstrating that the pooled estimates were robust to single-study influence.

In the bivariate model, Lee et al.⁷ contributed approximately 17.2% of the in-

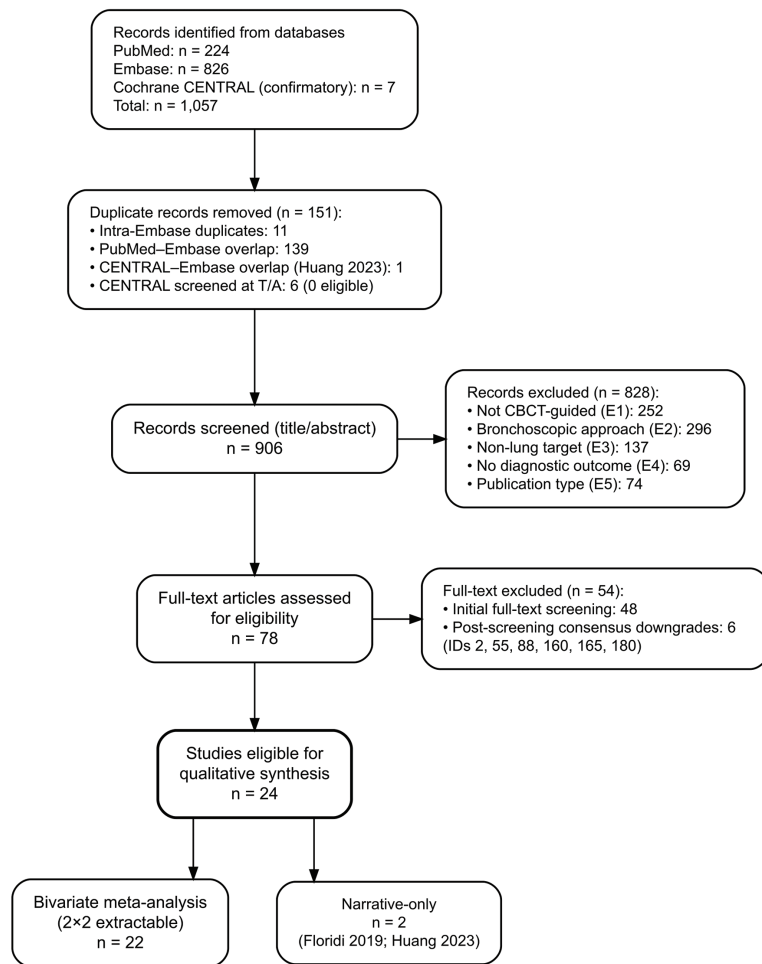


Figure 1. PRISMA flow diagram. PRISMA-DTA 2020 flow diagram for the systematic review of CBCT-guided percutaneous transthoracic lung biopsy, showing study identification (n = 1,057), deduplication (n = 906 screened), title and abstract exclusions (n = 828), full-text assessment (n = 78), full-text exclusions (n = 54), and final inclusion in the qualitative synthesis (n = 24) and bivariate meta-analysis (n = 22). Per-record primary exclusion codes are listed in Supplementary Material 3. CBCT, cone-beam computed tomography.

verse-variance weight for logit sensitivity but only 3.5% for logit specificity. This asymmetry was attributable to the small benign denominator (TN + FP = 323). Leave-one-out recalculation of specificity heterogeneity after exclusion of Lee et al.⁷ left I^2 unchanged at 0.0%, indicating that the near absence of specificity heterogeneity is driven by the structural FP distribution rather than by any single large study.

The second analysis, added during manuscript revision to address non-diagnostic-handling heterogeneity, was restricted to the 18 studies in which a consistent ITD approach could be applied. Four studies (Zou et al.,²⁰ Rotolo et al.,¹¹ Lee et al.,¹² and Floridi et al.⁸) were excluded because they reported per-protocol 2 × 2 tables with indeterminate cases removed. This analysis yielded a sensitivity of 92.3% (95% CI: 90.4–93.9), specificity of 96.2% (95% CI: 93.2–98.0), and AUC of 0.973 (k: 18; n = 3,054).

The close agreement between these ITD-only estimates and the primary analysis (Δ sensitivity +0.1 percentage points, Δ specificity –0.5 percentage points, Δ AUC –0.001) indicates that heterogeneity in the handling of non-diagnostic specimens had minimal impact on pooled diagnostic accuracy.

Complications

Pneumothorax was the most common procedural complication. The pooled pneumothorax incidence across the 22 studies included in the bivariate analysis was 18.4% (95% CI: 15.5–21.7; 95% PI: 8.3–35.8%) using GLMM with logit transformation and Hartung–Knapp CI adjustment. Study-level incidence ranged from 7.8% to 38.8%.

Pulmonary hemorrhage or hemoptysis was reported in 19 of 22 studies (3 studies did not report this outcome: Cheung et al.,³ Akkkrisee and Hongsakul,¹⁴ and Floridi et

al.⁸). Among reporting studies, the pooled incidence was 6.1% (95% CI: 3.5–10.6; 95% PI: 0.5–47.0%), with study-level rates ranging from 0% to 45.7%.

The highest hemorrhage rate (45.7%) was reported by Lee et al.⁴ for a single-center fine-needle-aspiration cohort (n = 94) in which any CBCT-detected perilesional hemorrhagic change was counted rather than only clinically significant hemoptysis. Because this definition was not applied consistently across studies, the wide hemorrhage PI (I^2 : 90.9%, between-study τ : 1.20 on the logit scale; these are GLMM estimates, and the univariate REML re-estimates in Table 3 give I^2 : 93.0% and τ^2 : 1.037, the difference reflecting estimator-specific variance components) likely reflects this heterogeneity rather than true cross-study variation in procedural bleeding risk.

Per-study pneumothorax rates (k: 22) and hemorrhage rates (k: 19) are provided in Supplementary Material 8. Chest tube insertion was reported inconsistently across studies. Explicit rates were documented in only 2 of the 24 eligible studies (Cheung et al.:³ 1.4%; Akkkrisee:¹⁴ 3.0%); therefore, pooled estimation was not performed. This reporting inconsistency is acknowledged as a review-level limitation.

Heterogeneity and publication bias

Cochran's Q test, together with I^2 , τ^2 , and 95% PIs, is summarized by outcome in Table 3. Sensitivity demonstrated significant heterogeneity (Q: 48.4, df: 21, $P < 0.001$; I^2 : 50.2%; PI: 84.7–96.4%), consistent with the Reitsma bivariate I^2 estimate of 57.4%.

Specificity was nominally homogeneous on the univariate scale (Q: 18.0, df: 21, $P = 0.646$; I^2 : 11.5%). However, for the structural reasons discussed above (specificity ceiling effect and universal differential verification bias), this finding should not be interpreted as evidence of true cross-study homogeneity.

Pneumothorax showed substantial heterogeneity (Q: 89.0, df: 21, $P < 0.001$; I^2 : 79.9%; PI: 8.6–36.7%), consistent with the GLMM-derived PI (8.3–35.8%) reported in the Complications section above. Hemorrhage demonstrated extreme heterogeneity (Q: 201.8, df: 18, $P < 0.001$; I^2 : 93.0%; PI: 0.9–43.8%), consistent with the GLMM-derived I^2 of 90.9% reported in the Complications section above. This heterogeneity is interpreted as definition variability rather than true between-study variation in clinically significant bleeding (see Discussion).

Table 1. Characteristics of the 22 studies included in the bivariate meta-analysis. Per-study sensitivity and specificity with 95% Clopper–Pearson confidence intervals are provided in Supplementary Material 7

Author	Year	Country	n	TP	FP	FN	TN	Design	CBCT system	Needle
Hwang et al. ²	2010	Korea	26	16	1	1	8	R	Siemens	CNB
Cheung et al. ³	2011	Korea	74	48	0	5	21	R	Siemens	Mixed
Lee et al. ⁴	2012	Korea	94	54	0	4	36	R	Siemens	FNA
Choi et al. ⁵	2012	Korea	99	69	0	3	27	R	Siemens	CNB
Braak et al. ⁶	2012	Netherlands	84	63	0	7	14	P	Philips	CNB
Lee et al. ⁷	2014	Korea	1089 [†]	733	0	33	323	R	Both	CNB
Floridi et al. ⁸	2014	Italy	95	68	0	7	20	R	Siemens	CNB
Cheng et al. ⁹	2015	Taiwan	35	32	0	1	2	R	Philips	CNB
Jiao et al. ¹⁰	2016	China	99	77	2	1	19	R	Siemens	CNB
Rotolo et al. ¹¹	2016	Italy	103	64	0	10	29	R	Philips	CNB
Lee et al. ¹²	2018	Korea	268	162	0	4	102	R	Siemens	CNB
Fior et al. ¹³	2019	Italy	375	283	0	40	52	R	Philips	CNB
Gulias-Soidan et al. ¹⁵	2020	Spain	98	87	0	8	3	R	Siemens	CNB
Akkakrisee and Hongsakul ¹⁴	2020	Thailand	100	70	0	5	25	R	Philips	CNB
Fontana et al. ¹⁶	2021	Italy	84	69	0	4	11	R	Siemens	CNB
Ren et al. ¹⁸	2022	China	137	101	1	6	29	R	Siemens	CNB
Yang et al. ¹⁹	2022	China	135	98	0	1	36	R	Siemens	CNB
Han et al. ¹⁷	2022	Korea	122	85	0	7	30	R	Siemens	CNB
Cho et al. ²¹	2024	Korea	245	206	0	28	11	R	Siemens	CNB
Zou et al. ²⁰	2024	China	161	129	0	10	22	R	Siemens	CNB
Chen et al. ²²	2026	Taiwan	77	56	0	4	17	P	Philips	CNB
Yuan et al. ²³	2026	China	81	50	0	5	26	R	Siemens	CNB

[†]Lee et al.⁷ originally reported a cohort of 1,108 patients; the present analysis uses the primary diagnostic-accuracy subset (n = 1,089) after exclusion of non-evaluable cases as defined in that report.

TP, true positive; FP, false positive; FN, false negative; TN, true negative; R, retrospective study design; P, prospective study design; CBCT, cone-beam computed tomography; CNB, core needle biopsy; FNA, fine-needle aspiration.

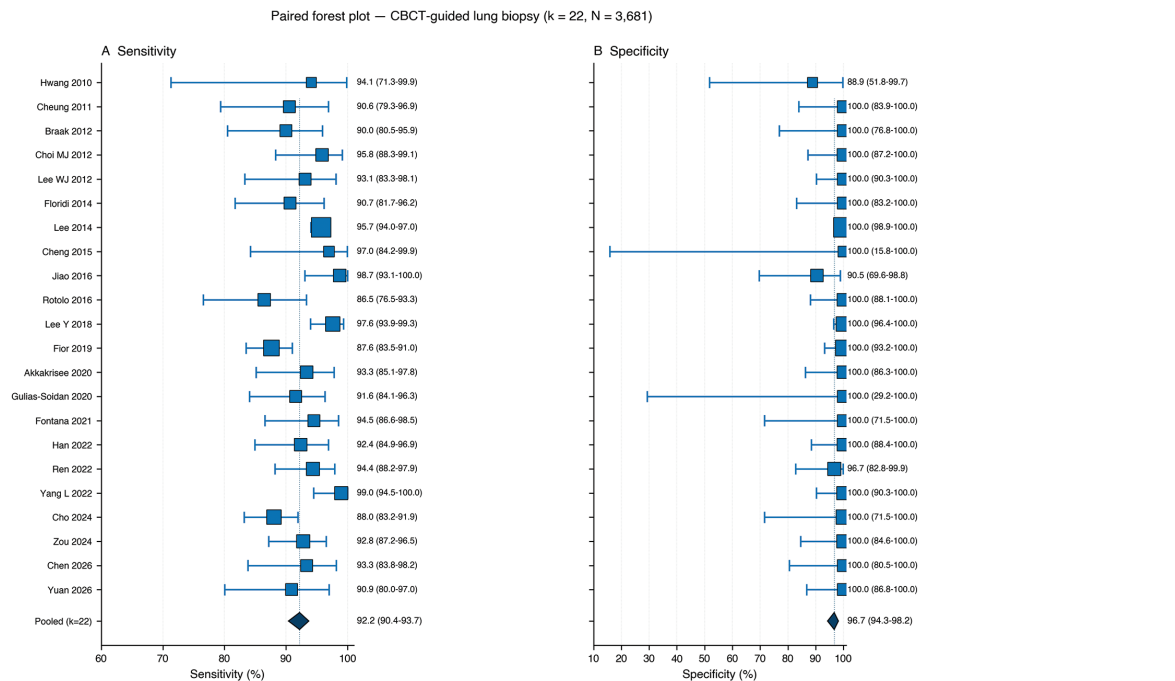


Figure 2. Forest plot—sensitivity and specificity. Paired forest plot of per-study sensitivity (left) and specificity (right) with 95% Clopper–Pearson confidence intervals (CIs), pooled using the bivariate Reitsma random-effects model (k: 22; n = 3,681). Squares are scaled by $\sqrt{n}$. Pooled sensitivity: 92.2% (95% CI: 90.4–93.7); pooled specificity: 96.7% (95% CI: 94.3–98.2). Left-truncated specificity CIs (Cheng et al.⁹ and Gulias-Soidan et al.¹⁹) are indicated by arrowheads. CBCT, cone-beam computed tomography.

The Deeks funnel plot asymmetry test (Figure 4) was significant overall ($P < 0.001$) and was confined to pre-2017 publications ($P = 0.001$; post-2017 $P = 0.279$). To comple-

ment the Deeks test, the Duval and Tweedie trim-and-fill procedure was applied on the univariate logit-transformed scale to each pooled outcome (Table 3). Trim-and-fill imputed 10 left-sided studies for sensitivity (adjusted estimate 89.5%, 95% CI: 86.7–91.8%) and 7 left-sided studies for specificity (adjusted estimate 94.9%, 95% CI: 91.5–97.0%). For pneumothorax, 2 right-sided studies were imputed (adjusted estimate 20.2%, 95% CI: 16.9–24.0%), whereas 4 right-sided studies were imputed for hemorrhage (adjusted estimate 10.0%, 95% CI: 6.2–15.7%).

Because trim-and-fill methods are not well developed for bivariate Reitsma models, these results are presented as robustness analyses rather than replacements for the primary bivariate estimates. The downward adjustment of sensitivity and specificity is consistent with the Deeks asymmetry observed among pre-2017 studies. Accordingly, the trim-and-fill estimates are interpreted as plausible lower bounds rather than definitive corrections.

Comparison with Yan et al.¹

The meta-analysis conducted by Yan et al.¹ included 8 studies and reported a pooled sensitivity of 96% (95% CI: 93–98%) and specificity of 100% (95% CI: 91–100%). All 8 studies from that review were included in the present analysis.

The current update adds 14 studies to the bivariate model, almost tripling the evidence base. The lower pooled sensitivity observed in the present review (92.2% vs. 96%) likely reflects the inclusion of larger and more heterogeneous study populations, as well as studies with different lesion size distributions and CBCT technology generations.

Table 2. Pooled diagnostic accuracy estimates from the bivariate Reitsma model (k: 22, n = 3,681)

Metric	Estimate	95% CI
Sensitivity	92.2%	90.4–93.7%
Specificity	96.7%	94.3–98.2%
AUC (SROC)	0.974	—
LR+	28.3	—
LR–	0.080	—
DOR	351.5	—
I ² (sensitivity)	57.4%	—
I ² (specificity)	0.0%	—
Pneumothorax	18.4%	15.5–21.7%
Hemorrhage	6.1%	3.5–10.6%

CI, confidence interval; AUC, area under the curve; SROC, summary receiver operating characteristic curve; LR+, positive likelihood ratio; LR–, negative likelihood ratio; DOR, diagnostic odds ratio.

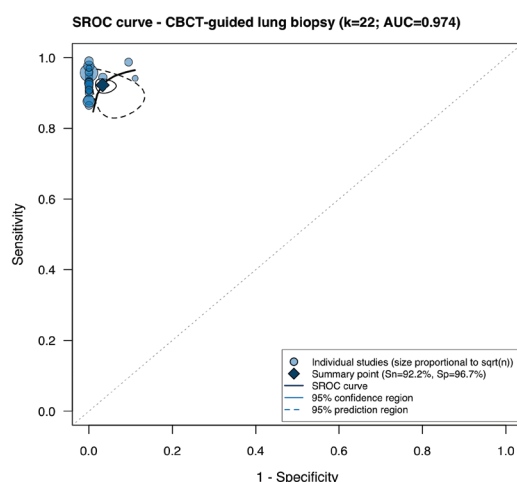


Figure 3. SROC curve. SROC curve from the bivariate Reitsma model. The summary point (solid diamond), 95% confidence region (solid ellipse), and 95% prediction region (dashed ellipse) are shown. Individual study points are scaled by $\sqrt{n}$. The SROC area under the curve: 0.974. SROC, summary receiver operating characteristic; CBCT, cone-beam computed tomography.

Table 3. Heterogeneity (Cochran's Q, I², τ^2) and trim-and-fill publication-bias analyses for pooled outcomes

Outcome	k	Q	df	p (Q)	I ² (%)	τ^2	95% PI (%)	Imputed studies (side)	Adjusted estimate (%)	Adjusted 95% CI (%)
Sensitivity	22	48.4	21	< 0.001	50.2	0.127	84.7–96.4	10 (left)	89.5	86.7–91.8
Specificity	22	18.0	21	0.646	11.5	0.220	90.7–99.0	7 (left)	94.9	91.5–97.0
Pneumothorax	22	89.0	21	< 0.001	79.9	0.178	8.6–36.7[‡]	2 (right)	20.2	16.9–24.0
Hemorrhage [†]	19	201.8	18	< 0.001	93.0	1.037	0.9–43.8	4 (right)	10.0	6.2–15.7

[†]Hemorrhage outcomes were restricted to 19 of 22 studies that reported this complication (not reported in Cheung et al.,³ Akkakisree and Hongsakul,¹⁴ Floridi et al.⁸). Heterogeneity statistics (Q, I², τ^2) were computed on the univariate logit-transformed scale using the restricted maximum likelihood (REML) estimator implemented in metafor 4.8-0; REML-based I² estimates may differ from DerSimonian–Laird closed-form values, particularly when Q is small or non-significant (e.g., specificity Q: 18.0, df: 21, $P = 0.646$ yielded a small but non-zero REML I² of 11.5%, reflecting REML's non-zero τ^2 estimate, whereas the DerSimonian–Laird estimator would return 0% when Q < df).

Trim-and-fill was performed using the Duval–Tweedie procedure on the same logit scale (bivariate Reitsma trim-and-fill is not well-developed; Deeks 2005, Schwarzer 2015). “Side” indicates the direction of funnel-plot asymmetry used for study imputation: “left” denotes underrepresentation of small studies with lower estimates (sensitivity and specificity), whereas “right” denotes overrepresentation of small studies with higher estimates (pneumothorax and hemorrhage). Adjusted estimates should be interpreted as plausible bounds rather than definitive corrections.

[‡]The pneumothorax PI shown here (8.6–36.7%) was derived from the univariate REML model used for this heterogeneity table. The Abstract and Results sections report a pneumothorax PI of 8.3–35.8%, obtained from the GLMM with logit transformation and Hartung–Knapp adjustment used for the primary complication-rate synthesis. These intervals are consistent and differ only because of the estimation method.

PI, prediction interval; CI, confidence interval.

Risk of bias

Per-study QUADAS-2 domain-level judgments adjudicated by dual-reviewer consensus are presented as a traffic-light plot (Figure 5), and the aggregate distribution of Low, Unclear, and High ratings across the four QUADAS-2 domains is summarized as a stacked bar plot (Figure 6).

All 22 studies were rated as high-risk for Domain 4 (flow and timing) because of universal differential verification, whereby malignant biopsy results were confirmed by surgical pathology, whereas benign results were confirmed by imaging follow-up. Consequently, all studies received an overall high-risk judgment.

Inter-reviewer agreement was perfect for Domains 2–4 (Cohen's κ : 1.000 for each domain), with all 10 disagreements confined to Domain 1 (patient selection).

Discussion

This updated systematic review and meta-analysis synthesizes evidence from 24 eligible studies of CBCT-guided percutaneous transthoracic lung biopsy, with 22 contributing to the bivariate meta-analysis of diagnostic accuracy. The pooled sensitivity of 92.2% (90.4–93.7%) and specificity of 96.7% (94.3–98.2%) demonstrate that CBCT-guided PTNB provides reliable tissue diagnosis for pulmonary lesions, with an SROC AUC of 0.974.

The pooled sensitivity was lower than the 96% reported by Yan et al.,¹ whereas the pooled specificity remained high and consistent with their finding of 100%. The lower sensitivity likely reflects several factors: (1) the inclusion of larger and more heteroge-

neous study populations, including studies with small (≤ 2 cm) and difficult-to-access (lung base, juxtaphrenic) lesions; (2) more rigorous reference-standard requirements with longer follow-up; (3) a broader range of CBCT technology generations represented in the updated evidence base; and (4) consistent application of an ITD approach in which non-diagnostic specimens were reclassified as test-negative with reference-standard final diagnosis (notably for Cho et al.,²¹ where 23 non-evaluable results were reconciled to the ITD framework, contributing 22 additional false negatives). All eight studies included by Yan et al.¹ were captured in the present analysis, confirming complete overlap with the prior evidence base.

Pneumothorax rates ranged from 7.8% to 38.8%, consistent with rates reported in the broader PTNB literature (15–25%). Although the pooled incidence was 18.4%, the 95% PI (8.3–35.8%) was clinically wide, indicating that future single-center cohorts may report substantially different rates depending on patient case-mix (emphysema prevalence, lesion location), operator experience, and procedural protocols. This uncertainty should be considered when counseling patients on procedural risk and should temper any attempt to generalize a single pooled rate across CBCT-PTNB settings. Hemorrhage rates ranged from 0% to 45.7%, with the highest estimate reported by Lee et al.,⁴ a fine-needle-aspiration cohort in which the authors classified any CBCT-detected perilesional hemorrhagic change as hemorrhage rather than limiting the definition to clinically significant hemoptysis. Hemorrhage definitions, therefore, varied across the evidence base, and the wide hemorrhage PI (0.5–47.0%) reflects this definitional heterogene-

ity rather than true cross-study variation in clinically significant bleeding. Both complication rates are broadly comparable to those reported for conventional CT-guided PTNB.

The present evidence base includes CBCT navigation technologies introduced after the Yan et al.¹ review, including augmented fluoroscopy with real-time needle tracking, PET-CT fusion for metabolic-guided targeting, laser-guided needle placement, and electromagnetic navigation. However, inferential subgroup comparisons between navigation-enhanced and conventional CBCT platforms were not performed because per-patient data on needle-pass counts, targeting workflow, and lesion-size distributions required for stratified bivariate pooling were not consistently available, and a temporal stratification would conflate the technology era with the reporting-standard era. Consequently, the inclusion of these technologies should be viewed as descriptive of the current CBCT landscape rather than evidence of technology-specific superiority. The pooled diagnostic accuracy and safety estimates represent average performance across heterogeneous CBCT platforms, and where a clinician is selecting a specific navigation-enhanced platform, direct comparative studies remain necessary. A dedicated technology-comparison review incorporating per-patient reconstructions is a logical next step for this literature.

Practical implications for the interventional radiologist

Across the included studies, CBCT guidance was most commonly used in clinical scenarios in which conventional CT or CT-fluoroscopy guidance was constrained, including small (< 2 cm) or peripheral lesions, juxtaphrenic lesions affected by respiratory motion, and lesions adjacent to vascular or pleural structures requiring precise trajectory control. Viewed within the broader patient pathway from diagnosis to treatment, the intraprocedural 3D acquisition and angio-suite environment of CBCT position CBCT-guided PTNB as a potential entry point to a diagnosis-to-treatment continuum: it may facilitate same-session adjunctive management (for example, treatment of post-biopsy bleeding) and, when malignancy is confirmed and the lesion is suitable, can in principle support an immediate transition to image-guided local therapy—such as percutaneous thermal ablation—in appropriately selected patients with preplanned, same-session treatment and on-site pathology support, without patient transfer. The present aggregate-level

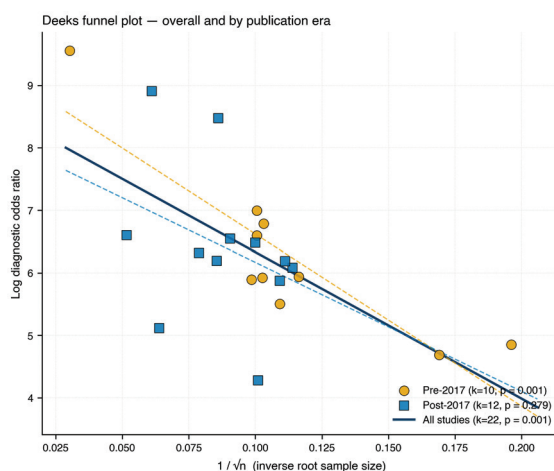


Figure 4. Deeks funnel plot. Deeks funnel plot for assessment of small-study effects (log diagnostic odds ratio vs. $1/\sqrt{n}$). All-studies regression asymmetry $P < 0.001$ (k : 22); pre-2017 subgroup $P = 0.001$ (k : 10); post-2017 subgroup $P = 0.279$ (k : 12).

evidence does not directly evaluate such combined diagnostic-therapeutic workflows, which warrant dedicated prospective evaluation.

The available evidence suggests that CBCT-guided PTNB is most reproducibly delivered in centers with dedicated angio-suite throughput and operators experienced in CBCT navigation. Radiation-dose reporting was inconsistent across studies, and a head-to-head comparison against conventional CT-guided PTNB on radiation exposure cannot be derived from the present aggregate-level synthesis; this remains a target for future prospective comparative studies.

Generalizability

The 22 studies included in the bivariate analysis originated from Asia (16 of 22; Korea $n = 8$, China $n = 5$, Taiwan $n = 2$, Thailand $n = 1$) and Europe (6 of 22; Italy $n = 4$, Spain $n = 1$, the Netherlands $n = 1$). No studies from North or South America, Africa, or Australia met the eligibility criteria. Because background emphysema prevalence, patient case-mix, lesion-size distributions at presentation, and procedural practice patterns vary considerably across health systems, the pooled estimates may not be directly generalizable to other geographic settings.

The cohort homogeneity is in part attributable to single-center series from experienced CBCT centers, which is a separate concern from geographic homogeneity but reinforces the importance of replication in centers with different referral pathways and operator experience profiles. Future prospective multicenter studies including North American and Australasian cohorts are needed to test whether the present pooled diagnostic accuracy and safety estimates hold across these settings.

Several limitations should be acknowledged. First, two eligible studies (Huang et al.²⁴ Floridi et al.²⁵) lacked sufficient data for 2×2 table reconstruction and were included only in the narrative synthesis. Author contact to recover unreported cell data was not undertaken, and although the narrative-only fraction is small, selection bias toward studies with more complete reporting cannot be fully excluded.

Second, 20 of the 22 studies included in the bivariate analysis were retrospective, limiting the ability to control for confounding and selection bias.

Third, all included studies exhibited differential verification bias, with malignant



Figure 5. QUADAS-2 traffic light. QUADAS-2 per-study risk-of-bias traffic-light plot across the four domains (D1, patient selection; D2, index test; D3, reference standard; D4, flow and timing) together with overall judgement for the 22 studies included in the bivariate meta-analysis. Ratings reflect dual-reviewer consensus for the original 21 studies and concordant blinded dual review of Yuan et al.²³ All 22 studies were rated as high-risk for Domain 4, and therefore overall, due to universal differential verification bias. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2.

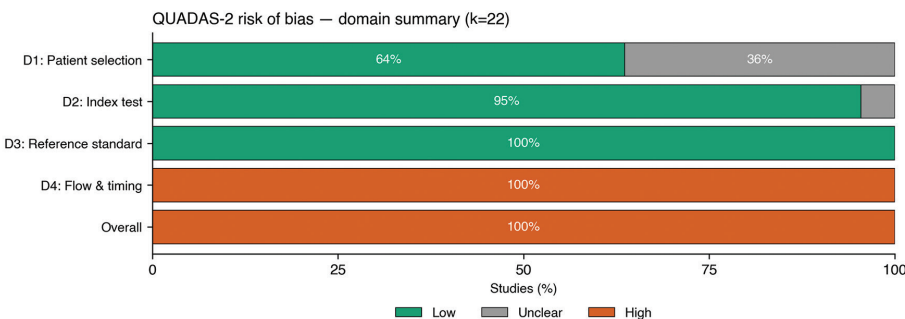


Figure 6. QUADAS-2 summary. QUADAS-2 domain-level summary plot aggregating risk-of-bias judgements across the 22 included studies (Low/Unclear/High). Domain 4 (flow and timing), and therefore the overall judgement, was rated as high-risk in all 22 studies. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2.

biopsy results typically confirmed by pathology and benign findings verified through imaging follow-up (QUADAS-2 Domain 4 high-risk). Consequently, the pooled specificity of 96.7% should be interpreted as a plausible upper-bound estimate rather than an unbiased measure. Nevertheless, the tipping-point sensitivity analysis (Supplementary Material 9) demonstrated that corrected pooled specificity remained at 96.1% or higher across plausible missed-malignancy fractions up to f : 20%, suggesting that the true specificity is unlikely to fall substantially below 90%.

Fourth, the Deeks funnel plot asymmetry test was significant overall ($P < 0.001$), although the effect was confined to pre-2017 publications ($P = 0.001$; post-2017 $P = 0.279$). This is consistent with the adoption of STARD 2015, although selective outcome reporting in retrospective single-center cohorts cannot be excluded. The pooled sensitivity should therefore be interpreted as a plausible upper-bound estimate, and pneumothorax and hemorrhage point estimates should be read together with their wide PIs rather than as definitive single-number rates.

Fifth, sensitivity heterogeneity was moderate ($I^2 = 57.4\%$), partly driven by studies with high non-diagnostic rates (Fior et al.¹³ Cho et al.²¹). However, the ITD-only sensitivity analysis (k : 18) yielded near-identical estimates, indicating that primary-study handling of non-diagnostic specimens had minimal influence on pooled accuracy estimates.

Sixth, although the primary literature search was conducted in PubMed and Embase, a confirmatory Cochrane CENTRAL search (Issue 3 of 12, March 2026) was subsequently executed on April 22, 2026, using the same conceptual blocks, and retrieved 7 records of which none were eligible (5 trial-registration records without reported results, 1 electromagnetic-navigation bronchoscopy study, and 1 record already captured through Embase and retained as narrative-only). A post-hoc Web of Science (WoS) Core Collection comprehensiveness check was attempted to address the substantial Asian literature representation (16 of 22 included studies); however, institutional access could not be established within the revision window. To compensate, several converging lines of indirect comprehensiveness evidence are documented in Supplementary Material 10: (i) PubMed indexes the major Asian radiology journals from which the included studies originate (Korean Journal of Radiology,

Journal of Korean Medical Science, Journal of Thoracic Disease, Chinese Medical Journal, European Radiology); (ii) Embase covers East-Asian conference proceedings and grey literature, and retrieved one Chinese-language publication (Huang et al.²⁴) that was retained as narrative-only; (iii) the Cochrane CENTRAL confirmatory search retrieved 7 records of which none were eligible; (iv) backward citation searching of all 24 qualitative-eligible studies and the prior Yan et al.¹ review identified no further eligible studies; and (v) a six-sentinel PMID sensitivity check confirmed retrieval of all known eligible records. Inclusion of the WoS would nonetheless have strengthened search comprehensiveness, particularly for imaging physics-engineering journals where some CBCT methodology studies may appear, and the absence of direct WoS retrieval is acknowledged as a residual limitation.

Seventh, the reference-standard requirement of six-month imaging follow-up for benign classification represents a conservative but not universal threshold. Slowly progressing adenocarcinomas with growth rates requiring longer observation may be misclassified as benign, and studies applying twelve-month follow-up (included within the present evidence base) may provide marginally more reliable benign classification.

Finally, cell-level dual extraction was completed with an independent reconciliation audit (22 of 22 studies matched), which strengthens internal accuracy but does not address uncertainty attributable to primary-study reporting ambiguity.

CBCT-guided PTNB demonstrates high diagnostic accuracy for pulmonary lesions, with a pooled sensitivity of 92.2%, specificity of 96.7%, and an AUC of 0.974. This updated meta-analysis incorporates 22 studies and 3,681 patients, almost tripling the evidence base available to Yan et al.¹ and extending it to contemporary CBCT navigation technologies, including augmented fluoroscopy, PET-CT fusion guidance, laser guidance, and electromagnetic navigation.

As pneumothorax rates varied widely across settings (95% PI: 8.3–35.8%), individual-center risk should be communicated to patients within this range rather than as a single point estimate. Prospective multicenter studies adhering to STARD 2015 reporting standards, direct comparisons of navigation-enhanced and conventional CBCT and CT guidance, and standardized complication-rate definitions that distinguish radiologically detected perilesional

hemorrhage from clinically significant hemoptysis are needed to refine risk-stratified guidance selection.

Footnotes

Conflict of interest disclosure

The authors declared no conflicts of interest.

Data and code availability

All raw 2×2 data, PRISMA artifacts, and analysis scripts are deposited at Zenodo (concept DOI: 10.5281/zenodo.19680315, resolving to the current release, v19). PROSPERO registration: CRD420261370382 (current public record Version 1.3, published 16 May 2026; methodological amendment log in Version 1.2, published 11 May 2026, 10:53 UTC).

AI-use disclosure

Large language model-based coding assistants (Claude, Anthropic; Codex CLI, OpenAI) were used for manuscript editing (prose refinement, section structuring, and internal numerical-consistency checks against analysis outputs) and for a reconciliation cross-check of 2×2 data extraction. All scientific content and decisions were verified by the authors.

Supplementary Materials: https://d2v96fpxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/documents/DIR-4084_Supplementary_Materials.docx

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