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CHEST IMAGING

ORIGINAL ARTICLE

Diagnostic performance of radiomics analysis for pulmonary cancer airway spread: a systematic review and meta-analysis

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PURPOSE

Spread through air spaces (STAS) is a unique metastatic pattern of pulmonary cancer closely associated with patient prognosis. This study evaluates the application of radiomics in the diagnosis of pulmonary cancer STAS through meta-analysis and explores its clinical significance and potential limitations.

METHODS

We systematically searched the PubMed, Embase, and Cochrane Central Register of Controlled Trials databases for relevant studies between inception and April 1, 2024. The main evaluation indicators included sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and area under the curve (AUC). A total of 18 studies, covering 6,642 lung cancer cases, were included in the systematic review.

RESULTS

In the development cohort, the sensitivity of radiomics for diagnosing STAS was 0.80 [95% confidence interval (CI): 0.75–0.84; $P < 0.001$; I^2: 72.8%], and the specificity was 0.79 (95% CI: 0.71–0.85; $P < 0.001$; I^2: 93.4%). In the validation cohort, the sensitivity was 0.81 (95% CI: 0.75–0.86; $P < 0.001$; I^2: 45.8%), and the specificity was 0.74 (95% CI: 0.68–0.80; $P < 0.001$; I^2: 65.0%). The summary AUC for both cohorts was 0.85 (95% CI: 0.82–0.88). Deeks' funnel plot analysis showed no significant publication bias in either cohort (*P* values: 0.963 and 0.106, respectively).

CONCLUSION

Radiomics analysis demonstrates important clinical significance in the diagnosis of pulmonary cancer STAS, with promising sensitivity and specificity results in both development and validation cohorts.

CLINICAL SIGNIFICANCE

While radiomics analysis offers valuable diagnostic insights for STAS in pulmonary cancer, its limitations must be carefully considered. Future research should focus on addressing these limitations and further exploring the application prospects of radiomics in lung cancer diagnosis and treatment.

KEYWORDS

Lung cancer, spread through air spaces, radiomics, computed tomography, meta-analysis

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Lung cancer is a highly lethal disease with significant implications for patients' quality of life and lifespan.[1] In addition to its high incidence and mortality, lung cancer also exhibits diverse invasive patterns, including a particularly unique metastatic mode termed spread through air spaces (STAS).[2] First proposed by Kadota et al.[2] and definitively defined by the World Health Organization (WHO) in 2015, STAS refers to the invasion of tumor micropapillary clusters, solid nests, or single cells beyond the tumor edge into the air spaces of surrounding lung parenchyma.[3] This form of invasion complicates the diagnosis, treatment, and prognosis

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of lung cancer. Before the concept of STAS, research in peritumoral radiomics primarily focused on the tumor microenvironment and its interactions, which play a critical role in tumor progression and metastasis. The presence of STAS often suggests a higher risk of postoperative recurrence and a poorer prognosis compared with traditional modes of lung cancer metastasis.[4] Therefore, accurate diagnosis and assessment of STAS in patients with lung cancer are of paramount importance. Studies have shown that patients with lung cancer with positive STAS typically require more extensive surgical resection, reflecting their poorer prognosis.[5,6] The presence of STAS is also associated with tumor recurrence, metastasis, and chemotherapy efficacy.[7] Thus, understanding and evaluating the manifestation and impact of STAS in lung cancer are crucial for devising personalized treatment strategies and improving patient prognosis.

Traditional imaging parameters, such as tumor size and morphological features, although important indicators for evaluating lung cancer, rely on subjective judgments of physicians and have certain limitations. Traditional imaging parameters may lack sufficient accuracy and sensitivity, particularly in identifying tiny STAS lesions. Moreover, due to the complex and diverse imaging manifestations of lung cancer, visual estimation alone often cannot fully leverage the potential of imaging in lung cancer diagnosis. The emergence of radiomics fills this gap by utilizing both machine learning (ML) and deep learning (DL) methods to perform quantitative analysis of lung cancer images, extracting a wealth of implicit information, including hand-crafted features such as shape, grayscale, texture, and wavelet characteristics, as well as deep radiomics features derived from advanced neural networks. This approach provides more comprehensive, objective, and accurate information for early diagnosis, staging, and prognostic evaluation of lung cancer.[8] In recent years, radiomics has made significant progress in the field of lung cancer diagnosis. Many studies have shown that analyzing lung cancer images using radiomics analysis can significantly improve the accuracy and sensitivity of diagnosis, and can even detect tiny STAS lesions.[9] This provides clinicians with more reliable information to help formulate personalized treatment plans and improve patient survival rates and quality of life. However, despite a few individual studies, there still lacks a systematic and comprehensive meta-analysis to provide a thorough and objective assessment of radiomics in the diagnosis of lung cancer STAS.

With the continuous development of ML technology and the application of radiomics, there is a unique opportunity to leverage big data and intelligent algorithms to enhance the identification and evaluation of STAS in patients with lung cancer. This study systematically evaluates the performance of radiomics analysis in detecting STAS lesions, specifically focusing on the capability to identify small STAS manifestations that may be missed by traditional imaging methods. We hypothesize that integrating advanced radiomic features, both hand-crafted and DL-derived, will significantly improve the accuracy and sensitivity of STAS detection. By providing robust evidence-based insights, this study seeks to inform clinical decision-making and improve patient outcomes in lung cancer management.

Main points

- Radiomics employs both machine learning and deep learning methods to quantitatively analyze lung cancer images and extract rich hidden information. This includes hand-crafted features such as shape, grayscale, texture, and wavelet, as well as features derived from deep radiomics techniques. By integrating these diverse features, radiomics provides more comprehensive, objective, and accurate information for the early diagnosis of lung cancer, as well as for staging and prognostic assessment.
- This study explores the performance of radiomics analysis in the diagnosis of lung cancer spread through air spaces (STAS) through a systematic review and meta-analysis, providing reliable evidence-based support for clinical practice.
- Analyzing lung cancer images using radiomics analysis can significantly improve the accuracy and sensitivity of diagnosis, and can even detect tiny STAS lesions.

Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies guidelines.[10] The detailed protocol is accessible in INPLASY (INPLASY2024100103). As this meta-analysis did not involve human or animal participants, ethics approval was not required.

Search strategy and literature selection

We systematically searched three major electronic databases, namely PubMed, Embase and the Cochrane Central Register of Controlled Trials databases, between inception and April 1, 2024, without language restrictions. The search strategy combined MeSH or Emtree terms with free terms to ensure comprehensive results. Keywords were set to search in the title and abstract mode for greater accuracy. Additionally, reference lists of relevant studies or reviews were manually searched to retrieve potentially missed literature. The search topics included radiomics, artificial intelligence (AI), ML, lung cancer, and airway spread. These terms were combined using Boolean operators to ensure comprehensive coverage of relevant studies (Supplementary File 1). The search process was conducted independently by two researchers, and records were imported into reference management software for automatic removal of duplicates and subsequent manual exclusion. Disagreements were resolved through consultation with a third researcher.

Inclusion and exclusion criteria

Based on the Population, Intervention, Comparator, Outcome, Study design principle, studies meeting the following criteria were included: 1) the study population comprised patients with lung cancer; 2) the intervention involved AI-assisted radiomics; 3) histopathology was used as the reference standard; 4) the primary outcome was pulmonary cancer airway spread; and 5) the study design was either a cohort study or case-control study. Studies meeting the following criteria were excluded: 1) irrelevant study types, such as animal studies, case reports, or conference papers; 2) studies with incomplete data; and 3) studies that did not report predefined outcomes or did not adhere to the intervention and control settings.

Data extraction and risk of bias assessment

Two researchers independently extracted data using a pre-designed form from the included studies, including author names, publication dates, study designs, sample sizes, locations of conduct, characteristics of patient populations (e.g., age and gender), model validation methods, algorithms used for modelling, imaging equipment parameters, use of clinical information, primary inclusion variables, and diagnostic performance. Quantitative data in 2×2 tables, including true positives, true negatives, false positives, and false negatives, were collected. The methodological quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool, which covers patient selection, index test, reference standard, flow, and timing, among other as-

pects. Disagreements were resolved through consultation with a third researcher.

Statistical analysis

Data analysis in this study was performed using RevMan 5.4 and Stata SE 15.0 software. Sensitivity and specificity were calculated based on 2 × 2 table data and presented graphically, with squares representing values and horizontal lines representing corresponding confidence intervals (CIs). Summary receiver operating characteristic curves were used to represent the performance of diagnostic tests. The approximate classification criteria for area under the curve (AUC) values were as follows: 0.50–0.60 = inadequate, 0.60–0.70 = poor, 0.70–0.80 = fair, 0.80–0.90 = good and 0.90–1 = excellent. Additionally, summary statistics of positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio, along with their 95% CIs, were calculated. Heterogeneity of results was assessed using Cochran's Q test and the I^2 statistic test, and meta-analysis was conducted using either fixed-effects or random-effects models accordingly. The possibility of publication bias was assessed using Deeks' funnel plot analysis, and sensitivity analysis was performed to evaluate the stability of the results. Fagan's nomogram was used to evaluate the clinical utility of radiomics and calculate the post-test probability of STAS.

Results

Literature search

The flowchart of the literature search process for this meta-analysis is depicted in Figure 1. Initially, 125 records were identified from the databases, and an additional 2 records were manually retrieved from other sources. After removing duplicates, 97 records remained. Subsequently, based on screening of titles and abstracts, 70 irrelevant records were excluded, leaving 27 articles for full-text assessment. Finally, a total of 18 articles[11-28] were included in the systematic review, with data from 13 articles used for the meta-analysis.

Characteristics of included studies

The basic characteristics of the included studies are presented in Table 1. All studies were retrospective in design, with the majority (66.7%) being single-center studies and only 6 being multi-center studies. Among the 18 included studies, 14 were conducted in China, 2 in Japan, and 1 each in Italy and South Korea. Most studies focused on patients with lung adenocarcinoma, with sample sizes ranging from 92 to 681 and mean/median ages ranging from 53.1 to 70 years. The proportion of men ranged from 31.3% to 58.9%. External validation was performed in 8 studies.

Details of the radiomics predictive models included in the studies are summarized in Table 2. Common ML algorithms used included the least absolute shrinkage and selection operator, random forest, and decision tree algorithms. Although a variety of imaging equipment manufacturers were involved, all models were based on chest computed tomography. In addition to radiomics, 6 studies incorporated clinical information such as gender, age, smoking status, and tumor size in model construction. The definition of STAS was generally consistent across studies, primarily based on WHO criteria (i.e., micropapillary clusters, solid nests, or single cells beyond the edge of the tumor extending into the air spaces in the surrounding lung parenchyma). The AUC values of the constructed models ranged from 0.66 to 0.99.

Risk of bias assessment

Understanding risk of bias is crucial for evaluating the reliability of study findings. Bias can be introduced at various stages of a study, including patient selection, index test application, and reference standards. High or unclear risk of bias can affect the internal validity and generalizability of the study results.

The methodological quality of the 18 included studies is detailed in Figure 2. One study was at high risk of bias in the "patient selection" domain due to a case-control study design, and another study had an unclear risk due to insufficient description. Additionally, 12 studies had unclear risks of bias in the "index test" and "reference stan-

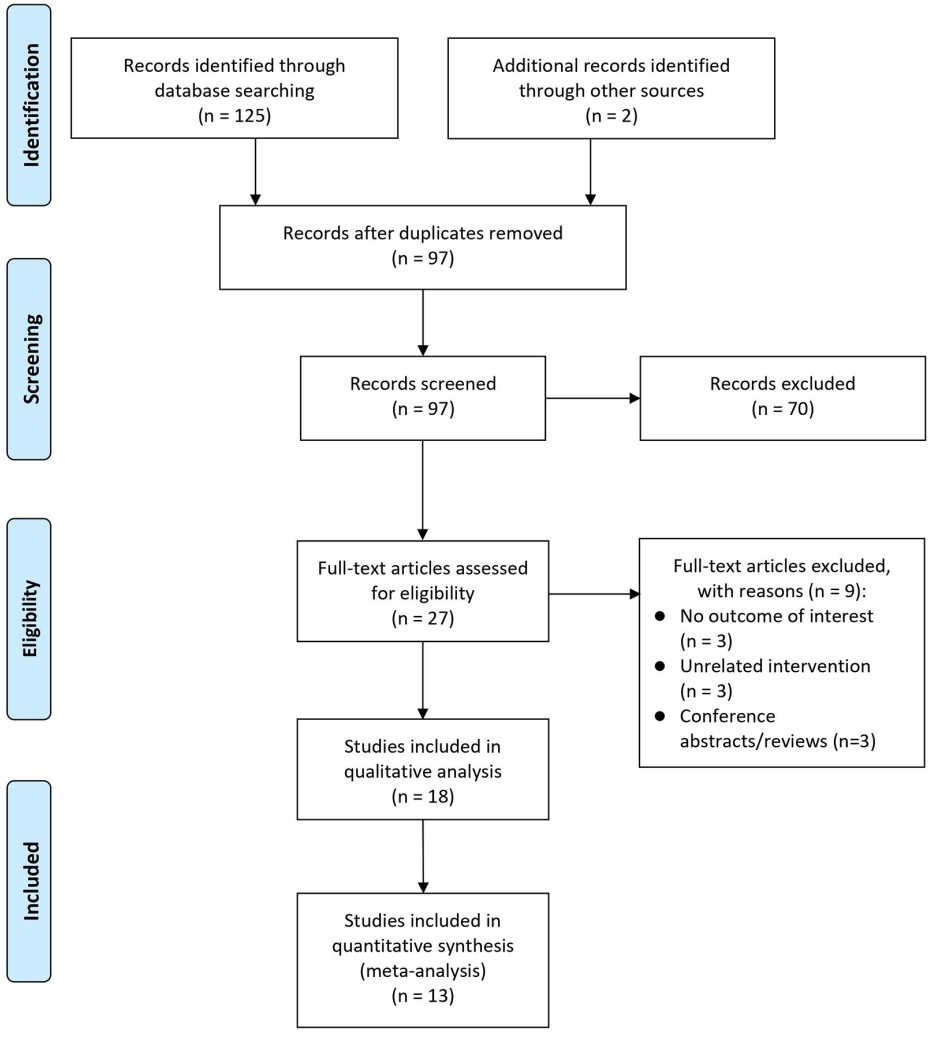

Figure 1. PRISMA flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Main characteristics of the included studies

Author, year	Design	Sites	Country	Population	Sample size	Age, years	Men, %	Validation approach
Bassi et al.[11], 2022	Retrospective	Single-center	Italy	Patients with resected lung adenocarcinoma	149	68.0 (61.5–74.0); 69.0 (61.0–73.8)	57.0	External validation
Chen et al.[12], 2020	Retrospective	Multi-center	China	Patients with stage I invasive lung adenocarcinoma	345	60 (35–82); 60 (34–76)	43.2	External validation
Chen et al.[13], 2022	Retrospective	Multi-center	China	Patients with lung adenocarcinoma	327	58.9 (25–85)	40.1	External validation
Gong et al.[14], 2023	Retrospective	Single-center	China	Patients undergoing surgery for lung cancer	537	62 (56–67); 62 (55–67)	49.3	Random splitting
Han et al.[15], 2022	Retrospective	Single-center	China	Patients with stage AI lung adenocarcinoma	395	59 ± 10	52.4	Random splitting
Jiang et al.[16], 2020	Retrospective	Single-center	China	Patients with lung adenocarcinoma	462	Mean: 58.06	44.6	Random splitting
Jin et al.[17], 2023	Retrospective	Multi-center	China	Patients with primary lung cancer	674	Mean: 57.8–61.5	38.6	External validation
Liao et al.[18], 2022	Retrospective	Single-center	China	Patients with pathologically confirmed invasive clinical stage I lung adenocarcinoma who accepted surgical resection	256	60.7 ± 10.7; 59.5 ± 10.9	47.7	Random splitting
Lin et al.[19], 2024	Retrospective	Multi-center	China	Patients with lung adenocarcinoma who underwent complete lung resection	681	56.9 ± 11.2	31.3	External validation
Liu et al.[20], 2022	Retrospective	Single-center	China	Patients with stage AI lung adenocarcinoma who underwent surgical resection	92	53.1 ± 10.9; 56.9 ± 7.6	40.2	N/A
Onozato et al.[21], 2021	Retrospective	Single-center	Japan	Patients who underwent surgical resection of lung cancer	226	70 (39–88); 68 (38–89)	54.4	Cross-validation
Qi et al.[22], 2021	Retrospective	Single-center	China	Patients with primary lung adenocarcinoma confirmed by surgical resection and pathology	216	56 ± 11	58.9	External validation
Suh et al.[23], 2024	Retrospective	Single-center	South Korea	Patients who underwent surgical r section for clinical stage AI (tumor size ≤3 cm) lung adenocarcinoma	521	Mean: 61.2–66.6	45.5	Temporal validation
Takehana et al.[24], 2022	Retrospective	Single-center	Japan	Patients with pathologically confirmed lung adenocarcinoma	339	67 (61–73)	47	Random splitting
Tao et al.[25], 2022	Retrospective	Single-center	China	Patients with non-small cell lung cancer	203	59.6 ± 9.8; 61.3 ± 8.6	55.2	Random splitting
Wang et al.[26], 2024	Retrospective	Multi-center	China	Patients with confirmed lung adenocarcinoma	602	Mean: 56.69–60.48	46.7	External validation
Wang et al.[27], 2024	Retrospective	Multi-center	China	Patients with clinical stage AI non-small cell lung cancer	405	≥65 years: 31.9%	49.4	External validation
Zhuo et al.[28], 2020	Retrospective	Single-center	China	Patients with confirmed lung adenocarcinoma	212	58.84 ± 9.92	42.92	Random splitting

Age was expressed as mean ± standard deviation or median (25th quartile–75th quartile). AI, artificial intelligence; N/A, not available.

Table 2. Characteristics of radiomics-based prediction models

Author, year	Algorithms	Imaging equipment	Clinical information	Included variables	Reference standard of STAS	AUC
Bassi et al.[11], 2022	NB, k-NN, RF, LR	Unlimited	No	Radiomics, radiological features and mixed features	The presence of a rim of normal lung surrounding the entire tumor circumference	0.66–0.79
Chen et al.[12], 2020	NB	SOMATOM Definition AS scanner (64 × 0.625 mm detector, 1.0 pitch) or Brilliance 40 scanner (40 × 0.625 mm detector configuration, 0.4 pitch)	No	Radiomics (sphericity, 90 percentile, gray level variance, cluster tendency, gray level variance)	Tumor cells emerging in paracarcinoma normal alveolar spaces, which are far from the main tumor and appear in the form of micropapillary clusters, small solid tumor nests, or single cells	0.69
Chen et al.[13], 2022	NR	GE (LightSpeed Pro 32, LightSpeed Pro 16, BrightSpeed, and Revolution EVO), Philips (iCT 256, Brilliance and Ingenuity), Siemens (Definition AS+, Emotion 16 and Sensation 64), and Toshiba (Aquilion ONE)	No	Radiomics on the basis of "near-pure" subtype data using patch-wise analysis within a tumor border area	Tumor cells within air spaces in the lung parenchyma at a distance of at least 1 alveolus away from the main tumor	0.81, 0.83
Gong et al.[14], 2023	NR	Spiral CT scanners (Siemens SOMATOM Definition AS+ and Siemens SOMATOM Drive)	No	44 radiomics features	Tumor cells in airspaces outside the main tumor boundary	0.802–0.834
Han et al.[15], 2022	LASSO, LR	Multislice spiral CT scanners (SOMATOM Definition AS+ and Siemens Healthineers, Germany)	Yes	Sex, age, smoking, size, radiomics	Tumor cells were found in the lung air spaces beyond the edge of the primary tumor	0.812, 0.850
Jiang et al.[16], 2020	RF	A 16-detector CT scanner (Philips Brilliance 16, Philips Medical Systems)	Yes	Age and 12 radiomics features	The discovery of tumor cells in the lung air spaces beyond the edge of the main tumor	0.754
Jin et al.[17], 2023	Deep CNN	NR	No	Radiomics	Micropapillary clusters, solid nests, or single cells beyond the edge of the tumor extending into the air spaces in the surrounding lung parenchyma	0.84, 0.94
Liao et al.[18], 2022	LASSO	NR	No	Radiomics	Tumor cells within air gaps in paracarcinoma normal alveolar spaces beyond the margin of the primary tumor	0.871, 0.869
Lin et al.[19], 2024	DL	CT: Toshiba (Tokyo, Japan), Philips (Best, The Netherlands), GE (Waukesha, Wisconsin, USA), and Siemens (München, Germany)	No	Radiomics	Tumor cells emerging in paracarcinoma normal alveolar spaces, which are far from the main tumor and appear in the form of micropapillary clusters, small solid tumor nests, or single cells.	0.80, 0.82
Liu et al.[20], 2022	RF	Shanghai United Imaging uCT550 multislice spiral	Yes	Sex, age, and radiomics	NR	NR
Onozato et al.[21], 2021	XGBoost	Aquilion Prime (Canon Medical Systems Corporation, Tochigi, Japan), Aquilion ONE (CANON), Alexion (CANON), Activion16 (CANON), and Aquilion64 (CANON)	No	Radiomics	Micropapillary clusters, solid nests, or single cells beyond the edge of the tumor extending into the air spaces in the surrounding lung parenchyma	0.77
Qi et al.[22], 2021	AdaBoost	General Electric (LightSpeed VCT; Waukesha, Wis) or Siemens (Definition Flash, Erlangen, Germany)	No	Radiomics	Micropapillary clusters, solid nests, or single cells spread within the air spaces beyond the edge of the main tumor	0.909, 0.907, 0.897
Suh et al.[23], 2024	LASSO, LR	NR	Yes	Lesion type on CT, solid portion size on CT, male, radiomics	Tumor cells within the air spaces in the lung parenchyma, beyond the edge of the main tumor	0.815–0.878

Table 2. Continued

Author, year	Algorithms	Imaging equipment	Clinical information	Included variables	Reference standard of STAS	AUC
Takehana et al.[24], 2022	LASSO, LR	A 64-detector-row CT scanner (Aquilion 64, Canon Medical Systems, Otawara, Japan) or a 320-detector-row scanner (Aquilion ONE, Canon Medical Systems)	No	Peritumor radiomics	Tumor aggregates floating in the air cavity at least one alveolus away	0.76, 0.79
Tao et al.[25], 2022	CNN, LR, DT, LDA, SGD, PSVM, SPSVM, XGBoost, AdaBoost	A single-source, 64-multidetector CT scanner (Brilliance CT, Philips Healthcare)	No	Radiomics	Tumor cells in the lung air spaces beyond the edge of the primary tumor	0.80, 0.93
Wang et al.[26], 2024	Squeeze-and-excitation attention module with the ResNet50 architecture		No	Radiomics	Micropapillary clusters, solid nests, or single cells spread within the air spaces beyond the edge of the main tumor	0.783, 0.806, 0.933
Wang et al.[27], 2024	LR, mRMR, LASSO	Toshiba Aquilion16 row, GE Light Speed VCT64 row, Philips Ingenuity 64 row, and Brilliance iCT 128 row CT, American Light Speed 16, and Dutch Philips iCT 256-row CT, SOMATOM Definition Flash and SOMATOM Drive 64-row CT machines	Yes	Sex, CEA, CTR, density type, distal ribbon sign, radiomics	Micropapillary clusters, solid nests, or single cells spread within the air spaces beyond the edge of the main tumor	0.901, 0.875, 0.878
Zhuo et al.[28], 2020	LASSO	SOMATOM Force (Siemens, Germany), Aquilion One/320 (Toshiba, Japan), and uCT128 (UIH, China)	Yes	The maximum diameter of the solid component, mediastinal lymphadenectasis, radiomics	Micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma	0.98, 0.99

STAS, spread through air spaces; AUC, area under the curve; NB, naïve bayes; RF, random forest; LR, logistic regression; NR, not reported; LASSO, the least absolute shrinkage and selection operator; CNN, convolutional neural network; DL, deep learning; DT, decision tree; LDA, linear discriminant analysis; SGD, stochastic gradient descent; PSVM, poly support vector machine; SPSVM, sigmoid poly support vector machine; mRMR, maximal redundancy minimal relevance; CEA, carcinoembryonic antigen; CT, computed tomography; CTR, consolidation-to-tumor ratio.

dard" domains due to unreported blinding. Notably, all studies had low risks in the "flow and timing" domain and overall showed few concerns.

Meta-analysis

Meta-analysis was conducted separately for data from development/internal validation and external validation/random splitting, and the results are shown in Figure 3. The figure presents forest plots illustrating the diagnostic performance of radiomics for predicting STAS in both training and validation cohorts. Forest plots are commonly used in meta-analyses to provide a visual representation of the results from individual studies and the overall summary effect. Each study's estimate of sensitivity and specificity is displayed as a square, with the size of the square reflecting the weight of the study in the meta-analysis. The horizontal lines represent the CIs for each estimate. The diamond at the bottom of each plot represents the pooled estimate of sensitivity and specificity, providing a combined result from all studies.

In the development/internal validation cohort (Panel A of Figure 3), as the forest plot shows, the sensitivity of radiomics for diagnosing STAS was 0.80 (95% CI: 0.75–0.84), and the specificity was 0.79 (95% CI: 0.71–0.85), with the presence of substantial heterogeneity ($P < 0.001$, I^2: 72.8% for sensitivity and $P < 0.001$, I^2: 93.4% for specificity).

In the external validation/random splitting cohort (Panel B of Figure 3), the forest plot showed similar performance, with a sensitivity of 0.81 (95% CI: 0.75–0.86) and a specificity of 0.74 (95% CI: 0.68–0.80) (heterogeneity: $P = 0.040$, I^2: 45.8% for sensitivity and $P < 0.001$, I^2: 65.0% for specificity).

As shown in Figure 4, the pooled AUC was 0.85 (95% CI: 0.82–0.88) for both development/internal validation and external validation/random splitting cohorts.

Publication bias and sensitivity analysis

Publication bias occurs when the outcome of the research influences the decision whether to publish it. This can lead to an overestimation of the effect in published studies. Sensitivity analysis assesses how the results vary with changes in the data or analytical methods. Both publication bias analysis and sensitivity analysis are critical for understanding the robustness and reliability of the meta-analysis findings.

Deeks' funnel plot analysis revealed no significant publication bias in either cohort ($P = 0.963$ and 0.106, respectively), as shown in Figure 5. Sensitivity analysis indicated that the exclusion of individual studies did not significantly affect the pooled results, indicating the stability of the study findings.

Clinical utility

In the development/internal validation cohort (Panel A of Figure 6), the Fagan plot indicated that when the pretest probability of STAS was positive, the post-test probability increased significantly from 20% to 48% after applying the radiomics test. Conversely, when the pretest probability was negative, the post-test probability decreased to 6%, indicating a low likelihood of STAS when the test result is negative.

In the external validation/random splitting cohort (Panel B of Figure 6), similar trends were observed. As the Fagan plot shows, the use of radiomics increased the post-test probability from 20% to 44% when

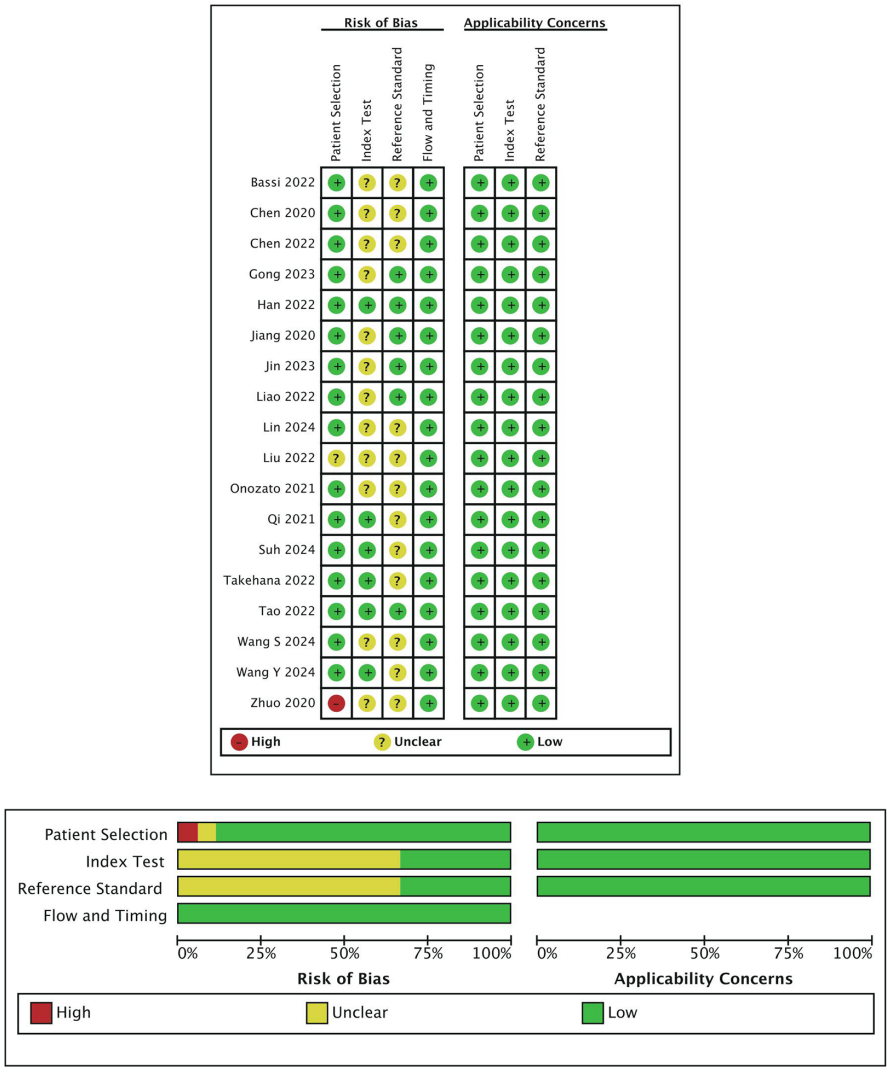

Figure 2. Methodological evaluation of the included studies.

the pretest probability was positive, and decreased it to 6% when the pretest probability was negative.

Discussion

Main findings

This study comprehensively analyzed the diagnostic value of radiomics analysis for lung cancer STAS by synthesizing multiple recent studies. The main findings are as follows: 1) regardless of whether it was in the development or validation cohorts, radiomics showed good sensitivity and specificity in diagnosing lung cancer STAS; 2) radiomics demonstrated good discriminative ability for diagnosing lung cancer STAS, accurately distinguishing between two patient groups; and 3) no significant publication bias was found in the included studies, although methodological quality assessment indicated uncertain risk of bias in some studies. The results of this study confirm the potential clinical utility of radiomics analysis, providing new insights and methods for the diagnosis of lung cancer STAS and promoting the development of imaging and AI in this field.

Importance of spread through air spaces in lung cancer diagnosis and treatment

As a unique mode of metastasis, STAS plays a crucial role in the diagnosis and treatment of lung cancer. First, the presence of STAS is closely related to the prognosis of patients with lung cancer. Multiple studies have shown that patients with positive STAS generally have poorer prognosis, with significantly increased rates of postoperative recurrence and distant metastasis, as well as significantly shortened survival periods.[5,6,29] In addition to STAS, peritumoral radiomics, which analyzes the regions surrounding the tumor, and the tumor microenvironment, including immune cells, blood vessels, and the extracellular matrix, are also critical factors in lung cancer progression and prognosis. These elements provide additional insights into tumor behavior and help refine lung cancer classification, aiding in more accurate prognostication and personalized treatment planning. Second, the detection of STAS also provides important references for clinical treatment decisions. Depending on the extent and range of STAS, physicians can more accurately assess the invasiveness and metastatic risk of lung cancer and formulate corresponding treatment plans. For example, for patients with lung cancer with positive STAS, more extensive surgical resection is often required to ensure complete tumor clearance and reduce the risk of postoperative recurrence.[30] Therefore, accurate identification and assessment of the presence of STAS are of great significance for guiding the scope and depth of surgery, improving the thoroughness of surgery and treatment outcomes.

Application of machine learning and radiomics in diagnosing lung cancer spread through air spaces

ML algorithms have increasingly been applied in the diagnosis and treatment of lung cancer, revolutionizing the field by enabling more accurate and efficient analysis of complex datasets. Techniques such as convolutional neural networks and recurrent neural networks have shown significant promise in enhancing the accuracy of lung cancer detection, prognostication, and classification. While the broader scope of AI in lung cancer therapeutics includes applications such as drug discovery and treatment personalization, this discussion specifically focuses on the role of radiomics in improving diagnostic accuracy and clinical decision-making.

A comprehensive review highlighted the critical role of AI in analyzing extensive clinical datasets to improve patient management strategies.[31] These advancements can optimize therapeutic approaches and potentially enhance patient outcomes in lung cancer care.[32] However, the specific application of radiomics—defined as the extraction of quantitative features from medical imaging—plays a pivotal role in distinguishing between various tumor characteristics and predicting clinical outcomes.

The present study's findings on the diagnostic value of radiomics analysis for lung cancer STAS align well with these broader applications of ML in oncology. Specifically, our results demonstrate that radiomics, powered by ML algorithms, exhibits good

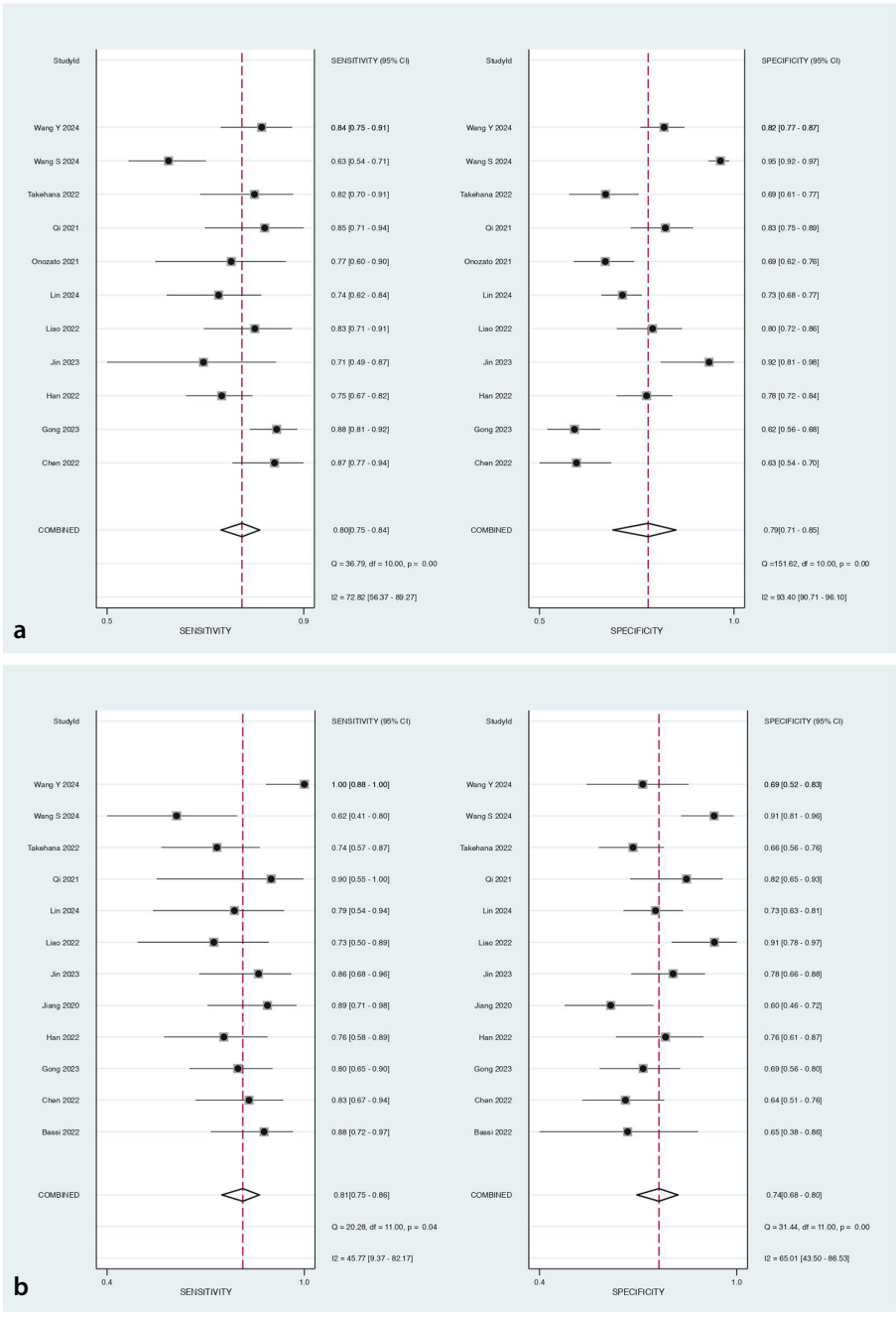

Figure 3. Forest plots of radiomics for prediction of STAS in training (**a**) and validation (**b**) cohorts. STAS, spread through air spaces.

sensitivity and specificity in diagnosing lung cancer STAS. This capability is critical as it enables accurate distinctions between patient groups, facilitating the formulation of personalized treatment plans.

By employing advanced feature engineering techniques, as utilized in this study, radiomics can extract and analyze intricate imaging features that are otherwise imperceptible to human observers.[33] These features include tumor shape, grayscale variations, texture patterns, and wavelet transformations, which collectively contribute to accurately predicting STAS status. For example, this study observed AUC values ranging from 0.66 to 0.99 for different models, reflecting the robust discriminative ability of radiomics in diagnosing lung cancer STAS.

Integrating clinical information, such as age, gender, smoking status, and tumor size, into radiomics models enhances their predictive performance. This approach aligns with the review's emphasis on leveraging large, multifaceted datasets to improve treatment recommendations and outcomes.[31] Future research should focus on addressing current limitations, such as selection bias and lack of blinding, to further validate and enhance the clinical applicability of ML techniques in lung cancer diagnosis and treatment.

The synergy between ML algorithms, comprehensive datasets, and sophisticated feature engineering techniques holds great promise for advancing lung cancer diagnostics and therapeutics. The present study contributes to this growing body of evidence, underscoring the potential of radiomics in accurately diagnosing lung cancer STAS and supporting personalized treatment strategies. Radiomics analysis can help clinicians more accurately identify patients with positive STAS, thereby assisting in assessing patient prognosis more effectively and formulating rational treatment plans. Additionally, radiomics can provide crucial reference points for surgical planning, helping physicians determine the scope and depth of surgery while reducing the risk of postoperative recurrence. Furthermore, radiomics offers objective and accurate indicators for follow-up and prognosis assessment, enabling timely detection and intervention for changes in patient condition, thereby improving treatment effectiveness and patient survival rates.

Novelty and future directions

To the best of our knowledge, this study is the first meta-analysis of radiomics in the diagnosis of lung cancer STAS. By integrating data from multiple relevant studies, we obtained the most comprehensive and comprehensive data, allowing us to provide a more reliable and objective evaluation of the effectiveness of radiomics in diagnosing STAS. A comprehensive summary of the current research on radiomics in the diagnosis of lung cancer STAS provide important references and inspiration for further research in this field. First, with the continuous development and improvement of radiomics analysis, we can further explore how to improve its accuracy and reliability in diagnosing STAS. It is possible to endeavor to combine more imaging parameters and clinical data to build more complex and comprehensive predictive models, thereby improving the diagnostic accuracy of STAS. In addition, the fusion and integration of multi-modal imaging data can be explored to further improve the diagnostic ability of STAS through various imaging techniques.[34] Second, the application of radiomics in the treatment of lung cancer STAS can be further studied. In addition to diagnosis, radiomics analysis can also be used to evaluate patients' treatment

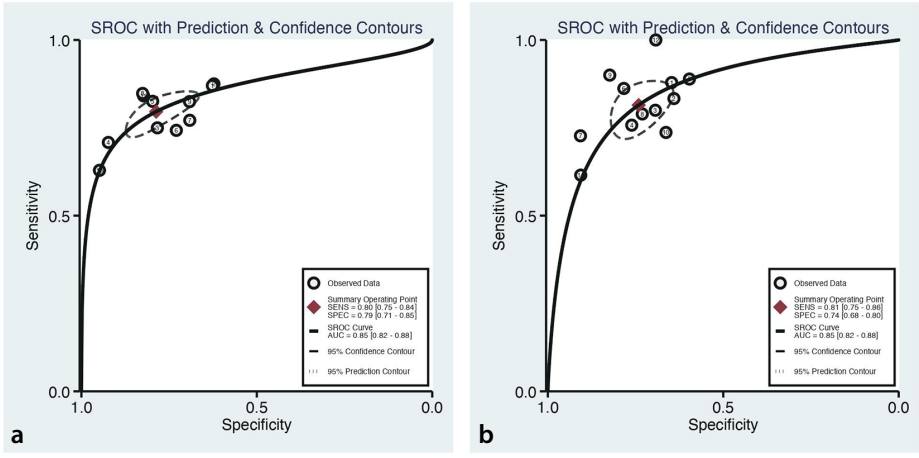

Figure 4. Summary receiver operating curves of radiomics for prediction of STAS in training **(a)** and validation **(b)** cohorts. STAS, spread through air spaces.

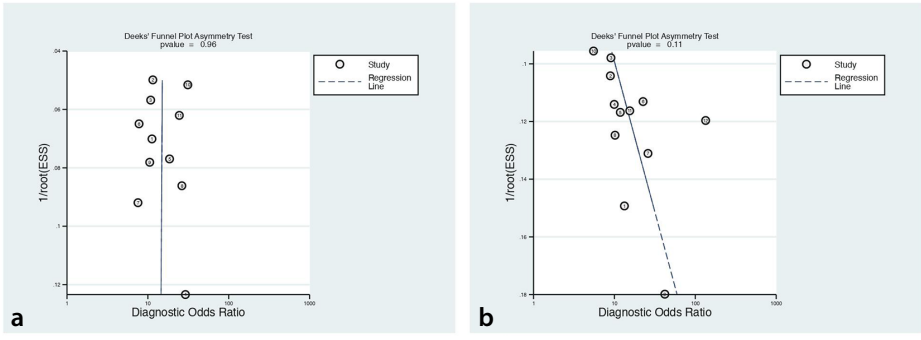

Figure 5. Funnel plots of radiomics for prediction of STAS in training **(a)** and validation **(b)** cohorts. STAS, spread through air spaces.

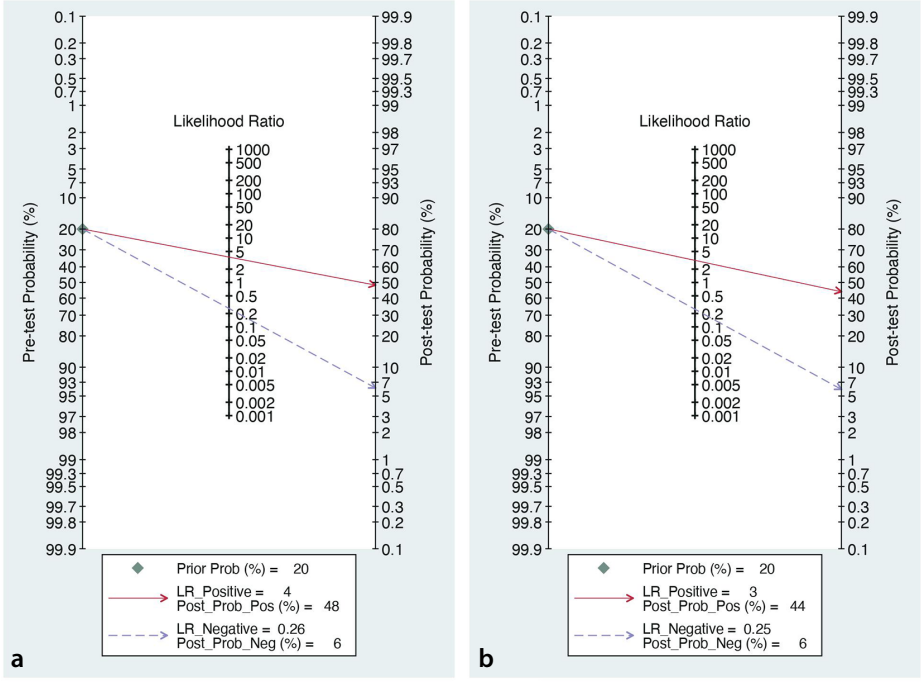

Figure 6. Fagan plots of radiomics for prediction of STAS in training **(a)** and validation **(b)** cohorts. STAS, spread through air spaces.

response and prognosis, guiding the formulation and adjustment of treatment plans. As such, future research can focus on the application of radiomics in the treatment decision-making and efficacy evaluation of lung cancer STAS. In addition, the combined application of radiomics with other fields, such as genomics and transcriptomics, can be further explored. By integrating various omics data, a multi-angle and comprehensive evaluation of lung cancer STAS can be achieved, providing more comprehensive and personalized treatment plans for clinical practice.[35] Finally, larger-scale, longer-term prospective studies can be conducted to verify the effectiveness and clinical application prospects of radiomics in the diagnosis and treatment of lung cancer STAS. These studies will provide important scientific evidence and clinical support for the further promotion and application of radiomics analysis in the diagnosis and treatment of lung cancer.

Although this study provides important insights and inspiration for the diagnosis of STAS via radiomics, there are also some potential limitations that need to be considered. First, all studies included in this study were retrospective in design. Although this is a common design in radiological research, there may still be a risk of selection bias. Due to the characteristics of retrospective studies, the study results may be affected by patient selection and data collection and may not fully represent the entire population. Second, many studies did not set up blinding when analyzing images or pathology. The lack of blinding may lead to subjective bias of observers, affecting the accuracy and reliability of the study results. To reduce the risk of bias, future studies should adopt double-blind or single-blind designs to ensure that researchers are unaware of the data analysis. In addition, more than half of the included studies were conducted in China, and the universality of the results may be limited by geographical restrictions, and it is uncertain whether they are applicable to other populations. Therefore, future research should diversify the selection of study samples to ensure the reliability and universality of the study results.

In conclusion, this study confirms the potential clinical utility of ML-assisted radiomics for diagnosing STAS of lung cancer. Our analysis reveals that radiomics analysis achieves good sensitivity, specificity, and discriminative ability across multiple cohorts. Although publication bias was not significant, some studies showed uncertain risk of bias, which should be addressed in future research. Radiomics analysis offers a valuable tool for clinical decision-making in STAS diagnosis, but limitations such as selection bias, lack of blinding, and geographical restrictions must be carefully considered. Future studies should focus on mitigating these limitations

to improve the robustness and generalizability of radiomics in clinical settings.

Footnotes

Conflict of interest disclosure

The authors declared no conflicts of interest.

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Supplementary File 1.

Search strategy

PubMed

((radiomics[MeSH] OR radiomics) AND (artificial intelligence[MeSH] OR AI OR artificial intelligence OR machine learning[MeSH] OR ML OR machine learning) AND (lung cancer[MeSH] OR lung neoplasms OR pulmonary cancer) AND (spread through air spaces[MeSH] OR STAS OR airway spread))

Embase

('radiomics'/exp OR radiomics) AND ('artificial intelligence'/exp OR AI OR 'artificial intelligence' OR 'machine learning'/exp OR ML OR 'machine learning') AND ('lung cancer'/exp OR 'lung neoplasms' OR 'pulmonary cancer') AND ('spread through air spaces'/exp OR STAS OR 'airway spread')

CENTRAL

((radiomics OR "radiomics") AND (artificial intelligence OR AI OR "artificial intelligence" OR machine learning OR ML OR "machine learning") AND (lung cancer OR "lung neoplasms" OR "pulmonary cancer") AND (spread through air spaces OR STAS OR "airway spread"))