Original Study

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Tumor Spread Through Air Spaces Is a Survival Predictor in Non–Small-Cell Lung Cancer

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Abstract

Tumor spread through air spaces (STAS) is associated with poor survival of non–small-cell lung cancer (NSCLC). The histology type, Tumor, Node, Metastases stage, and region did not alter prognostic value of STAS. STAS is associated with clinicopathologically aggressive features in NSCLC.

Background: Tumor spread through air spaces (STAS) is a newly recognized invasion pattern in non–small-cell lung cancer (NSCLC). However, the clinical application value of STAS in NSCLC remains to be clarified. We aimed to comprehensively explore the potential role of STAS as a prognostic indicator in NSCLC. **Patients and Methods:** A systematic search was performed in PubMed, Embase, Cochrane Library, and Web of Science until April 15, 2018. A quantitative meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. **Results:** A total of 3231 patients from 8 studies were included. STAS was observed in 1204 cases (37.3%). A significant association was found between STAS and poor progression-free survival (PFS) (hazard ratio [HR], 1.789; $P < .001$) and overall survival (OS; HR, 1.488; $P < .001$). STAS was also an independent prognostic factor for PFS (HR, 1.632; $P < .001$) and OS (HR, 1.475; $P < .001$) without obvious heterogeneity. Subgroup analyses and meta-regression showed histology type, tumor, node, metastases (TNM) stage, publication year, sample size, region, and quality score did not alter prognostic value of STAS. Tumor STAS was associated with male sex ($P < .001$), history of smoking ($P < .001$), tumor budding ($P = .038$), vascular invasion ($P < .001$), lymphatic invasion ($P < .001$), pleural invasion ($P < .001$), T stage ($P < .001$), N stage ($P < .001$), and TNM stage ($P < .001$). The publication bias was observed. After adjustment using a nonparametric "trim-and-fill" method, corrected HRs had no significant change. **Conclusion:** Tumor STAS is associated with clinicopathologically aggressive features and could be exploited as a novel prognostic predictor in NSCLC.

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Introduction

Non–small-cell lung cancer (NSCLC) is the most common cancer worldwide.[1] Despite recent advances in treatment, the prognosis of NSCLC remains poor. Tumor invasion, such as lymphovascular, pleural invasion, or infiltration of stroma is related to poor prognosis of NSCLC. The presence of tumor cells in air spaces is also regarded as a manifestation of the invasion in lung cancer. As early as 2002, micropapillary component or micropapillary differentiation had been found in primary and metastatic lung adenocarcinoma (ADE).[2] In 2011, the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society recommended the addition of micropapillary predominant ADE as a major histologic subtype because of its association with poor prognosis.[3] The micropapillary component was defined as small papillary clusters of glandular cells growing within air spaces. Onozato et al[4] proposed tumor islands of NSCLC in 2013, which referred to an isolated, large collection of tumor cells present within alveolar spaces that lacked well demarcated micropapillary configuration. In 2015, the World Health Organization classification of lung cancer proposed the concept of spread through air spaces (STAS) as a new pattern of invasion in ADE. STAS includes one or more pathologic micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma.[5]

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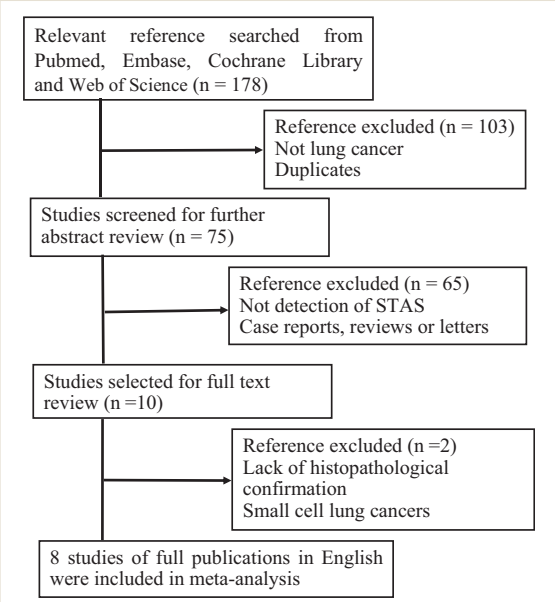
Figure 1 Study Flow Chart Showing Process for Selecting Eligible Publications



Abbreviation: STAS = spread through air spaces.

The role of STAS in NSCLC had been investigated in many studies, however, the results were inconsistent. Previous studies have shown that the frequency of STAS in NSCLC ranges from 14.8% to 55.4%.[6-13] Several retrospective studies have shown that STAS is an independent prognostic factor for overall survival (OS) and progression-free survival (PFS).[6-9] However, Lu et al[10] reported there was no statistically significant difference in OS between patients with and without STAS. Kadota et al[11] also reported that STAS was not associated with recurrence ($P = .50$) in patients with lobectomy. Dai et al[12] suggested that STAS failed to stratify the clinical outcomes among patients with ADE $\leq$2 cm. These studies drew different and even contradictory conclusions. The clinical values of STAS in NSCLC remain unclear. Pooled analysis of currently available studies is needed to clarify the prognostic significance of STAS in NSCLC. Therefore, we systematically reviewed previous literature to investigate whether STAS was closely correlated with prognosis of NSCLC. The frequency of STAS and its clinicopathological values were further analyzed in the present study.

Patients and Methods

Study Selection

According to guidelines for meta-analyses of prognostic studies,[14] we performed this systematic review to determine the prognostic value of STAS for NSCLC patients. We searched the PubMed, Embase, Cochrane Library, and Web of Science databases to identify publications with the combination of the following terms: "spread through air spaces" or "STAS" or "tumor invasion" or "lung cancer." The reference lists of original articles and review articles were also manually searched to increase the search sensitivity. The published language was limited to English and the literature search was conducted to April 15, 2018.

Results from the initial search that matched the following criteria were considered eligible: (1) the studies must determine STAS in NSCLC; (2) individuals with NSCLC must be histopathologically confirmed; (3) STAS must be confirmed using histopathological examination; and (4) the association between STAS and patient survival was clarified. Studies had no restrictions on the methods of obtaining the tissue specimens. The studies were excluded if patients had: (1) small-cell lung cancer or pulmonary benign tumors; or (2) metastatic cancers from organ other than the primary cancers. Case reports, reviews, letters, or meeting abstracts were also excluded. If the same patient population was used in more than one study, only the complete study was included.

Data Extraction and Quality Assessment

To validate the accuracy of extraction data, 2 authors (S.W., J.H.) extracted data independently from the eligible studies using standardized data compilation forms and disagreements were resolved via discussion. For all included studies, the following information was collected: first author, year of publication, region, sample size, cases with STAS, study design, treatment modality, and follow-up. The clinicopathological features of patients were also extracted from studies that included the data. Quality assessment was performed independently by 2 investigators (S.W., J.H.) and reached a consensus on all items through discussion. All articles were scored according to quality scale established by the National Cancer Institute (NCI)-European Organisation for Research and Treatment of Cancer (EORTC) working group.[14] The final scores were expressed as percentages and ranged from 0 to 100; higher scores suggest better methodological quality.

Statistical Analysis

The hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted as in our previous reports.[15,16] The χ^2-based Q test and I^2 statistic were performed to analyze heterogeneity across studies. I^2 statistics with values >50% and χ^2 test with $P < .05$ indicate strong heterogeneity.[17] The Mantel-Haenszel method and the DerSimonian and Laird method were used to determine the choice of fixed effects model or the random effects model. Subgroup analysis and meta regression were conducted according to histology type, tumor stage, publication year, sample size, region, and quality score. The odds ratios (ORs) and corresponding 95% CIs were also pooled to analyze correlations between STAS and clinicopathological features. Sensitivity analysis was performed to test the effect of individual studies on the pooled data. Begg funnel plots and Egger linear regression test were performed to estimate publication bias.[18] This meta-analysis was performed using the software Stata 11.0 (Stata Corp, College Station, TX). All of the P values were 2-sided. Differences were considered statistically significant at $P < .05$.

Results

Literature Search and Study Characteristics

Our initial search retrieved 178 references. After carefully screening the abstract and full-text, 8 articles were finally included in current meta analysis. The selection steps are summarized in Figure 1. The accrual period of 8 studies ranged from 2015 to 2018. Among those 8

Table 1 Characteristics of Studies Included in the Meta-Analysis

Reference	Region	Cases	STAS (%)	Histology	Stage	PT	Study Design	Quality Score
Dai et al[12]	China	788	243 (30.8)	ADE	I (788)	No	R	85.4
Kadota et al[11]	USA	411	155 (37.7)	ADE	I (411)	No	R	84.6
Kadota et al[8]	Japan	216	87 (40.3)	SCC	I (134), II (56), III (22), IV (4)	No	R	84.2
Lu et al[10]	USA	445	132 (29.7)	SCC	I (249), II (131), III (65)	No	R	86.5
Shiono et al[6]	Japan	318	47 (14.8)	ADE	IA (242), IB (76)	NA	R	85.6
Toyokawa et al[7]	Japan	276	153 (55.4)	ADE	IA (206), IB (70)	NA	R	83.6
Uruga et al[9]	Japan	208	99 (47.6)	ADE	I (208)	NA	R	84.1
Warth et al[13]	Europe	569	288 (50.6)	ADE	I (227), II (124), III (199), IV (19)	No	R	86.9

Abbreviations: ADE = adenocarcinoma; PT = pretreatment before sample collection; R = retrospective; SCC = squamous cell carcinoma; STAS = spread through air spaces.

studies, 6 studies were on ADE,[6,7,9,11-13] 2 studies were on lung squamous cell carcinoma (SCC).[8,10] All studies were described as retrospective research and selected NSCLC patients who underwent surgery. Pretreatment information before sample collection was described in 5 articles, however, 3 studies[6,7,9] did not describe the pretreatment information. Five studies did not provide the information on adjuvant therapies. In study from Kadota et al,[8] 35 patients received adjuvant therapies, whereas 162 patients received adjuvant chemotherapy and 108 received adjuvant mediastinal radiation in the study from Warth et al.[13] Dai et al[12] also showed that STAS was not connected to adjuvant chemotherapy ($P = .710$) in the cohort of 229 patients who had adjuvant chemotherapy. Two studies showed STAS was related to *EGFR* (epidermal growth factor receptor) mutation status,[6,13] but Toyokawa et al[7] did not report positive results ($P = .129$). Two studies showed the carcinoembryonic antigen level was not associated with the presence of STAS.[6,12] Data on proliferative activity (Ki-67) were available in 2 studies, but the results were inconsistent.[10,13] Only 1 study reported that the presence of STAS was tightly linked to the *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) gene mutation status ($P = .016$).[13] The relationship between STAS and programmed death ligand 1 (PD-L1) expression ($P = .872$)[7] or maximum standardized uptake value ($P = .181$)[6] was not significant. All studies detected STAS in surgical samples. Descriptions of pathological analysis in different sample sizes or small biopsies increased the reliability of clinical implications of STAS, especially in very early or late stage disease. However, none of studies reported the sample or biopsy sizes. So, we did not analyze the value of STAS in different sample sizes or biopsies. Quality assessment of eligible studies was scored in a quantitative manner. The mean quality score was 85.1, with a maximum quality score of 86.9 and a minimum quality score of 83.6. The characteristics of included studies are shown in Table 1.[6-13]

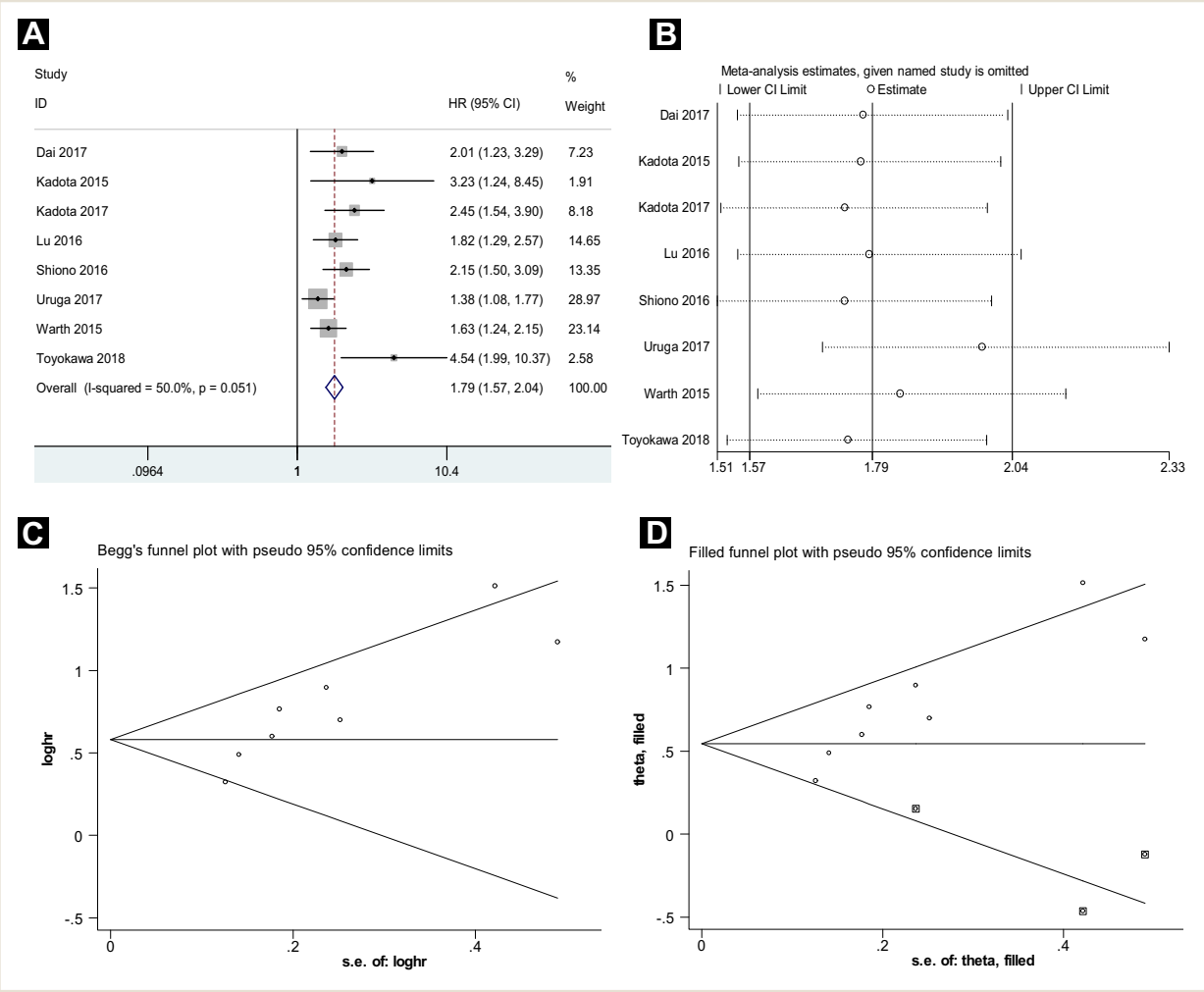
In total, 3231 patients were included and incidence of STAS was 37.3% (1204/3231) in patients with NSCLC. Our data indicated patients of Asian origin (34.8%, 629/1806) had a lower prevalence compared with those with European origin (40.4%, 575/1425). However, the overall STAS rate differed among Asian regions: 30.8% (243/788) in China, and 37.9% (386/1018) in Japan. We also found that the STAS rate in unselected cases of ADE was 38.3% (985/2570), which was slightly higher than the results from SCC population-based studies (33.1%, 219/661).

Prognostic Value of STAS

Eight studies reported the PFS of NSCLC patients. Heterogeneity analysis revealed that there was no between study heterogeneity across 8 studies ($\chi^2 = 14.00$; $P = .051$; $I^2 = 50.0\%$). Therefore, meta-analysis was carried out using the fixed effects model. Overall, there was a significant association between STAS and poor PFS of patients with NSCLC (HR, 1.789; 95% CI, 1.566-2.042; $P < .001$; Figure 2). Subgroup analyses indicated histology type, tumor, node, metastases (TNM) stage, publication year, sample size, region, and quality score did not result in interstudy heterogeneity (Table 2). As was found in the subgroup analyses, meta-regression showed those factors did not alter the significant prognostic value of STAS in PFS. We carried out a sensitivity analysis to assess the stability of the results. The leave-one-out sensitivity analysis indicated that no individual study significantly changed the pooled HRs (Figure 2), suggesting that our results were stable and reliable. However, the shapes of the funnel plots seemed asymmetrical and publication bias was significant after Begg test ($z = 2.35$; $P = .019$) and Egger test [t(bias) = 5.04; $P = .002$]. Nonparametric "trim-and-fill" method was used to replace 3 missing studies (Figure 2). After the trim-and-fill adjustment, the estimated pooled HR was 1.673, with 95% CI being 1.476-1.895 ($P = .007$).

The meta-analysis of OS was on the basis of 6 studies that provided the required data. We detected a significant relationship between STAS and OS of NSCLC (HR, 1.488; 95% CI, 1.292-1.715; $P < .001$). There was evidence for significant heterogeneity between studies ($\chi^2 = 13.72$; $P = .017$; $I^2 = 63.6\%$). The association between STAS and OS was significant in all stratified analyses (Table 2). Meta regression suggested that histology type ($P = .398$), TNM stage ($P = .480$), publication year ($P = .484$), sample size ($P = .522$), region ($P = .748$), and quality score ($P = .374$) did not significantly alter HRs. Moreover, HRs and corresponding 95% CIs did not change qualitatively after exclusion of any of studies in the sensitivity analysis (Figure 3). However, we found that the shape of the funnel plot was asymmetrical (Figure 3). Continuity corrected z value of the Begg test was 2.24 ($P = .024$) and t value (bias) of the Egger test was 5.37 ($P = .006$). Statistical data showed there was significant publication bias. We estimated the 2 missing studies using the "trim-and-fill" method (Figure 3). After correction, the adjusted pooled HR was 1.404 (95% CI, 1.224-1.610; $P < .001$).

Figure 2 Meta-Analysis of Hazard Ratios (HRs) of Progression-Free Survival of Non–Small-Cell Lung Cancer Patients With Spread Through Air Spaces. (A) Forest Plots of Meta-Analysis of the HRs and 95% CIs. (B) Results of Sensitivity Analysis. (C) Begg Funnel Plot Analysis for Publication Bias. (D) Filled Funnel Plot of Meta-Analysis Using "Trim-and-Fill" Method. Open Circles Indicate Observed Studies; Circles in Squares Indicate Missed Studies



Abbreviations: loghr = log(HR); s.e. = standard error.

Independent Prognostic Value of STAS

Cox multivariate analyses were performed in 6 studies to explored whether STAS was an independent predictive factor for PFS. Between study heterogeneity could be ignored ($\chi^2 = 5.66$; $P = .341$; $I^2 = 11.6\%$). Meta analysis suggested that STAS was an independent prognostic factor for PFS (HR, 1.632; 95%CI, 1.382-1.927; $P < .001$). Subgroup analysis and meta-regression showed that histology type, TNM stage, publication year, sample size, region, and quality score did not alter the independent predictive value of STAS for PFS. Five studies provided information on multivariate analyses about OS. STAS was found to be an independent prognostic indicator of OS (HR, 1.475; 95% CI, 1.239-1.756; $P < .001$). For the heterogeneity test, χ^2 was 13.45 ($P = .009$) and I^2 was 70.3%. HRs and corresponding 95% CIs did not change qualitatively after exclusion of any of studies. Our data showed that patients with STAS were more likely to have significantly shorter OS.

Clinicopathological Value of STAS

We also examined the relationship between STAS and clinicopathological characteristics. STAS was significantly related to sex ($P < .001$), smoking ($P < .001$), tumor budding ($P = .038$), vascular invasion ($P < .001$), lymphatic invasion ($P < .001$), pleural invasion ($P < .001$), T status ($P < .001$), N status ($P < .001$), and TNM stage ($P < .001$; Table 3). However, no significant association was found between STAS and age (OR, 0.799; 95% CI, 0.603-1.057; $P = .116$), or surgery (OR, 0.801; 95% CI, 0.611-1.048; $P = .105$). The analyses of the relationship between STAS and clinicopathological variables showed no significant heterogeneity across studies. Subgroup analysis, meta-regression, and sensitivity analysis were not conducted because of little heterogeneity and the limited number of included studies. Publication bias was not significant with P values $> .05$ in Egger and Begg tests (Table 3).

Table 2 Subgroup Analyses of NSCLC Patients With STAS

Stratified Analysis	Cases, n	STAS, n (%)	Pooled HR (95% CI)		Meta-Regression *P*	
			PFS	OS	PFS	OS
Histology Type					.775	.398
ADE	2570	985 (38.3)	1.724 (1.482-2.005)	1.612 (1.358-1.913)		
SCC	661	219 (33.1)	2.024 (1.534-2.672)	1.250 (1.097-1.610)		
TNM stage					.059	.480
I	2001	697 (34.8)	1.766 (1.474-2.115)	1.664 (1.346-2.059)		
I-III	445	132 (29.7)	1.820 (1.287-2.574)	1.250 (0.970-1.610)		
I-IV	492	240 (48.7)	1.813 (1.430-2.298)	1.520 (1.139-2.028)		
Publication Year					.876	.484
2015-2016	1298	490 (37.8)	1.846 (1.539-2.215)	1.452 (1.220-1.727)		
2017-2018	1933	714 (36.9)	1.725 (1.422-2.094)	1.565 (1.224-2.001)		
Sample Size					.310	.522
≥400	1920	683 (35.6)	2.132 (1.646-2.760)	1.492 (1.189-1.873)		
<400	1311	521 (39.7)	1.680 (1.439-1.960)	1.486 (1.240-1.782)		
Region					.829	.748
Asian countries	1806	629 (34.8)	1.813 (1.555-2.113)	1.479 (1.256-1.740)		
Western countries	1425	575 (40.4)	1.717 (1.317-2.238)	1.520 (1.139-2.028)		
Quality Score					.338	.374
≥85.0	1827	575 (31.5)	2.094 (1.687-2.598)	1.593 (1.303-1.947)		
<85.0	1404	629 (44.8)	1.625 (1.373-1.923)	1.488 (1.292-1.715)		

Abbreviations: HR = hazard ratio; NSCLC = non–small-cell lung cancer; OS = overall survival; PFS = progression-free survival; STAS = spread through air spaces; TNM = tumor, node, metastases.

Discussion

Our recent study showed that STAS is a new pathologic morphology in NSCLC,[19] but the incidence and prognostic role of STAS is unclear. To our limited knowledge, this is the first meta-analysis about the clinical value of STAS in NSCLC. The present study with updated data improves our understanding about STAS in NSCLC, as it could direct patient stratification and provide valuable information for clinical decision-making.

In this meta-analysis of 3231 NSCLC patients, overall incidence of STAS was 37.3%. Many studies have reported ratios of STAS, but the results ranged from 14.8% to 55.4%.[6-13] Our results showed obvious associations between STAS and poor PFS (HR, 1.789; $P < .001$) and OS (HR, 1.488; $P < .001$) in NSCLC. Significant heterogeneity did not exist across studies. Subgroup analyses were performed on the basis of histology type, TNM stage, publication year, sample size, region, and quality score (Table 2). It was observed that those factors did not alter significantly predictive value of STAS in PFS and OS. Our results were strengthened by the meta-regression analyses and sensitivity analyses. However, publication bias was observed, suggesting our data should be interpreted with caution. The nonparametric "trim and fill" method was used to detect the stability of results. The adjusted HR was 1.673 for PFS (95% CI, 1.476-1.895; $P = .007$) and 1.404 for OS (95% CI, 1.224-1.610; $P < .001$), respectively. The HRs had no significant alternations compared with primary data, which showed the reliability of our findings. Alternatively, unpublished studies might be a resource of heterogeneity, which was not analyzed in our meta-analysis. Some studies with negative results might be not reported. The adjusted HRs using "trim and fill" method showed the true clinical value of STAS. One interesting question attracted our attention: whether STAS could be exploited as an independent predictor for survival of NSCLC. By combining HRs from Cox multivariate analyses, we found that STAS was an important independent prognostic factor for PFS (HR, 1.632; $P < .001$) and OS (HR, 1.475; $P < .001$) in NSCLC.

In stratified analyses according to histology type, our results indicated that STAS was significantly related to decreased PFS and OS in patients with ADE and SCC (Table 2). In addition, subgroup analysis showed that TNM stage, region, publication year, and sample size did not change the overall results. We assessed the reliability and quality of studies using the NCI-EORTC quality scale.[14] Using subgroup analysis, we identified that pooled HRs in the studies with quality score ≥85.0 were larger than those with quality score <85.0. These results implied that some individual studies with relative poor quality might have underestimated the prognostic value of STAS. We also found HRs of PFS were greater than HRs of OS. Similar results was also observed in stratified analyses. Our findings suggest STAS might be more meaningful in predicting PFS than OS.

Shiono and Yanagawa[6] showed that STAS was detected at a high incidence in men and patients with lymphovascular or pleural invasion and advanced stage. Lu et al[10] and Kadota et al[11] reported strong correlations of STAS with aggressive tumor behaviors such as high stage and lymphovascular invasion. Our data supported previous results and showed that male sex ($P < .001$), vascular invasion ($P < .001$), lymphatic invasion ($P < .001$), pleural invasion ($P < .001$), T status ($P < .001$), N status ($P < .001$), and TNM stage ($P < .001$) were significantly related to STAS (Table 3). These

Figure 3 Meta-Analysis of Hazard Ratios (HRs) of Overall Survival of Non–Small-Cell Lung Cancer Patients With Spread Through Air Spaces. (A) Forest Plots of Meta-Analysis of the HRs and 95% CIs. (B) Results of Sensitivity Analysis. (C) Begg Funnel Plot Analysis for Publication Bias. (D) Filled Funnel Plot of Meta-Analysis Using "Trim-and-Fill" Method. Open Circles Indicate Observed Studies; Circles in Squares Indicate Missed Studies

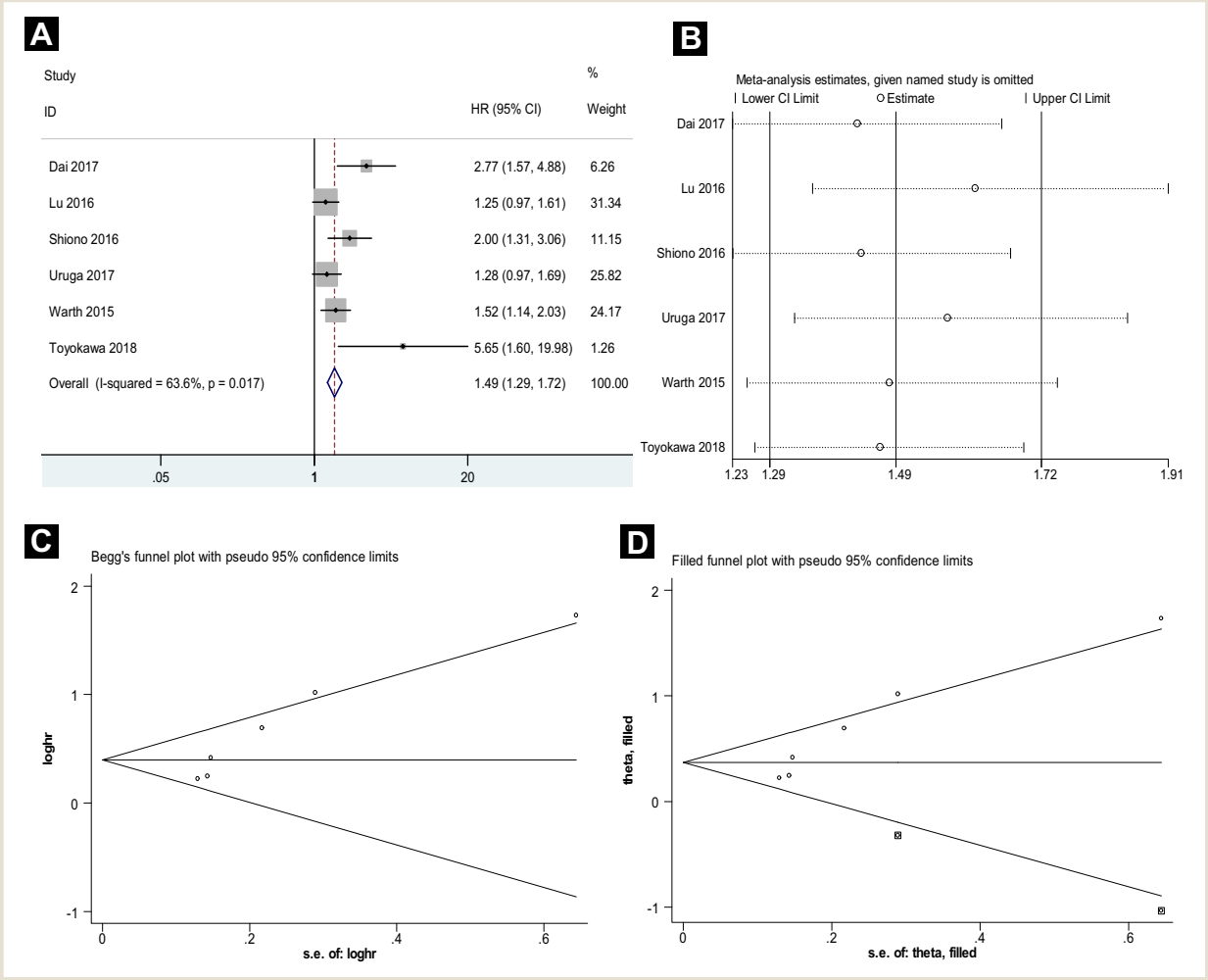


Table 3 Meta-Analysis of STAS and Clinicopathological Features in NSCLC

Stratified Analysis	Ratio of STAS, %	Begg Test		Egger Test		Pooled OR (95% CI)	*P*
		Z	*P*	*t* (Bias)	*P*		
Age, ≥65/<65	31.5/36.0	0.00	1.000	−0.75	.589	0.799 (0.603-1.057)	.116
Sex, Female/Male	31.3/39.2	0.00	1.000	0.15	.887	0.705 (0.593-0.839)	<.001
Smoker, No/Yes	25.5/37.1	0.00	1.000	−0.16	.879	0.594 (0.457-0.771)	<.001
Surgery, LR/LE	26.6/32.3	0.73	.462	−0.58	.603	0.801 (0.611-1.048)	.105
Tumor Budding, Low/High	30.5/42.1	0.00	1.000	—	—	0.664 (0.451-0.978)	.038
Vascular Invasion, No/Yes	31.5/52.7	0.00	1.000	−1.33	.411	0.511 (0.374-0.699)	<.001
Lymphatic Invasion, No/Yes	24.0/49.2	1.22	.221	−1.44	.245	0.369 (0.292-0.467)	<.001
Pleural Invasion, No/Yes	29.8/48.3	1.04	.296	−2.26	.265	0.412 (0.272-0.623)	<.001
T Status, T1/T2-4	22.4/43.9	1.04	.296	−1.76	.330	0.593 (0.453-0.776)	<.001
N Status, N^-/N^+	32.3/52.5	0.00	1.000	—	—	0.530 (0.407-0.690)	<.001
TNM Stage, I/II-IV	30.0/49.8	0.00	1.000	−0.45	.731	0.523 (0.413-0.663)	<.001

Abbreviations: LE = lobectomy; LR = limited resection; NSCLC = non–small-cell lung cancer; STAS = spread through air spaces; TNM = tumor, node, metastases.

factors are generally considered prognosticators of poor survival. So, STAS might be a surrogate factor for the aggressive behavior of NSCLC. Although Lu et al[10] did not find an association between STAS and tumor budding, Kadota et al[8] showed that STAS was more frequently identified in tumors with high-grade tumor budding ($P = .006$). Whether the sample error could be the reason for this discrepancy has to be further investigated. Alternatively, we cannot exclude that intratumoral heterogeneity has effects on the results. In this meta-analysis, we found that STAS was more likely to be observed in the patients with high-grade tumor budding ($P = .038$). It is worth noting that obvious heterogeneity did not exist across studies regarding evaluation of clinicopathological significance of STAS. Subgroup analysis, meta-regression, and sensitivity analysis were not performed because of the limited number of studies, which might reduce statistical power. Therefore, large-scale studies are needed to confirm or refute these results.

The same morphologic findings of STAS had been described as reproducible artifact secondary to mechanical forces, and designated as "spreading through a knife surface."[20] Blaauwgeers et al[21] suggested loose tissue fragments within air spaces were associated with tissue handling by surgeons or knife contamination by pathologists. However, several studies did not find significant differences in the formation of STAS among variable surgical procedures.[6,11,12] Our data indicated the incidence of STAS was not significantly different between patients with lobectomy or limited resection ($P = .105$), which was similar to findings of previous reports. Moreover, STAS had been proven to be an insidious pattern of invasion as an independent prognostic indicator.[6-9,22,23] Tumor cells are prone to spread or invade under chaotic proliferation stress. Because of the presence of air spaces, lung anatomy is unique compared with other organs. Air spaces provide a pathway of tumor spread without physical limitations.[11,24] Importantly, the surgical manipulation and slide preparation should be further standardized to avoid the false STAS.

The molecular mechanisms underlying STAS are largely unknown. Lu et al[10] reported that STAS was associated with necrosis, larger nuclear diameter, increased mitoses, and high Ki-67 labeling index in lung SCC. Warth et al[13] observed that STAS was related to specific growth patterns of ADE. Wild type *EGFR*, *KRAS* (kirsten rat sarcoma viral oncogene homolog), and *BRAF* mutations were significantly associated with STAS,[6,13] however, Toyokawa et al[7] showed that STAS was not significantly correlated with wild type *EGFR* or PD-L1 expression. Because we found a strong correlation of STAS with tumor budding, similar molecular mechanisms might be involved. STAS might be the consequence of complex tumor microenvironment interaction, epithelial mesenchymal transition, and alveolar remodeling.[25,26] The cellular biological behaviors become more aggressive, including rapid proliferation, decreased cohesiveness, high mobility, and apoptosis resistance. Molecular alteration of STAS might be involved in downregulation of E-cadherin, laminin 5-integrin-focal adhesion kinase, and activation of EGFR signaling.[25-28] Although we clarified the prognostic significance of STAS, further research is needed to elucidate the mechanisms of STAS in NSCLC.

It should be emphasized that there were several limitations in our study. First, sample size was limited. Sample error could lead to deficient statistical power. Second, we did not perform stratified analysis according to treatment modalities, because there was no randomized clinical trial and original data were unavailable. We did not analyze the associations of STAS with tumor markers, gene mutations, and immunophenotype because of limited data of previous studies. We also did not perform subgroup analyses on the basis of separated TNM stage, because the survival HRs of STAS in separated TNM stage were not available. Third, most of the included studies reported positive results. It is possible that some unpublished research with negative results were missed, which might place a bias on our results. Herein we reported our interesting preliminary findings. We will further validate the clinical relevance of STAS in other data sets.

Conclusion

This meta analysis indicated that STAS could be a novel prognostic factor for NSCLC. Our data also demonstrated that STAS correlates with key adverse clinicopathological features. Further research with larger sample size and updated data are needed to identify unrecognized roles of STAS.

Clinical Practice Points

- The World Health Organization classification of lung cancer had defined STAS as a new pattern of invasion in lung ADE. However, the prognostic values and clinicopathological significance of STAS have not been widely accepted in NSCLC.
- This study suggested STAS was a novel predictive factor for poor PFS and OS in NSCLC. We further found that STAS was associated with male sex, history of smoking, tumor budding, vascular invasion, lymphatic invasion, pleural invasion, and TNM stage.
- Our findings suggest that presence or absence of STAS could improve stratification and management of NSCLC patients.

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Disclosure

The authors have stated that they have no conflicts of interest.

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