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Risk factors for malignant solid pulmonary nodules: a meta-analysis

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Abstract

Background Previous studies have indicated that clinical and imaging features may assist in distinguishing between benign and malignant solid lung nodules. Yet, the specific characteristics in question continue to be debated. This meta-analysis aims to identify risk factors for malignant solid lung nodules, thereby supporting informed clinical decision-making.

Methods A comprehensive search of databases including PubMed, Embase, Web of Science, Cochrane Library, Scopus, Wanfang, CNKI, VIP, and CBM was conducted up to October 6, 2024. Only publications in Chinese or English were considered. Data analysis was performed using Stata 16.0 software.

Results This analysis included 32 studies, comprising 7758 solid pulmonary nodules, of which 3359 were benign and 4399 were malignant. It was found that the incidence of spiculate signs in malignant solid pulmonary nodules (MSPN) was higher than in benign solid pulmonary nodules (BSPN) [OR = 3.06, 95% CI (2.35, 3.98), $P < 0.05$. Additionally, increases were observed in the incidences of vascular convergence[OR = 16.57, 95% CI (8.79, 31.24), $P < 0.05$], lobulated signs [OR = 5.17, 95% CI (3.83, 6.98)], air bronchogram sign[OR = 2.96, 95% CI (1.62, 5.41), $P < 0.05$], pleura traction sign [OR = 2.33, 95% CI (1.65, 3.29), $P < 0.05$], border blur [OR = 2.94, 95% CI (1.47, 5.85), $P < 0.05$], vacuole signs [OR = 5.25, 95% CI (2.66, 10.37), $P < 0.05$], and family history of cancer [OR = 3.85, 95% CI (2.43, 6.12), $P < 0.05$] compared to BSPN. Older age[OR = 1.06, 95% CI (1.04, 1.07), $P < 0.05$], higher prevalence in females [OR = 2.98, 95% CI (2.27, 3.92), $P < 0.05$], larger nodule diameters [OR = 1.25, 95% CI (1.13, 1.38), $P < 0.05$], and lower incidence of calcification [OR = 0.21, 95% CI (0.10, 0.48), $P < 0.05$] were also associated with MSPN. No significant differences were found between MSPN and BSPN regarding CEA and emphysema (all $P > 0.05$).

Conclusions This meta-analysis highlights that spiculate sign, vascular convergence sign, lobulated sign, diameter, border blur, vacuole sign, age, gender, family history of cancer, pleura traction, air bronchogram sign, and calcification are significant markers for predicting malignancy in SPNs, potentially influencing clinical management. However, further well-designed, large-scale studies are needed to confirm these findings.

Keywords Risk factors, Ssolid pulmonary nodules, Mmalignant, Meta-analysis

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Introduction

Lung cancer was the most common cancer in 2022, with nearly 2.5 million new cases [1]. The 5-year survival rate for Stage I lung cancer ranges from 60 to 80%, while it decreases dramatically to 12% for Stage IIIC [2, 3]. This underscores the critical need for early screening and diagnosis of lung cancer.

Recently, high-resolution CT (HRCT) has become prevalent in clinical settings. Compared to traditional chest radiography, HRCT earlier and more accurately detects small lung lesions, particularly nodules of small diameter [4], thereby significantly enhancing the detection of early-stage lung cancer.

Pulmonary nodules are categorized into ground glass and solid nodules based on their density [5, 6]. Solid pulmonary nodules (SPN) may represent hamartomas, infections, or other benign conditions that do not require surgical intervention and can be managed with regular monitoring [7]. However, 30–40% of solid lung nodules are malignant [8]. Compared to ground glass nodules, solid lung nodules exhibit a higher malignancy and poorer prognosis [9–11], necessitating early surgical intervention. This highlights the importance of distinguishing between benign and malignant solid lung nodules.

Previous studies have shown that preoperative clinical and imaging features can help distinguish benign and malignant solid pulmonary nodules, but scholars report conflicting results [12, 13]. Some scholars point out [13, 14] that spiculation sign was helpful in distinguishing benign and malignant solid pulmonary nodules, while Zhu et al. found the opposite [15]. Zhong et al. [16] pointed out that the diameter of nodules is related to their benign or malignant nature, but this conclusion is inconsistent with the results of Li et al. [17]. Other scholars believe [14, 18] that the older the age, the higher the risk of malignant solid pulmonary nodules, but this view is contradicted by the results of Yi et al. [19, 20]. Lobulation is also a common identification indicator, but the conclusions of different studies are still inconsistent [13, 16].

Given the small sample sizes and single-center nature of these studies, along with incomplete evaluation indicators, this study employs meta-analysis to integrate data from prior research, aiming to identify independent risk factors for MSPN and provide a scientific basis for clinical decision-making.

Methods

Literature search strategy

Search databases

Searches for publications in Chinese and English were carried out independently by two authors across the following databases: PubMed, Cochrane Library, Web of Science, Embase, Scopus, CNKI, Wanfang, VIP, and CBM. The search was conducted up to October 6, 2024.

Search terms

The search strategy included a combination of terms related to Benign, Malignant and Solid Pulmonary Nodules.

Additional literature

Additional relevant studies were identified by manually reviewing the references of the selected publications to ensure comprehensive coverage.

Conflict resolution

In cases where disputes arose regarding the inclusion of studies, a third researcher was consulted to reach a consensus.

Registration and standards

This meta-analysis is registered in the PROSPERO System Review Register under the number CRD42024524910 and complies with all PRISMA requirements.

Inclusion and exclusion criteria

Inclusion Criteria:

1. Investigate the correlation between clinical and CT features and the type of solid pulmonary nodule (SPN).
2. Use surgical procedures as the "gold standard" for pathological diagnosis.
3. Include both retrospective and prospective study designs.
4. Provide raw data and statistical analyses.

Exclusion Criteria:

1. Review articles, abstracts, or case reports.
2. Duplicate publications.
3. Studies with missing or incomplete data.
4. Studies published in languages other than English or Chinese.

Data extraction and quality assessment

Two independent authors screened the articles based on the inclusion and exclusion criteria. Each author cross-checked the other's work to ensure accuracy. In cases of disagreement, potential solutions were discussed, and unresolved conflicts were settled by the corresponding author.

The following variables were extracted from each eligible study:

Study characteristics first author, publication year, and sample size.

Clinical features age, sex, family history of cancer, and CEA level.

Imaging features spiculation, lobulation, vascular convergence sign, diameter, border blur, vacuole sign, air bronchogram sign, calcification, emphysema, and pleura traction sign.

The quality of each included article was independently assessed by two authors using the Newcastle-Ottawa Scale (NOS), which evaluates:

Study selection (0–4 points): Representativeness of the study and appropriateness of the control selection.

Comparability (0–2 points): Control for confounding factors.

Outcome assessment (0–3 points): Adequacy of outcome evaluation and follow-up.

Articles with a NOS score of 5 or higher were considered to be of high quality.

Statistical analysis

Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to evaluate the association between risk factors and malignant solid pulmonary nodules (MSPN).

Heterogeneity across studies was assessed using the Q-test and I^2 statistic. Significant heterogeneity was defined as a P-value < 0.10 or an I^2 > 50%. In such cases, a random-effects model was applied to compute pooled ORs and 95% CIs. When heterogeneity was not significant, a fixed-effects model was used.

To ensure the robustness of the results, sensitivity analyses were conducted by sequentially excluding individual studies. Publication bias was assessed using funnel plots and statistically tested with Egger's and Begg's tests. A P-value > 0.05 in these tests was considered indicative of negligible publication bias.

All statistical analyses were conducted using Stata software (version 16.0).

Results

Literature retrieval and screening

This meta-analysis screened 2452 publications initially, from which 32 were finally included after excluding duplicates, titles and abstracts irrelevant to the research questions, animal studies, and full-text reviews. The included publications were all retrospective, comprising 15 articles in English and 17 in Chinese (Fig. 1).

General information and quality estimation of qualified publications

The general information for these 32 publications is displayed in Table 1. Quality assessment was subsequently conducted, with 14 articles receiving a NOS score of 5, and 18 articles a score of 6. All scores exceeded 5, indicating high quality(Table 1).

Meta-analysis results

Spiculation sign

Nineteen studies evaluated the occurrence of spiculation in both BSPN and MSPN, revealing substantial heterogeneity ($I^2 = 62.4\%$). Meta-analysis demonstrated that spiculation was significantly more frequent in MSPN than in BSPN [OR = 3.06, 95% CI (2.35, 3.98), $P < 0.05$] (Fig. 2A). Sensitivity analysis confirmed the robustness of these results, with no sources of heterogeneity detected (Fig. 3A).

Lobulation sign

Eighteen studies assessed the presence of lobulation in BSPN and MSPN, indicating significant heterogeneity ($I^2 = 59.6\%$). Meta-analysis found a markedly higher incidence of lobulation in MSPN compared to BSPN [OR = 5.17, 95% CI (3.83, 6.98), $P < 0.05$] (Fig. 2B). Sensitivity testing verified the stability of these findings, identifying no sources of heterogeneity (Fig. 3B).

Diameter

Eleven studies investigated diameter discrepancies between BSPN and MSPN, showing pronounced heterogeneity ($I^2 = 80.3\%$). The meta-analysis revealed that MSPN typically exhibited larger diameters than BSPN [OR = 1.25, 95% CI (1.13, 1.38), $P < 0.05$] (Fig. 2C). Sensitivity analysis produced consistent results with no heterogeneity sources found (Fig. 3C).

Vascular convergence sign

Four studies explored the vascular convergence sign in BSPN and MSPN, displaying high heterogeneity ($I^2 = 0\%$). Results indicated a significantly greater incidence of this sign in MSPN [OR = 16.57, 95% CI (8.79, 31.24), $P < 0.05$] (Fig. 2D).

Border blur

Seven studies examined the occurrence of border blur in BSPN and MSPN, uncovering considerable heterogeneity ($I^2 = 79.2\%$). Meta-analysis showed that MSPN was significantly more likely to exhibit border blur than BSPN [OR = 2.94, 95% CI (1.47, 5.85), $P < 0.05$] (Fig. 4A). Sensitivity testing confirmed stable findings without identifiable sources of heterogeneity (Fig. 3D).

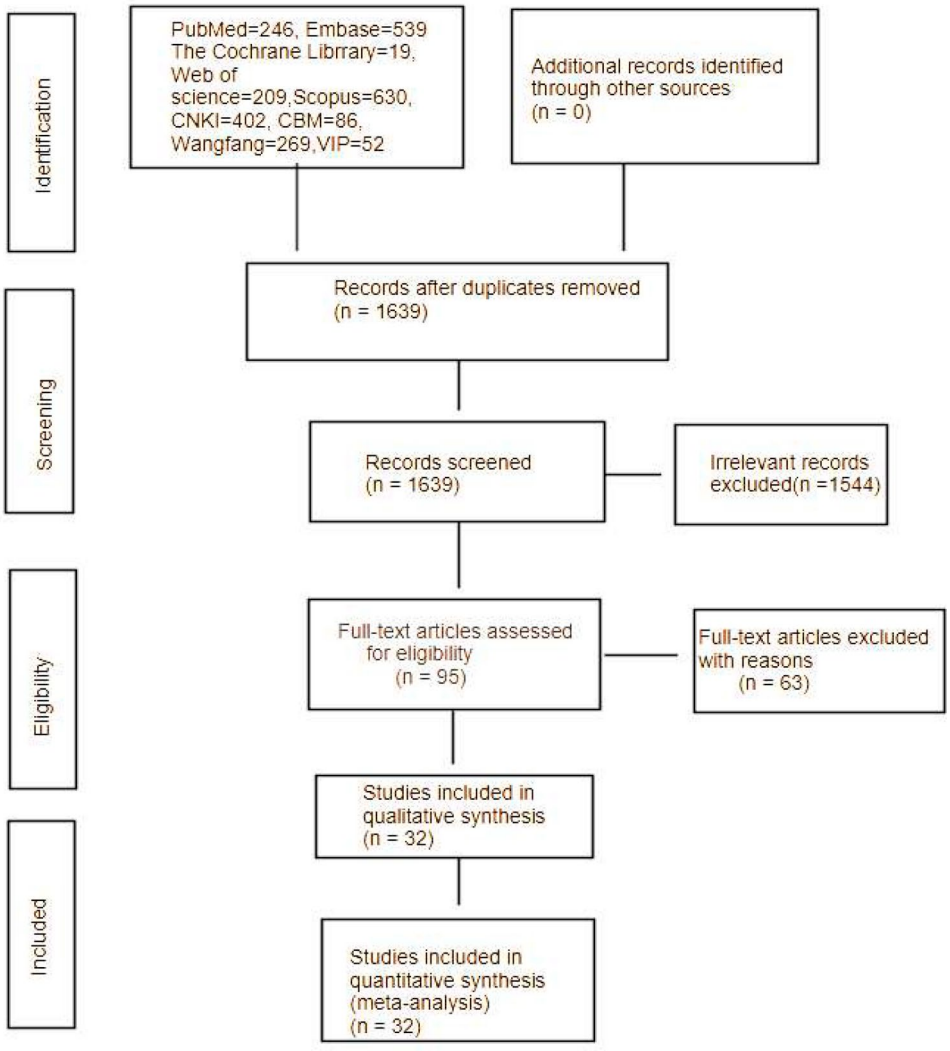

Fig. 1 Flowchart of literature search and screening

Age

Sixteen studies compared the ages of individuals with BSPN and MSPN, revealing extreme heterogeneity ($I^2 = 61.8\%$). The meta-analysis indicated that individuals with MSPN were typically older than those with BSPN [OR = 1.06, 95% CI (1.04, 1.07), $P < 0.05$] (Fig. 4B). Sensitivity analysis supported the consistency of these results (Fig. 3E).

Vacuole sign

Four studies assessed the vacuole sign in BSPN and MSPN, showing no heterogeneity ($I^2 = 0\%$). Meta-analysis identified a significantly higher incidence of the vacuole sign in MSPN compared to BSPN [OR = 5.25, 95% CI (2.66, 10.37), $P < 0.05$] (Fig. 4C).

Sex

Seven studies investigated sex differences regarding the vacuole sign in BSPN and MSPN, observing no heterogeneity ($I^2 = 8.7\%$). Results showed a higher prevalence of MSPN among women [OR = 2.98, 95% CI (2.27, 3.92), $P < 0.05$] (Fig. 4D).

Pleura traction sign

Eleven studies evaluated the pleura traction sign in BSPN and MSPN, with high heterogeneity found ($I^2 = 58.6\%$). No significant difference was detected in the occurrence of this sign between the groups [OR = 2.33, 95% CI (1.65, 3.29), $P < 0.05$] (Fig. 5A). Sensitivity analysis showed stable outcomes with no heterogeneity sources identified (Fig. 6A).

Table 1 Basic characteristics and quality evaluation results of the included literature

Author	Year	Sample size	Benign	malignancy	Outcomes	NOS scores
Chengyu Chen et al[21]	2023	147	82	65	(1)(3)	6
Mengqi Li et al[13]	2016	200	122	78	(6)(7)(8)	5
Jianing Liu et al[20]	2024	226	116	110	(1)(4)(5)(6)(9)(13)	6
Yangwei xiang et al[22]	2016	203	44	159	(1)(5)(7) (11)	6
Xiaodong Xie et al[23]	2023	132	30	102	(4)	6
Li Yi et al[24]	2022	200	95	105	(7)(8)	5
Fang Kong et al[25]	2021	235	54	181	(3)(12)	5
Chencheng Li et al[17]	2020	202	76	126	(1)(2))(3)(4)(6)(7)(9)(13)	5
Yun Li et al[18]	2011	371	142	229	(1) (4)(5)(7)(10)(11)	6
Xiang Ma et al[14]	2023	306	75	231	(1)(2)(4)((7)(12)(13)(14)	6
Li Yi et al[19]	2023	201	92	109	(7)(13)(14)	6
Kun Yuan et al[26]	2022	70	29	41	(2)(3)(5)(9)(12)	5
Qiang Zhang et al[27]	2022	105	34	71	(2)(9)	5
Wenjing Zhao et al[12]	2023	86	32	54	(1)(2)(9)	5
Chonhao Zhong et al[16]	2017	405	182	223	(1)(2)(4)(5)(7)(10)(13)	6
Wei Zhou et al[28]	2023	100	33	67	(1)(2)(11)(13)	5
Lili Zhu et al[15]	2022	266	91	175	(1)(2)(5)(9)(10)	6
Zhi Liu et al[29]	2020	164	50	114	(1)(2)(9)(13)	5
Bao Feng et al[30]	2020	123	58	65	(1)(7)(8)	6
Xiangmeng Chen et al[31]	2020	150	73	77	(2)(8)	6
Hao-Yue Guo et al[32]	2020	312	97	215	(1)(2)(4)(6)(7)(8)	6
Changjiu He et al[33]	2022	151	73	78	(4)	5
Xiao-Qun He et al[34]	2024	579	312	267	(2)(9)(11)(13)	6
Zhen Zhang et al[35]	2018	246	96	150	(1)(4)(7)	5
Jin Jiang et al[36]	2023	295	125	170	(2)(4)	5
Wei Yu et al[37]	2016	317	155	162	(1)(2)(7)(9)(10)(11)	6
Rui-Yu Lin et al[38]	2021	348	171	177	(1)(2)(7)(13)	6
Bai-Qiang Qu et al[39]	2024	360	147	213	(1)(2)(4)(7)(12)(13)	6
Jizheng Tang et al[40]	2021	141	81	60	(1)(2)	6
Chun-Ran Zhang et al[41]	2023	289	142	147	(7)(8)(12)(13)	6
Wei-hua Zhao et al[42]	2024	515	233	282	(7)(8)(9)	5
Yaoyao Zhuo et al[43]	2021	313	217	96	(6)(7)(8)	5

NOS = Newcastle-Ottawa Scale

1、spiculation;2、lobulation; 3、vascular convergence sign; 4、diameter; 5、border blur; 6、Vacuole sign; 7、age; 8、sex; 9、air bronchogram sign; 10、Family history of cancer; 11、Calcification;12、emphysema; 13、pleura traction sign; 14、CEA level

Air Bronchogram sign

Ten studies examined the air bronchogram sign in BSPN and MSPN, indicating high heterogeneity ($I^2 = 70\%$). Initial results showed no significant difference [OR = 2.96, 95% CI (1.62, 5.41), $P < 0.05$] (Fig. 5B). Sensitivity analysis corroborated these findings as stable, with no heterogeneity sources detected (Fig. 6B).

Family history of cancer

Four studies evaluated the prevalence of a family history of cancer in BSPN and MSPN, showing no heterogeneity ($I^2 = 0\%$). Meta-analysis indicated a higher incidence of family history of cancer in MSPN [OR = 3.85, 95% CI (2.43, 6.12), $P < 0.05$] (Fig. 5C).

Calcification

Six studies assessed the prevalence of calcification in BSPN and MSPN, displaying significant heterogeneity ($I^2 = 62.0\%$). Meta-analysis revealed a notably higher prevalence of calcification in BSPN compared to MSPN [OR = 0.21, 95% CI (0.10, 0.48), $P < 0.05$] (Fig. 5D). Sensitivity analysis corroborated these findings as stable, with no heterogeneity sources detected (Fig. 6C).

CEA level

Two studies evaluated CEA levels in BSPN and MSPN, exhibiting substantial heterogeneity ($I^2 = 87.4\%$). The analysis indicated no significant differences between the groups [OR = 2.88, 95% CI (0.39, 21.10), $P > 0.05$] (Fig. 5E).

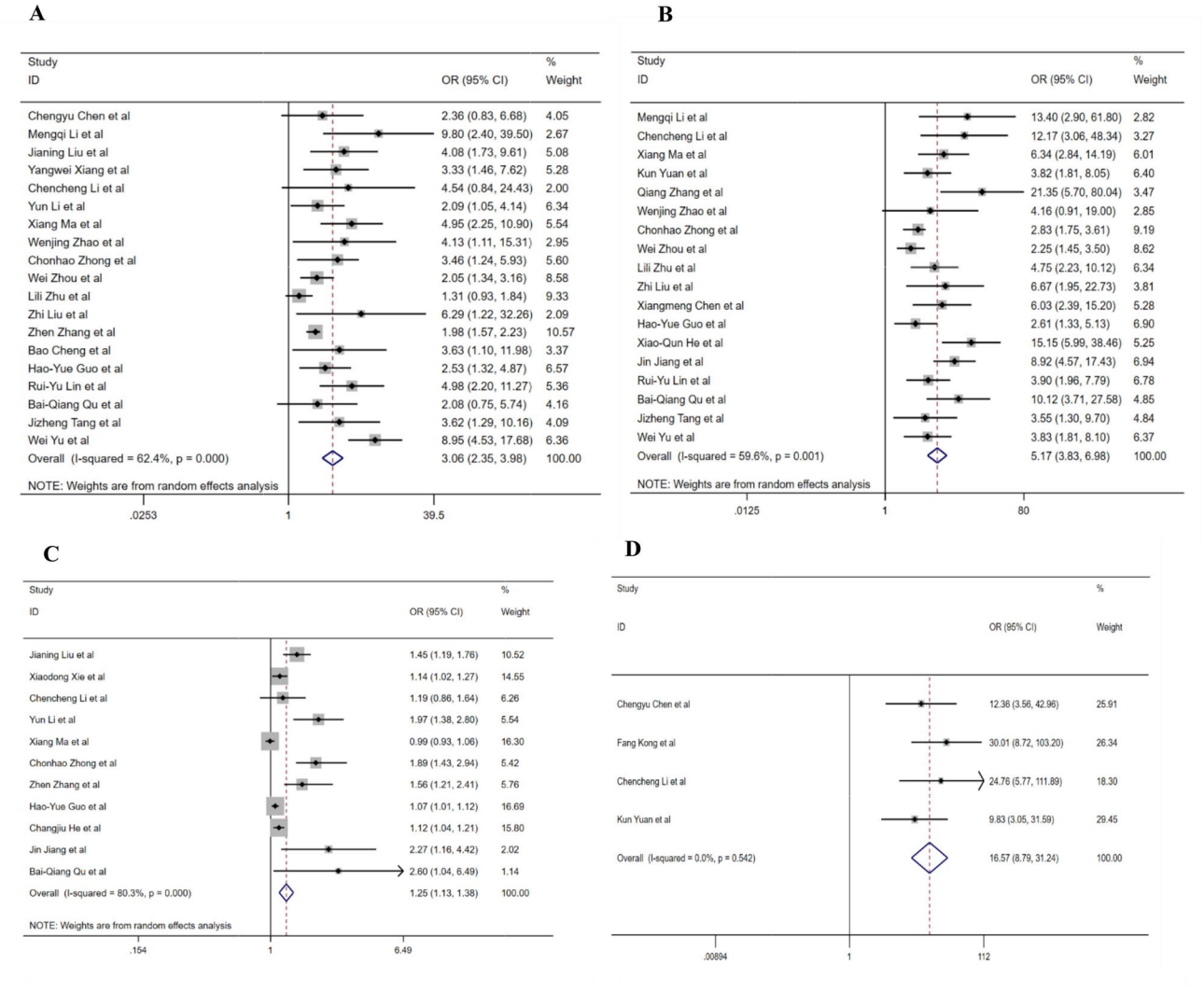

Fig. 2 A Forest plot of spiculation sign. B Forest plot comparing of lobulation sign. C Forest plot of the diameter. D Forest plot of vascular convergence sign

Emphysema

Five studies examined the frequency of emphysema in BSPN and MSPN, revealing high heterogeneity ($I^2 = 65.3\%$). Results showed no significant disparities in the incidence of emphysema between the groups [OR = 2.01, 95% CI (0.84, 4.81), $P > 0.05$] (Fig. 5F). However, excluding the study by Kong et al[OR = 2.79, 95% CI (1.69, 4.62), $P < 0.05$], a higher incidence was observed in MSPN, suggesting initial results were unstable (Fig. 6D).

Publication bias

Funnel plot showed publication bias in spiculation sign, lobulation sign, age, pleura traction, air bronchogram sign and diameter(provided in Supplementary 4), egger's test results showed that there was publication bias in spiculation sign, lobulation sign, calcification, sex and diameter($P<0.05$), and no publication bias was found in other risk factors($P>0.05$). Begg's test results showed that there was publication bias in lobulation sign and calcification($P<0.05$), and no publication bias was found in other risk factors($P>0.05$).

Discussion

As early screening for lung cancer becomes more prevalent, an increasing number of pulmonary nodules are identified, a substantial number of which are solid. Surveillance is typically the initial management approach for these solid nodules. Nevertheless, the high malignancy rates and poor prognoses associated with malignant solid nodules necessitate early surgical intervention as the primary therapeutic strategy. Consequently, precise differentiation between benign and malignant solid nodules is paramount.

Extant research has shown that both clinical and radiological features are instrumental in differentiating benign

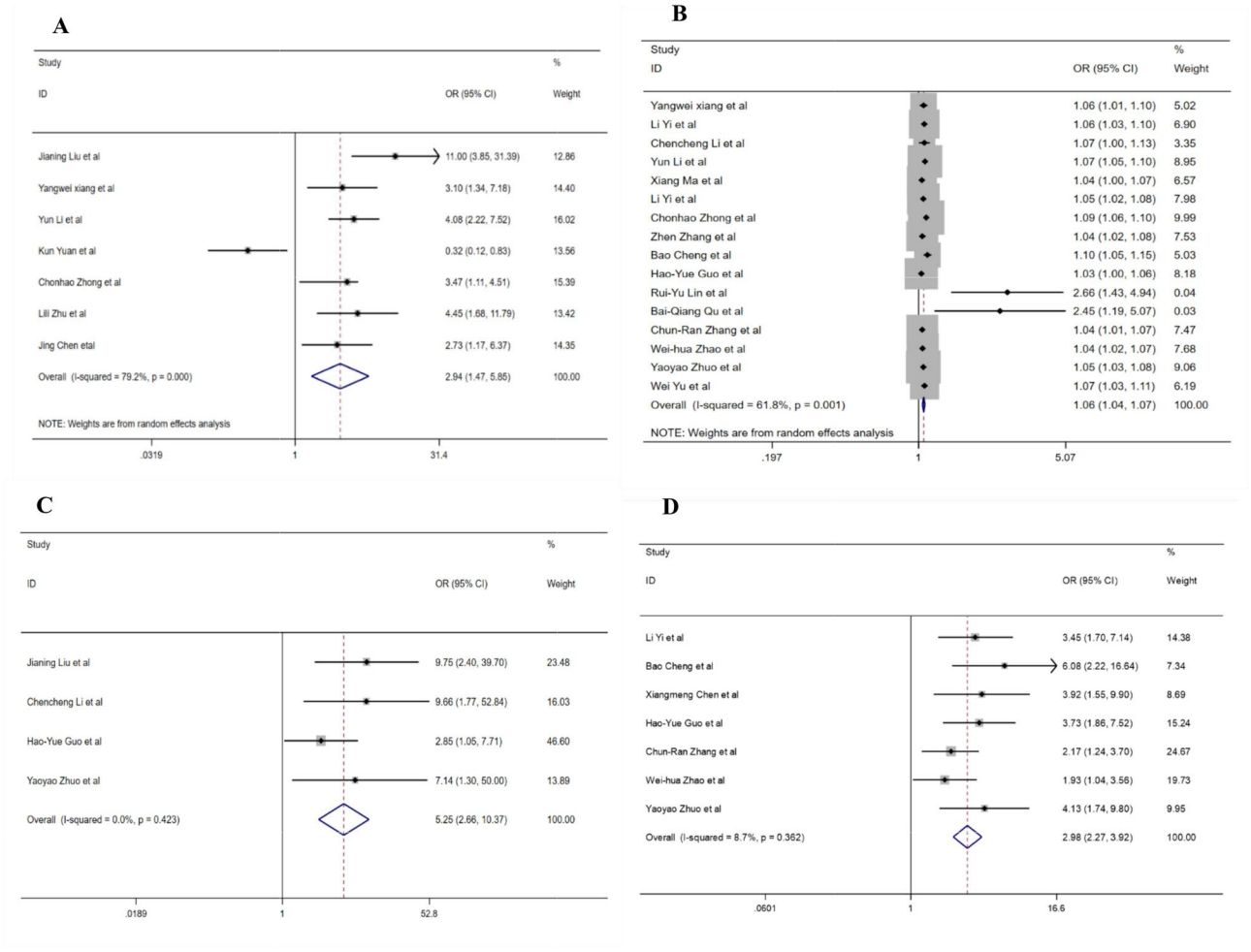

Fig. 3 The sensitivity analysis of clinical and CT features for the included studies. **A**) spiculation sign; **B**) lobulation sign; **C**) diameter; **D**) border blur; **E**) age

from MSPN, although the specific characteristics identified vary across studies [20, 21]. We conducted the first meta-analysis on the risk factors associated with malignant solid pulmonary nodules. A total of 7,758 solid pulmonary nodules from 32 studies were analyzed, focusing on their clinical and imaging characteristics. Twelve risk factors were identified as being significantly associated with malignancy in solid pulmonary nodules. These findings provide valuable insights that can aid clinicians in making more informed decisions.

Diameter is frequently employed to assess whether SPNs are benign or malignant. Our findings affirm that diameter is a reliable metric for differentiating these nodules, aligning with the findings of most studies [20, 23]. Conversely, the research by Li et al. contends that diameter may not reliably predict malignancy, particularly in nodules of smaller size, which might obscure significant group differences [17]. Lobulation describes the irregular proliferation of tumor cells or the constraints imposed by adjacent structures, leading to nodules with multiple protuberances of varying curvatures, creating a lobulated appearance [44]. Our data suggest that lobulation serves as a malignancy risk factor in solid nodules. Furthermore, spiculation, which involves the reformation of interlobular septa due to tumor invasion processes such as hemorrhage, exudation, and fibrosis [45], is identified in prior research as essential for recognizing malignant nodules, a conclusion supported by our results [14, 20]. Nonetheless, findings from Chen et al. differ, potentially due to the study of smaller nodules where spiculation is not as apparent, introducing some level of subjective bias into their analysis [21].

Malignant nodules exhibit continuous outward infiltration as they grow, leading to a blurred node-lung interface. In contrast, benign nodules typically lack peripheral infiltration, maintaining a clear and smooth interface [9]. Our findings identify border blur as an indicative feature of malignant pulmonary nodules. Conversely, Yuan et al. reported an opposite outcome, possibly due to the inclusion of non-specific inflammatory nodules with blurred margins in their sample [26]. The vessel convergence sign, often seen in MSPN, reflects the tumor's

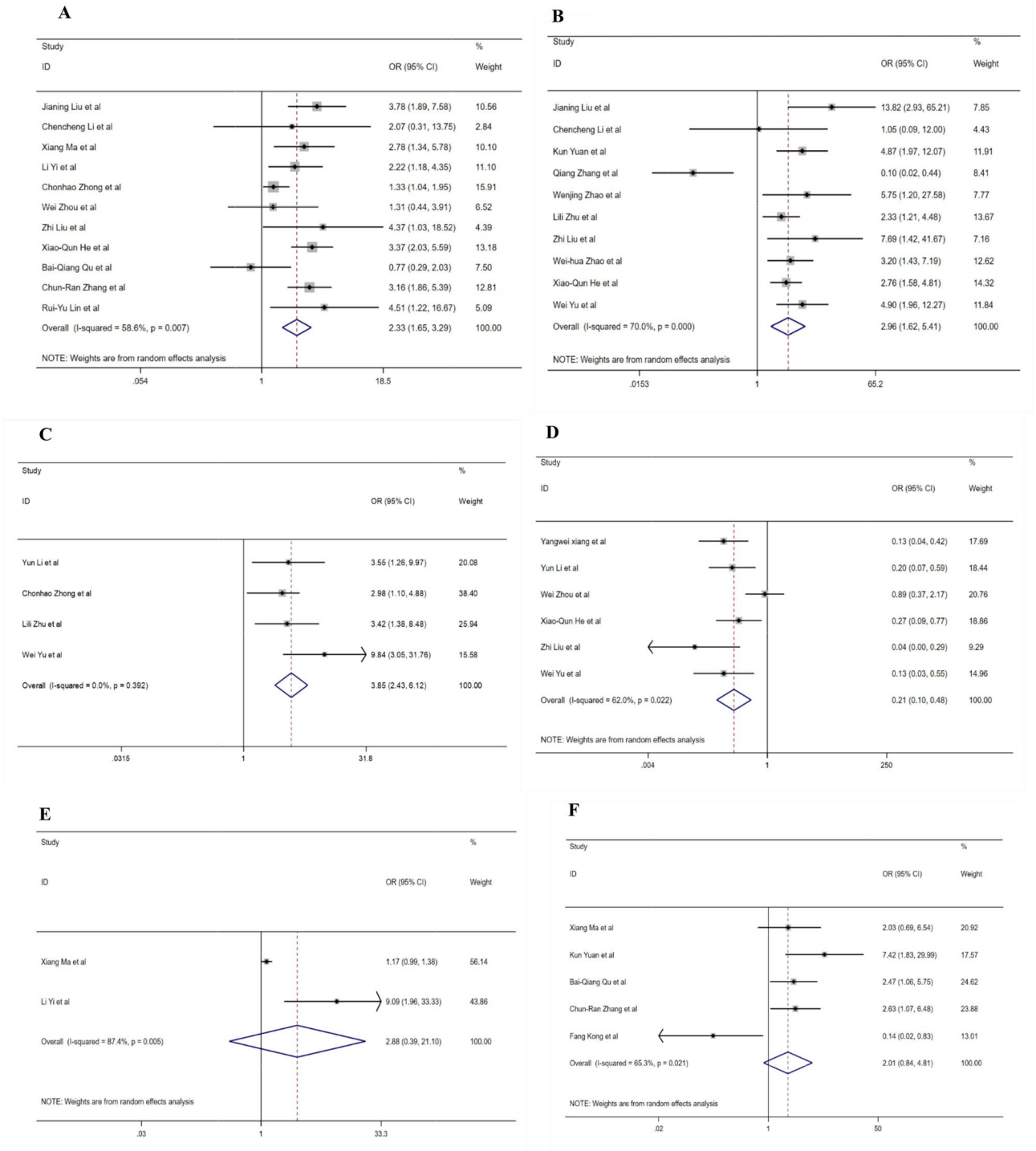

Fig. 4 **A** Forest plot of border blur. **B** Forest plot of the age. **C** Forest plot of vacuole sign. **D** Forest plot of the sex

ability to redirect adjacent vessels from their original paths by secreting large quantities of vascular endothelial growth factor. This factor not only promotes neovascularization but also enhances tumor growth and facilitates metastasis [46]. Our analysis confirms that the vessel convergence sign is a reliable marker for differentiating malignant from benign solid nodules. Additionally, the vacuole sign plays a crucial role in this differentiation process. Previous research has indicated that calcification typically signals the presence of benign pulmonary nodules [37]. Calcification generally results from chronic pulmonary disorders or acute inflammatory diseases. During the body's reparative processes, deposition of calcium salts in localized lung tissues creates dense shadows

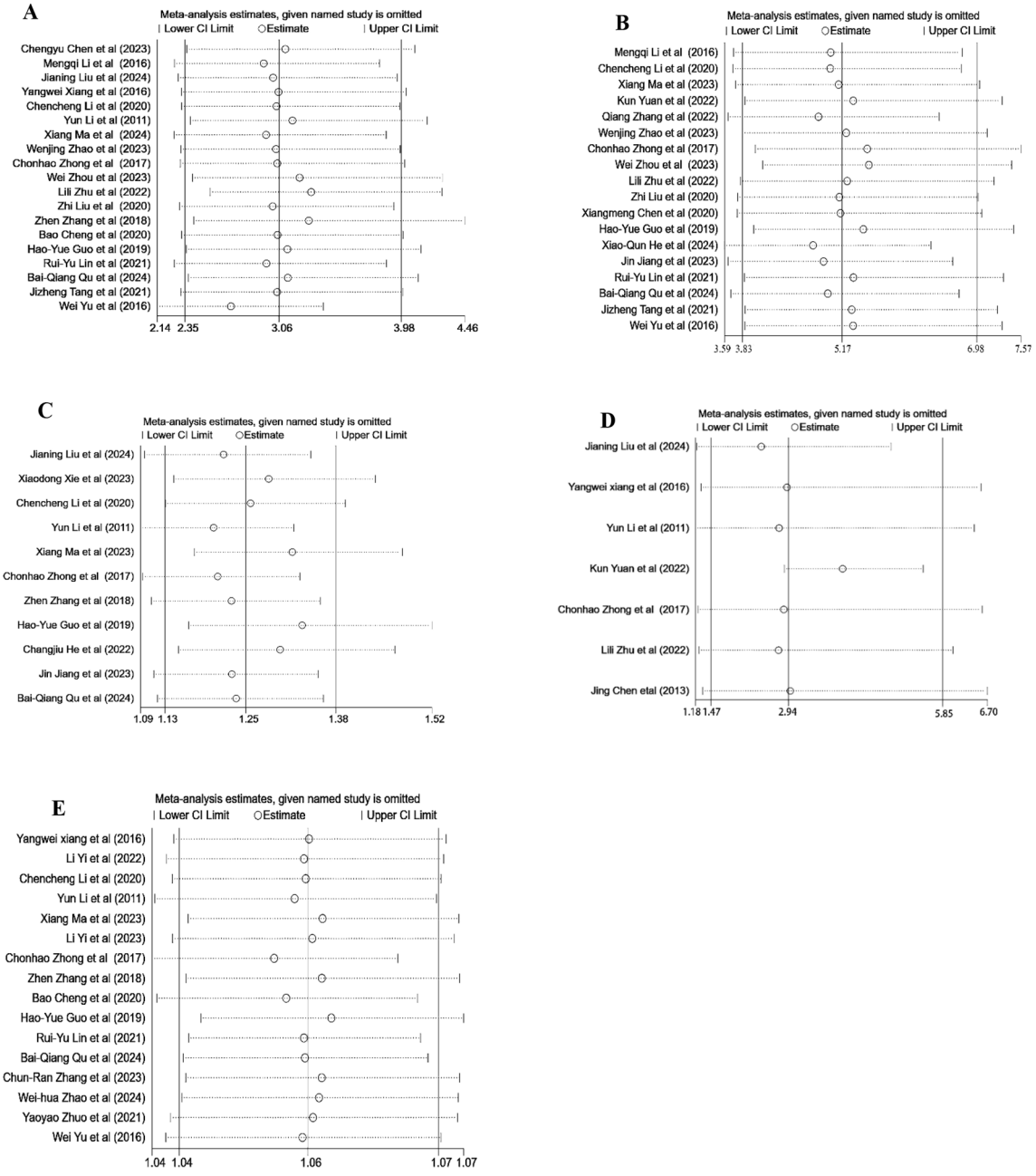

Fig. 5 **A** Forest plot of pleura traction sign. **B** Forest plot of air bronchogram sign **C** Forest plot of the Family history of cancer. **D** Forest plot of Calcification. **E** Forest plot of the CEA level. **F** Forest plot of the emphysema

[47], a characteristic commonly observed in benign solid lung nodules and corroborated by our results. Previous studies have indicated that as tumor cells infiltrate and grow into surrounding tissues, they cause tissue destruction, leading to the appearance of air bronchogram sign and pleura traction sign [14, 26]. Our study further confirms these findings.

Clinical characteristics are pivotal in differentiating between benign and MSPN. Our analysis demonstrates that the probability of malignancy in these nodules escalates with age, possibly due to the cumulative effect of carcinogenic factors that increase proto-oncogene mutations and decrease immune function, thereby facilitating lung cancer development [48]. Furthermore, our findings confirm that factors such as gender and familial cancer history are crucial in identifying malignancy in SPNs.

Our sensitivity analysis addressed variables showing significant heterogeneity. The analysis revealed stable results across most factors, except for the emphysema,

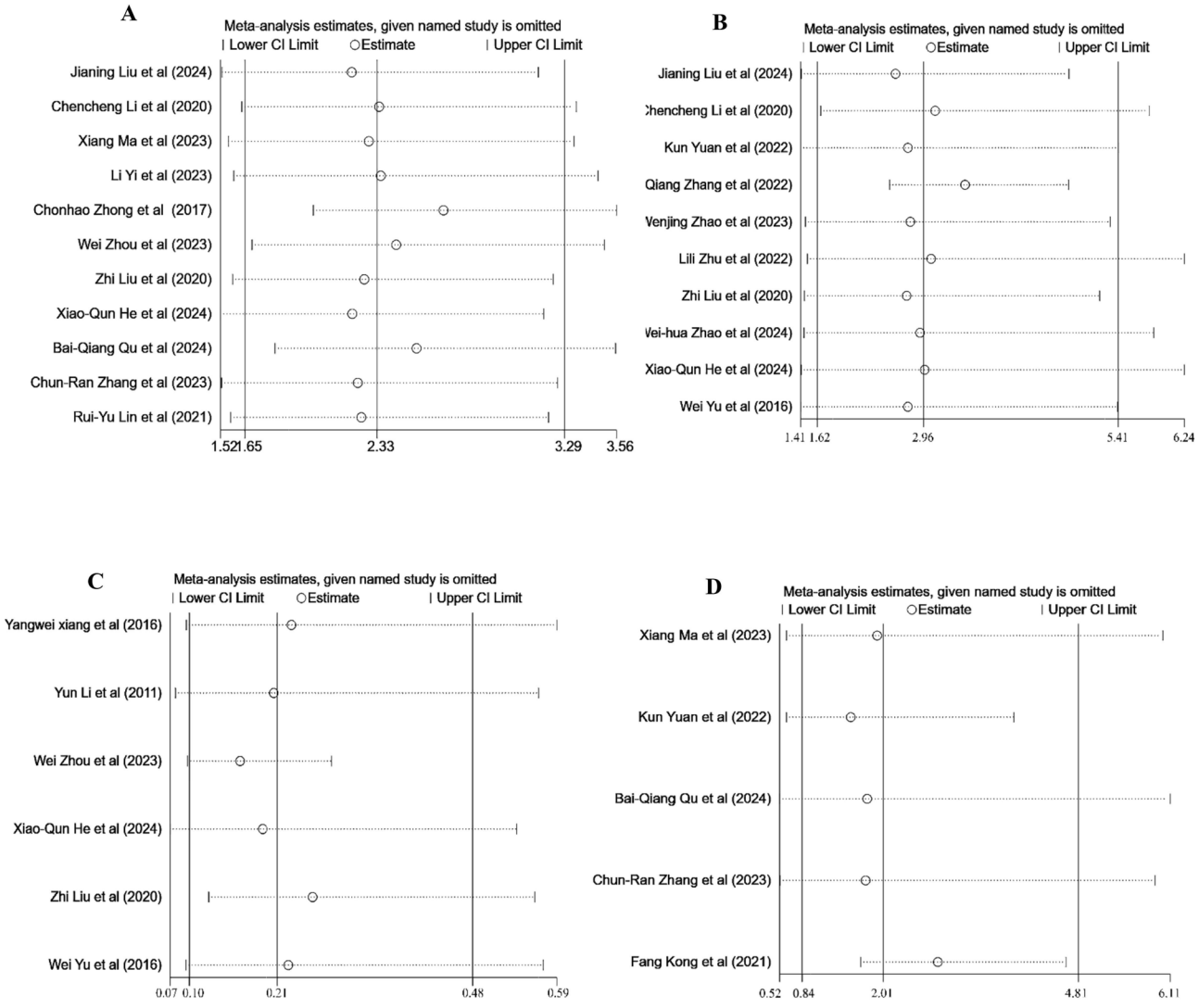

Fig. 6 The sensitivity analysis of clinical and CT features for the included studies. **A**) pleura traction sign; **B**) air bronchogram sign; **C**) Calcification; **D**) emphysema

which displayed variability. Upon excluding data from the study by Kong et al., a higher incidence of the emphysema in MSPN was observed. Efforts to extract more detailed data from original studies were hindered by inadequate reporting or difficulties in data extraction, limiting our capacity to further investigate the sources of heterogeneity.

Historically, research into the risk factors for malignant solid lung nodules has been constrained by small sample sizes and single-center studies, resulting in inconsistent and unreliable findings. Meta-analysis, representing the zenith of evidence-based medicine, offers substantial benefits by amalgamating data from diverse centers, enlarging sample sizes, and enhancing the robustness of evidence [49, 50]. This study is the first meta-analysis to investigate the risk factors for MSPN, filling an important gap in the literature. Our results reveal significant differences between MSPN and BSPN across multiple markers, including the spiculate sign, vascular convergence sign, lobulated sign, diameter, border blur, vacuole sign, age, gender, Calcification, air bronchogram sign, pleura traction sign and familial cancer history. These findings are consistent and stable, providing valuable clinical insights that could aid in the differentiation and management of SPNs.

Our study is not without its limitations. Firstly, the inclusion of only retrospective studies introduces potential selection biases that could affect the overall results. Secondly, the restriction of eligible studies to those conducted in China may limit the generalizability of our findings to other populations. Thirdly, by including only literature published in English or Chinese, we may have omitted pertinent studies in other languages, thereby introducing publication bias. Lastly, the limited number

of studies included necessitates the need for more comprehensive and larger-scale research to verify these conclusions.

Conclusion

In conclusion, this meta-analysis emphasizes that the spiculate sign, vascular convergence sign, lobulated sign, diameter, border blur, vacuole sign, air bronchogram sign, pleura traction sign, age, gender, familial history of cancer, and calcification are valuable markers for predicting malignancy in SPNs, with potential significant impact on clinical decision-making for SPN management. Nevertheless, further extensive, well-structured research is essential to substantiate these findings.

Abbreviations

BSPN	Benign solid pulmonary nodules
CI	Confidence Interval
HRCT	High-resolution CT
MSPN	Malignant solid pulmonary nodules
NOS	Newcastle-Ottawa Scale
OR	Odds Ratio
SPN	Solid pulmonary nodule

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13702-2 .

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

Supplementary Material 12

Supplementary Material 13

Supplementary Material 14

Supplementary Material 15

Supplementary Material 16

Supplementary Material 17

Supplementary Material 18

Supplementary Material 19

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Not Applicable.

Author contributions

Lianhua Ye is responsible for the research topic selection and design, data analysis and interpretation, paper review and revision suggestions; Yantao Yang and Xuancheng Li and Yaowu Duan were responsible for study design, data acquisition, and analysis, interpretation of the data, and preparation of the draft of the manuscript. Jie Zhao and Qiubo Huang were responsible for statistical analysis., Chen Zhou and Wangcai Li were responsible for study concept and design, interpretation of the data, study supervision, and revision of the manuscript.

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Data availability

All data included in Meta-analysis are available in the main manuscript and its supplementary information files.

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Ethics and consent to participate.

Not applicable.

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