European Journal of Cardio-Thoracic Surgery 2022, 62(3), ezac248
https://doi.org/10.1093/ejcts/ezac248 Advance Access publication 6 April 2022

ORIGINAL ARTICLE

Cite this article as: Ding Y, Chen Y, Wen H, Li J, Chen J, Xu M *et al.* Pretreatment prediction of tumour spread through air spaces in clinical stage I non-small-cell lung cancer. Eur J Cardiothorac Surg 2022; doi:10.1093/ejcts/ezac248.

Pretreatment prediction of tumour spread through air spaces in clinical stage I non-small-cell lung cancer

Yun Ding[a,†], Yiyong Chen[b,†], Hui Wen[a], Jiuzhen Li[a], Jinzhan Chen[b], Meilin Xu[a,c], Hua Geng[a,c], Lisheng You[b,d], Xiaojie Pan[b,e] and Daqiang Sun[a,f,*]

[a] Clinical School of Thoracic, Tianjin Medical University, Tianjin, China
[b] Shengli Clinical Medical College of Fujian Medical University, Fuzhou, China
[c] Department of Pathology, Tianjin Chest Hospital, Tianjin, China
[d] Department of Pathology, Fujian Provincial Hospital, Fuzhou, China
[e] Department of Thoracic Surgery, Fujian Provincial Hospital, Fuzhou, China
[f] Department of Thoracic Surgery, Tianjin Chest Hospital, Tianjin, China

* Corresponding author. Department of Thoracic Surgery, Tianjin Chest Hospital, No. 261, Taierzhuang South Road, Jinnan District, Tianjin 300222, China. Tel: +86-22-88185412; e-mail: sdqmd@163.com (D. Sun).

Received 27 December 2021; received in revised form 26 March 2022; accepted 4 April 2022

Key question

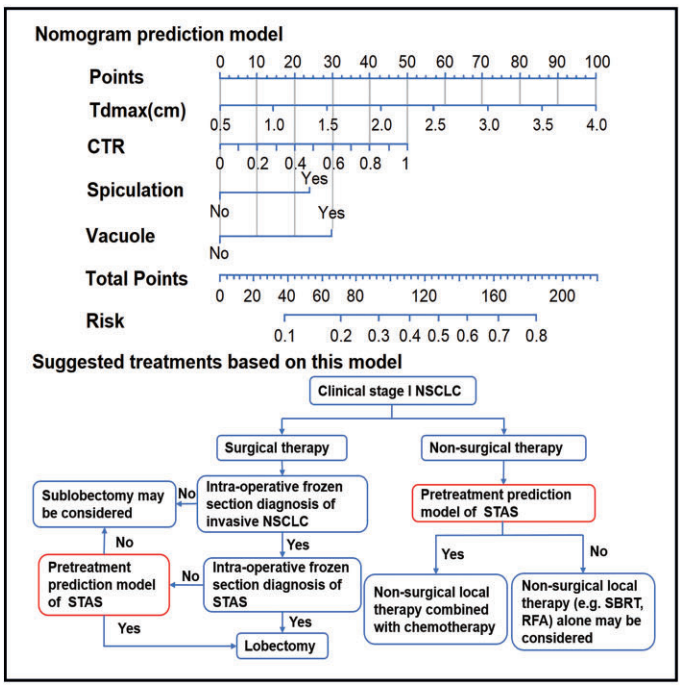
How can tumour spread through air spaces (STAS) in clinical stage I lung cancer be predicted before treatment?

Key finding(s)

A nomogram prediction model for STAS was constructed with reliable performance.

Take-home message

Preoperative prediction of STAS can potentially be applied to guide treatment selection.



Abstract

OBJECTIVES: The aim of this study was to construct a nomogram prediction model for tumour spread through air spaces (STAS) in clinical stage I non-small-cell lung cancer (NSCLC) and discuss its potential application value.

METHODS: A total of 380 patients with clinical stage I NSCLC in Tianjin Chest Hospital were collected as the training cohort and 285 patients in Fujian Provincial Hospital were collected as the validation cohort. Univariable and multivariable logistic regression analyses

†The first two authors contributed equally to this work.

were performed to determine independent factors for STAS in the training cohort. Based on the results of the multivariable analysis, the nomogram prediction model of STAS was constructed by R software.

RESULTS: The incidence of STAS in the training cohort was 39.2%. STAS was associated with worse overall survival and recurrence-free survival ($P < 0.01$). Univariable analysis showed that maximum tumour diameter, consolidation-to-tumour ratio, spiculation, vacuole and carcinoembryonic antigen were associated with STAS ($P < 0.05$). Multivariable analysis showed that maximum tumour diameter, consolidation-to-tumour ratio, spiculation sign and vacuole were independent risk factors for STAS ($P < 0.05$). Based on this, the nomogram prediction model of STAS in clinical stage I NSCLC was constructed and internally validated by bootstrap. The Hosmer–Lemeshow test showed a χ^2 value of 7.218 ($P = 0.513$). The area under the receiver operating characteristic curve and C-index were 0.724 (95% confidence interval: 0.673–0.775). The external validation conducted on the validation cohort produced an area under the receiver operating characteristic curve of 0.759 (95% confidence interval: 0.703–0.816).

CONCLUSIONS: The constructed nomogram prediction model of STAS in clinical stage I NSCLC has good calibration and can potentially be applied to guide treatment selection.

Keywords: Tumour spread through air spaces • Adenocarcinoma • Non-small-cell lung cancer • Nomogram • Predictive model

ABBREVIATIONS

AUC	Area under the receiver operating characteristic curve
CT	Computed tomography
CTR	Consolidation-to-tumour ratio
DCA	Decision curve analysis
GGO	Ground-glass opacity
NSCLC	Non-small-cell lung cancer
OS	Overall survival
RFS	Recurrence-free survival
STAS	Tumour spread through air spaces
Tdmax	Maximum tumour diameter

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in humans [1]. Thanks to the continuous development of imaging technology, the early detection rate of non-small-cell lung cancer (NSCLC) is increasing. More and more patients with clinical stage I NSCLC are being detected and treated. Surgery is currently the primary treatment for early-stage NSCLC, but tumour recurrence remains the leading cause of treatment failure. To reduce the postoperative recurrence rate and improve the prognosis, it is essential to understand the risk factors for recurrence in lung cancer fully and to take appropriate treatment measures for high-risk patients.

Recently, tumour spread through air spaces (STAS) has been recognized as an aggressive mode of lung cancer, and in 2015, the World Health Organization formally introduced this concept in its new classification of lung cancer, defined as the spread of micropapillary clusters, solid nests and/or individual cancer cells into the alveolar lumen beyond the margin of the main tumour in the alveolar cavity of the lung [2]. Many studies now point out STAS as an essential risk factor for postoperative recurrence in patients with stage I NSCLC [3, 4]. STAS occurred in residual lung segments of simulated sublobar resection [5]. Therefore, it is recommended that patients with STAS-positive stage I NSCLC undergo lobectomy. However, preoperative identification of STAS is complex, and the intraoperative frozen section is limited in detecting STAS [6]. The diagnosis of STAS depends on thorough sampling and examination of pathological specimens. Sometimes even STAS may not be detected in surgically resected specimens [7], leading to false-negative results. Conversely, some STAS may result from the spread of tumour cell masses due to knife cutting during specimen processing, which is an artificial false-positive result. In addition, it is controversial whether local non-surgical therapy without access to complete pathological specimens is suitable for clinical stage I NSCLC patients with STAS. Therefore, the construction of accurate predictive models of STAS in clinical stage I NSCLC patients before treatment is crucial for the choice of treatment and scope of surgical resection.

In this study, we aimed to investigate the risk factors for STAS in clinical stage I NSCLC and the application value of its nomogram prediction model and to provide a reference for selecting treatment modalities for clinical stage I NSCLC.

MATERIALS AND METHODS

Study population

We reviewed the clinical data of patients who visited Tianjin Chest Hospital for surgical treatment between January 2015 and December 2018 from the hospital database. The following inclusion criteria were applied: (i) patients with a preoperative diagnosis of primary clinical stage I NSCLC and (ii) underwent complete pulmonary lesion resection and pathologically confirmed invasive NSCLC. The exclusion criteria were the following: (i) preoperative neoadjuvant therapy; (ii) multiple primary lung cancer in the same lobe; (iii) missing preoperative chest imaging data; and (iv) lost to follow-up after surgery. Clinical staging was based on the 8th edition of the American Joint Committee on Cancer TNM classification. After screening, a total of 380 cases were included in the training cohort to analyse the prognostic impact of STAS and to construct a nomogram prediction model for the risk of STAS in clinical stage I NSCLC. Patients attending Fujian Provincial Hospital for the surgical treatment of NSCLC from January 2019 to June 2021 were also collected, using the same inclusion and exclusion criteria, except for the exclusion criteria (iv). A total of 285 cases were enrolled as the validation cohort for external validation of the model. The selection process for patients in this study is displayed in Fig. 1.

Ethical statement

This study was approved by the Ethics Committee of Tianjin Chest Hospital and the Ethics Committee of Fujian Provincial Hospital. The ethics committee waived the requirement for informed consent due to the retrospective nature of the study.

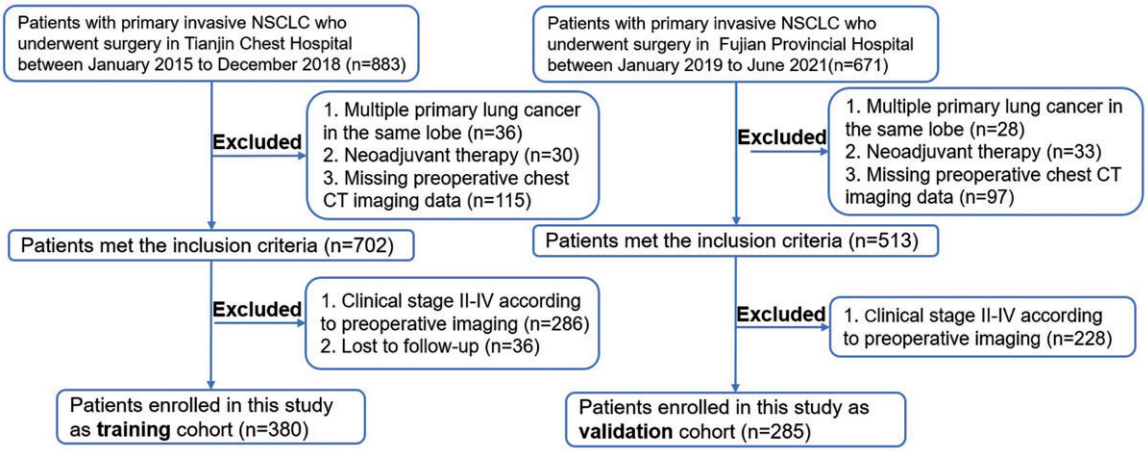


Figure 1: Patient selection process. NSCLC: non-small-cell lung cancer; STAS: tumour spread through air spaces.

Clinical characteristics

The clinical characteristics included the following. (i) General information includes: gender, age, smoking history, underlying pulmonary disease and preoperative symptoms. Positive smoking history was defined as continuous or cumulative smoking for >6 months. Underlying pulmonary disease included chronic obstructive pulmonary disease, interstitial pneumonia, asthma and previous tuberculosis. Positive symptoms were defined as a chief complaint of cough, sputum or haemoptysis. (ii) Preoperative investigations include: chest computed tomography (CT), carcinoembryonic antigen, preoperative bronchoscopy and puncture needle biopsy. CT features include: lobular location, tumour location, maximum tumour diameter (Tdmax), consolidation-to-tumour ratio (CTR), spiculation, lobulation, pleural traction, air bronchogram and vacuole. Vacuole referred to small bubble-like low-density shadows ranging from 1 to 3 mm in diameter in tumours. Tumours in the main, lobar or segmental bronchi were defined as central lung cancer and tumours in the subsegmental bronchi or more peripheral lung parenchyma were defined as peripheral lung cancer according to CT. The slice thickness of CT was 1.5 mm. CTR was defined as the proportion of solid components in mixed ground-glass opacity (GGO) nodule. GGO was defined as a limited increase in density without obscuring the bronchovascular structures passing through it in the lung windows (window width: 1,600 HU; window centre: -500 HU). Tdmax and the maximum diameter of the solid component (Cdmax) were measured under the lung window on the transverse CT section of the largest diameter of the tumour. CTR = Cdmax/Tdmax.

Evaluation of tumour spread through air spaces

Haematoxylin and eosin-stained sections of surgical specimens from all patients enrolled were reviewed by the pathologists who did not know the clinical information and survival of the patients. Referring to the 2015 World Health Organization classification of lung cancer and the study by Kadota *et al.* [2, 8], we defined a STAS positivity as single tumour cells or clusters of tumour cells present in the alveolar spaces at least one alveolar septum away from the main tumour in the section (Fig. 2A–C). In addition, the exclusion criteria for STAS, as reported by Kadota *et al.* [8], were (i) mechanically separated tumour floaters or rough clusters of tumour cells randomly distributed or located at the edge of the section and (ii) cytobands of tumour detached from the alveolar wall or interstitial lung parenchyma due to poor preservation. In cases where it is difficult to differentiate from other non-tumour cells, the results of immunohistochemistry can be consulted to determine STAS (Fig. 2D).

Follow-up

Prognostic data for patients in the training cohort were collected through postoperative electronic records and telephone. Overall survival (OS) was defined as the interval between the date of surgery and the date of death from any cause. Recurrence-free survival (RFS) was defined as the interval between the date of surgery and the initial diagnosis of recurrence. Patients without event were censored at the time of the last follow-up performed in September 2021.

Statistical analysis

Statistical analyses were conducted using SPSS statistical software, version 25.0 and R software, version 4.0.5. Normally distributed data were expressed as mean ± standard deviation; skewed distributed data were presented as median (quartile range) [*M* (P25∼P75)]. Survival curves were plotted using Kaplan–Meier method, and comparisons between the groups were made by the log-rank test. Univariable and multivariable analyses were analyzed by logistic regression in the training cohort, and those with $P < 0.05$ in the univariable were included in the multivariable analysis. Based on the results of the multivariable analysis, the rms package of R software was applied to construct the nomogram prediction model for STAS. The bootstrap method was used for internal validation, with the resampling of the original dataset, training and validation cohort constructed by bootstrap were the same size as the original dataset, repeating 1000 times to derive the calibration curve. The consistency index (C-index) was used to assess the calibration of the model and the Hosmer–Lemeshow test to assess the goodness-of-fit of the model. The area under the receiver operating characteristic curve (AUC) was used to evaluate the predictive power of the nomogram prediction model. Clinical usefulness was evaluated through decision

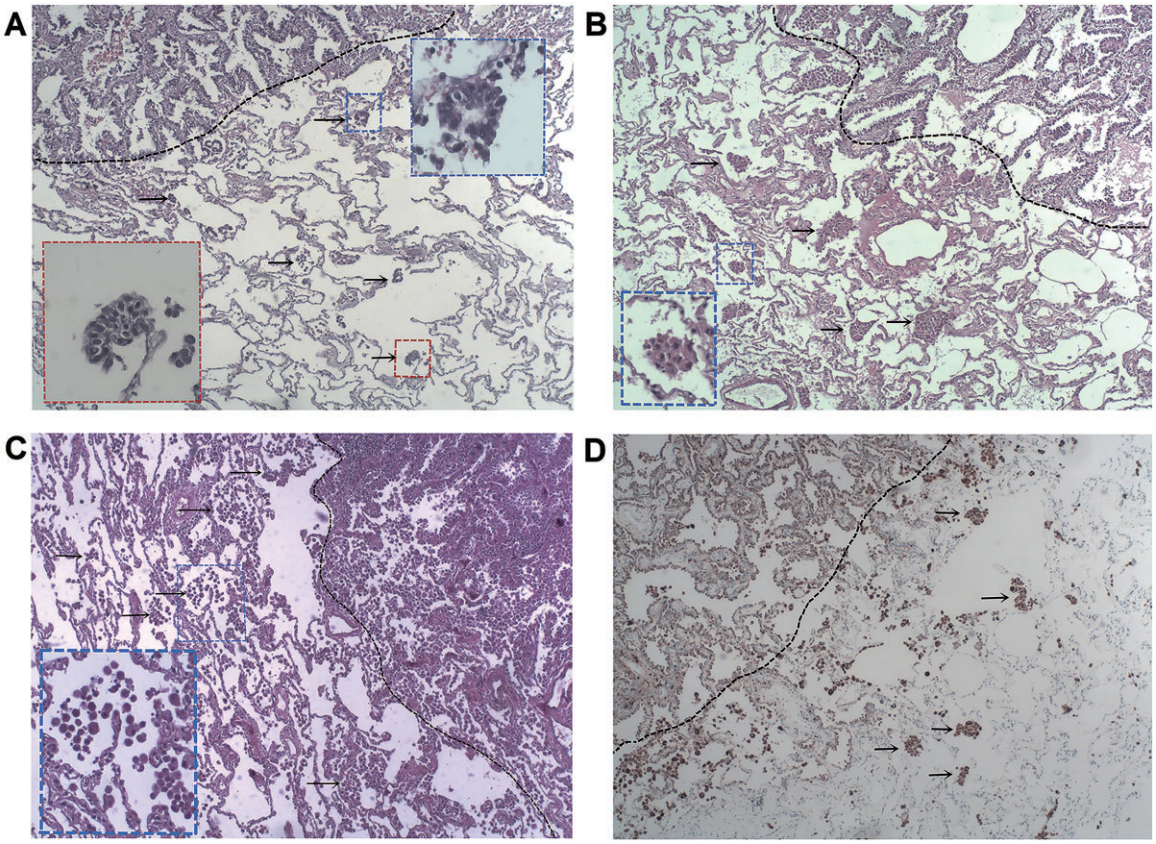


Figure 2: Histopathological features of tumour spread through air spaces. (**A**–**C**) Diagnosis of tumour spread through air spaces by haematoxylin and eosin staining. Tumour spread through air spaces (arrowheads) was located within the air spaces in the lung parenchyma, outside the edge (black dashed line) of the main tumour. The high-powered fields are included in the corresponding coloured dashed boxes. (**D**) Tumour spread through air spaces was identified by immunohistochemistry. Spread through air spaces (arrowheads, Napsin A positive) was located within the air spaces in the lung parenchyma, outside the edge of (black dashed line) the main tumour. STAS: tumour spread through air spaces.

curve analysis (DCA). $P < 0.05$ was considered a statistically significant difference.

RESULTS

Status and prognostic impact of tumour spread through air spaces in clinical stage I non-small-cell lung cancer

The rate of STAS positivity in the training cohort was 39.2% (149/380). The clinical characteristics of STAS-positive and negative patients are shown in Table 1. The median follow-up time of the 380 patients was 45.7 months (range: 1.5, 80.0). As shown in Fig. 3A, the OS of STAS-negative patients was significantly better than that of STAS-positive patients ($P < 0.001$). In addition, RFS was significantly better in patients without STAS than in patients with STAS ($P < 0.01$), as shown in Fig. 3B.

Analysis of clinical factors associated with tumour spread through air spaces

Univariable analysis showed that Tdmax, CTR, spiculation, vacuole and carcinoembryonic antigen were associated with STAS in patients with clinical stage I NSCLC ($P < 0.05$), as shown in Table 1.

The variables with $P < 0.05$ in the univariable analysis were included in the multivariable logistic regression analysis. The results showed that Tdmax, CTR, spiculation and vacuole were independent risk factors for STAS in clinical stage I NSCLC ($P < 0.05$), as shown in Table 2.

Construction and internal validation of the nomogram prediction model

The nomogram prediction model for the occurrence of STAS in clinical stage I NSCLC was constructed based on the 4 independent risk factors derived from the multivariable logistic regression analysis of the training cohort (Fig. 4A). The corresponding points of each factor can be obtained from the model, which can be further summed to the total points. The risk corresponding to the total points is the predicted risk of STAS. The AUC and C-index were 0.724 (95% confidence interval: 0.673–0.775) and the prediction model had good predictability (Fig. 4B). The model was internally validated using the bootstrap method, and the calibration curves showed good agreement between the STAS predicted probability of the nomogram prediction model and the actual probability (Fig. 4C). The Hosmer–Lemeshow test result was χ^2=7.218 (P = 0.513), which showed that the model was well calibrated. DCA showed that the nomogram prediction model had better clinical net benefit from intervention decisions than the baseline model at a risk threshold of 0.1–0.8 (Fig. 4D).

Table 1: Univariable analysis of tumour spread through air spaces in the training cohort (*n* = 380)

Variable	STAS+ (*n* = 149)	STAS- (*n* = 231)	OR	95% CI	*P*-Value
Age(years), mean ± SD	63.07 ± 7.64	62.29 ± 8.31	1.012	0.986–1.039	0.359
Gender, *n* (%)					
Female	60 (40.3)	107 (46.3)	1		
Male	89 (59.7)	124 (53.7)	1.280	0.842–1.943	0.246
Smoking history, *n* (%)					
No	92 (61.7)	153 (66.2)	1		
Yes	57 (38.3)	78 (33.8)	1.215	0.792–1.865	0.372
Underlying pulmonary disease					
No	135 (90.6)	214 (92.6)	1		
Yes	14 (9.4)	17 (7.4)	1.305	0.623–2.735	0.480
Preoperative symptoms, *n* (%)					
No	91 (61.1)	161 (69.7)	1		
Yes	58 (38.9)	70 (30.3)	1.466	0.951–2.259	0.082
Lobular location, *n* (%)					
Upper lobe	83 (55.7)	144 (62.3)	1		
Middle/lower lobe	66 (44.3)	87 (37.7)	1.316	0.866–2.001	0.198
Tumour location, *n* (%)					
Peripheral	117 (78.5)	194 (84.0)	1		
Central	32 (21.5)	37 (16.0)	1.434	0.848–2.426	0.178
Tdmax (cm), mean ± SD	2.56 ± 0.80	2.01 ± 0.78	2.352	1.764–3.066	<0.001
CTR, mean ± SD	0.78 ± 0.23	0.65 ± 0.30	6.452	2.836–14.680	<0.001
Spiculation, *n* (%)					
No	33 (22.1)	85 (36.8)	1		
Yes	116 (77.9)	146 (63.2)	2.046	1.279–3.275	0.003
Lobulation, *n* (%)					
No	51 (34.2)	94 (40.7)	1		
Yes	98 (65.8)	137 (59.3)	1.318	0.859–2.023	0.205
Pleural traction, *n* (%)					
No	56 (37.6)	110 (47.6)	1		
Yes	93 (62.4)	121 (52.4)	1.510	0.992–2.298	0.054
Air bronchogram, *n* (%)					
No	106 (71.1)	180 (77.9)	1		
Yes	43 (28.9)	51 (22.1)	1.432	0.894–2.294	0.135
Vacuole, *n* (%)					
No	107 (71.8)	200 (86.6)	1		
Yes	42 (28.2)	31 (13.4)	2.532	1.505–4.260	<0.001
CEA (ng/ml), *M* (P25, P75)	3.10 (2.01, 4.73)	2.73 (1.78, 4.02)	1.065	1.013–1.120	0.014
Percutaneous needle biopsy, *n* (%)					
No	136 (91.3)	210 (90.9)	1		
Yes	13 (8.7)	21 (9.1)	0.817	0.463–1.973	0.903
Preoperative bronchoscopy, *n* (%)					
No	71 (47.7)	128 (55.4)	1		
Yes	78 (52.3)	103 (44.6)	1.365	0.903–2.064	0.139

CEA: carcinoembryonic antigen; CI: confidence interval; CTR: consolidation-to-tumour ratio; OR: odds ratio; SD: standard deviation; STAS: tumour spread through air spaces; STAS+: positive for tumour spread through air spaces; STAS-: negative for tumour spread through air spaces; Tdmax: maximum tumour diameter.

External validation of the nomogram prediction model

Among the 285 patients in the validation cohort, STAS was observed in 123 (43.2%) cases of 285 cases. The clinical characteristics of these patients are shown in Supplementary Material, Table S1. The AUC was 0.759 (95% confidence interval: 0.703–0.816), suggesting good predictability of the prediction model (Fig. 5A). External validation using the bootstrap method showed that the calibration curve was close to the actual probability and the data were consistent (Fig. 5B).

DISCUSSION

In recent years, STAS has been recognized as an aggressive form of lung cancer and is closely related to the clinicopathological features and prognosis of lung cancer. In this study, OS and RFS were significantly better in STAS-negative patients than in STAS-positive patients. In addition, previous studies have shown that patients with STAS-positive stage I NSCLC undergoing lobectomy have a better prognosis than those undergoing sublobar resection [9]. Postoperative chemotherapy can also improve the prognosis of patients with STAS-positive stage I NSCLC after sublobar resection [10]. Therefore, appropriate treatment measures for patients with STAS or at high risk are important for patient prognosis.

Currently, there are still no standard criteria for the diagnosis of STAS, and many pathologists do not even report the presence of STAS. In addition, some experts still question STAS as an 'artefact' resulting from the phenomenon of knife cutting during specimen processing [7]. This has led to a wide variation in STAS incidence previously reported by individual centres. The incidence of STAS in stage I NSCLC reported in previous studies

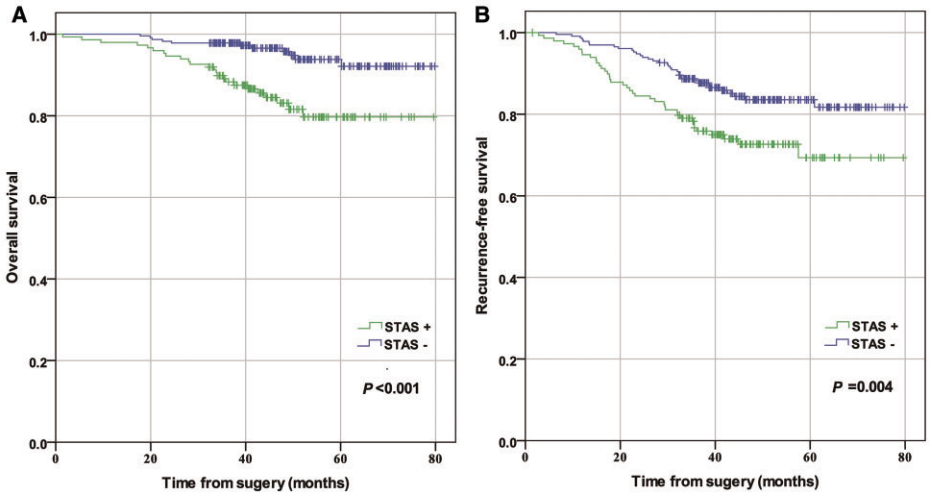


Figure 3: Overall survival (**A**) and recurrence-free survival (**B**) curve for patients with clinical stage I non-small-cell lung cancer according to the spread through air spaces status. STAS+: positive for tumour spread through air spaces; STAS-: negative for tumour spread through air spaces.

Table 2: Multivariable analysis of tumour spread through air spaces in the training cohort ($n = 380$)

Variable	β	SE	Wald χ^2	*P*-value	OR	95%CI
Tdmax	0.663	0.153	18.779	<0.001	1.941	1.438–2.619
CTR	1.067	0.478	4.980	0.026	2.905	1.139–7.413
Spiculation	0.625	0.271	5.308	0.021	1.869	1.098–3.181
Vacuole	0.711	0.294	5.857	0.016	2.035	1.145–3.618
CEA	0.032	0.026	1.528	0.216	1.033	0.981–1.087

CEA: carcinoembryonic antigen; CI: confidence interval; CTR: consolidation-to-tumour ratio; OR: odds ratio; STAS: tumour spread through air spaces; Tdmax: maximum tumour diameter.

ranged from 14.8% to 55.4% [4, 11]. As the understanding of STAS has improved, many studies have shown that STAS is an *in vivo* phenomenon rather than an artefact of specimen handling procedures [12, 13]. Therefore, there is a growing interest in the diagnosis of STAS. In addition to diagnosing the presence or absence of STAS, a semi-quantitative assessment of STAS has been proposed. Warth *et al.* [14] classified STAS according to its distance from the main tumour as limited STAS (≤3 alveolae away from the main tumour mass) and extensive STAS (>3 alveolae away from the main tumour mass). In that study, survival analysis showed that the presence of STAS was associated with a reduction in OS and RFS. However, there was no significant difference in OS or RFS between patients with limited STAS and those with extensive STAS. Therefore, we need to focus on diagnosing the presence or absence of STAS, and not necessarily the grading of STAS. In this study, pathologists from both centres agreed on the diagnosis of STAS by retrospective review of pathological sections. We constructed a model for the preoperative prediction of STAS through the training cohort, and internal validation suggested good calibration. At the same time, external validation also demonstrated good agreement. This indicates the need for a uniform standard for STAS and that it can be used as a routine part of pathological diagnosis.

Postoperative pathology is important for STAS diagnosis, but more critical is preoperative identification and prediction of STAS, which can guide our choice of early intervention and treatment options. For patients undergoing surgery, STAS status influences the current selection of the scope of surgical resection for patients with stage I NSCLC. Kadota *et al.* [9] showed that patients with STAS in the sublobectomy group had a higher risk of tumour metastasis and recurrence than those without STAS, while no difference was found in patients in the lobectomy group. They, therefore, recommend that lobectomy should be the first choice for patients with STAS, which requires preoperative or intraoperative detection of STAS. However, preoperative examinations and intraoperative frozen section are currently difficult for the identification of STAS. Preoperative percutaneous needle biopsy and bronchoscopic biopsy are difficult to reflect the spatial structure of the tumour. Medina *et al.* [15] have demonstrated that preoperative bronchial cytology cannot predict tumour STAS adequately. Furthermore, previous studies have shown that the sensitivity of identifying STAS on frozen sections is only 50–71% [16, 17]. Morimoto *et al.* [18] suggested that the diagnosis of STAS by intraoperative frozen biopsy is limited by the current technology, as the lung tissue in frozen sections is not sufficiently expanded to allow microscopic visualization of tumour cell clusters. Therefore, we cannot get a reliable determination of STAS during surgery and a reliable preoperative model for predicting STAS is even more necessary. In addition, some patients with clinical stage I NSCLC undergo non-surgical local therapy (e.g., stereotactic body radiation therapy, ablation). They do not have complete tumour specimens to determine STAS based on pathological sections. Therefore, the choice of treatment for these patients can only be predicted based on the pretreatment clinical information, which reinforces the importance of constructing pretreatment predictive models for STAS. Although, to date, no appropriate clinical study has reported the efficacy of any non-surgical local treatment compared with other treatments for patients with STAS positive stage I NSCLC, it would be inappropriate to assume that STAS is not associated with relapse after non-surgical local treatment [19]. Therefore, in this study, to address the prediction of STAS in stage I NSCLC before treatment, we developed a predictive model of STAS with extrapolation based on pretreatment clinical data. DCA showed that this model could lead to a higher clinical net benefit at a risk threshold of 0.1–0.8. We propose a reference flowchart for the

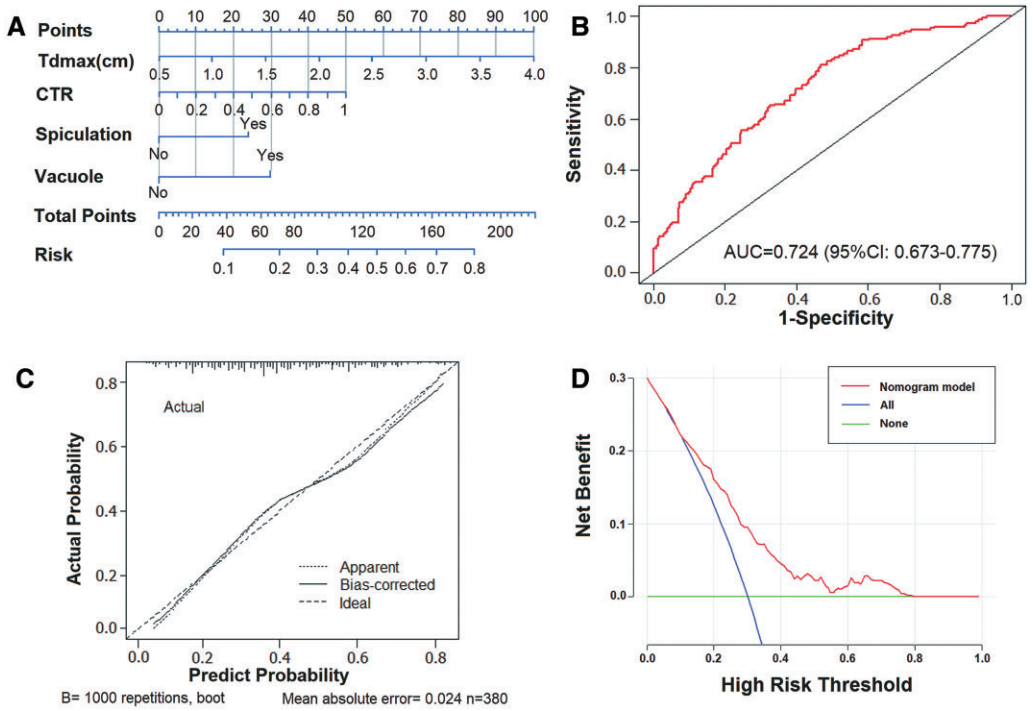


Figure 4: Construction and internal validation of the nomogram prediction model in traning cohort. (**A**) The nomogram prediction model for tumour spread through air spaces in clinical stage I non-small-cell lung cancer. (**B**) The receiver operating characteristic curve of the nomogram prediction model. (**C**) The calibration curve of the nomogram prediction model. (**D**) The decision curve of the nomogram prediction model. AUC: area under the curve; CTR: consolidation-to-tumour ratio; STAS: tumour spread through air spaces; Tdmax: maximum tumour diameter.

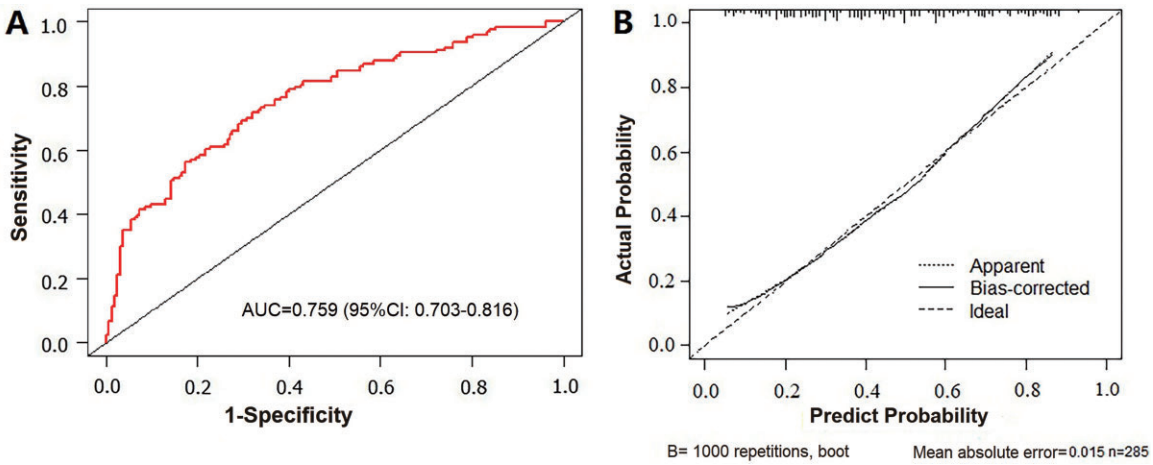


Figure 5: External validation of the nomogram prediction model in validation cohort. (**A**) The receiver operating characteristic curve of the nomogram prediction model. (**B**) The calibration curve of the nomogram prediction model. AUC: area under the receiver operating characteristic curve.

selection of surgical and non-surgical therapeutic approaches for stage I NSCLC based on the STAS prediction model (Fig. 6).

This study showed that Tdmax, CTR, spiculation and vacuole were independent risk factors for STAS in clinical stage I NSCLC, which is consistent with some previous studies. STAS in early-stage NSCLC correlates with tumour size [20], but the cut-off diameter is controversial. Uruga *et al.* [21] found a higher rate of STAS positivity when the tumour diameter was ≥1 cm, and de Margerie-Mellon *et al.* [22] found that STAS correlated with tumour size when the tumour diameter was ≥2 cm, whereas STAS was not correlated with tumour size when 1.5 cm was used as the cut-off value. In terms of imaging, previous studies have shown that STAS is associated with CT features such as spiculation and vacuole [23]. In addition, Yin *et al.* [24] found that CTR was an independent predictor of STAS, but GGO nodules also had STAS, although the incidence was low [23, 25]. In this study, we constructed a nomogram model based on these 4 risk factors for STAS. Compared with other predictive statistical models, its visualized results can reflect the probability of STAS in stage I NSCLC more intuitively and provide an individualized assessment of STAS for each patient. At the same time, these 4 above-mentioned indicators are easily accessible and widely used, making them suitable for routine application in clinical work.

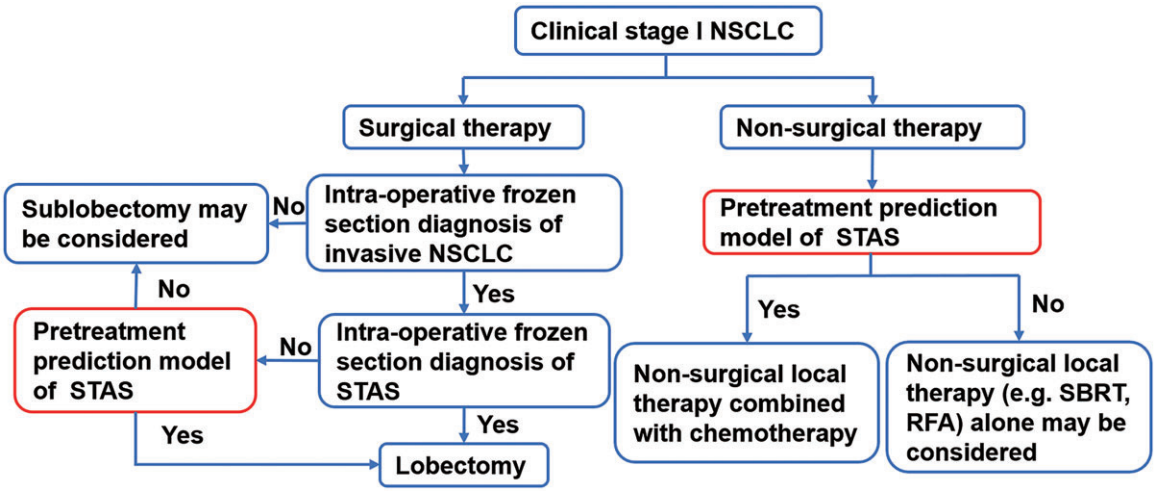


Figure 6: Suggested therapeutic approaches by tumour spread through air spaces positivity in clinical stage I non-small-cell lung cancer. NSCLC: non-small-cell lung cancer; RFA: radiofrequency ablation; SBRT: stereotactic body radiation therapy; STAS: tumour spread through air spaces.

Limitations

There are several limitations to our study. (i) This study is a retrospective study, and it is challenging to avoid selection bias. (ii) The preoperative investigations received by these patients before treatment were not uniform, and many patients did not have pretreatment maximum standardized uptake value, other tumour markers, etc. Therefore, prospective studies need to be conducted to include appropriate preoperative investigations to further improve the prediction model and enhance the predictive efficacy. (iii) This study only included patients from 2 centres for training and validation. The inclusion of more centres and patients for training and validation would also further improve the accuracy of the model.

CONCLUSION

In summary, pretreatment Tdmax, CTR, spiculation and vacuole signs were independent risk factors for STAS in clinical stage I NSCLC. The nomogram prediction model for clinical stage I NSCLC STAS constructed in this way is well calibrated and can be used as a reference for clinicians to assess the risk of STAS in patients with clinical stage I NSCLC before treatment and to formulate treatment plans.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Funding

This work was supported by the Natural Funding Project of Tianjin Science and Technology Bureau (No. 20JCYBJC01350).

Conflict of interest: none declared.

Data Availability Statement

All relevant data are within the manuscript and its Supporting Information files.

Author contributions

Yun Ding: Conceptualization; Methodology; Writing—original draft; Writing—review & editing. **Yiyong Chen:** Data curation; Formal analysis; Investigation; Writing—review & editing. **Hui Wen:** Data curation; Formal analysis; Software. **Jiuzhen Li:** Data curation; Investigation. **Jinzhan Chen:** Writing—review & editing. **Meilin Xu:** Methodology; Resources; Supervision. **Hua Geng:** Investigation; Validation. **Lisheng You:** Investigation; Resources. **Xiaojie Pan:** Supervision; Writing—review & editing. **Daqiang Sun:** Project administration; Supervision; Writing—review & editing.

Reviewer information

European Journal of Cardio-Thoracic Surgery thanks Amit Bhargava, Haruhisa Matsuguma, Hitoshi Igai and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30.
[2] Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. Introduction to the 2015 World Health Organization classification of tumors of the lung, pleura, thymus, and heart. J Thorac Oncol 2015;10:1240–2.
[3] Yanagawa N, Shiono S, Endo M, Ogata SY. Tumor spread through air spaces is a useful predictor of recurrence and prognosis in stage I lung squamous cell carcinoma, but not in stage II and III. Lung Cancer 2018; 120:14–21.
[4] Shiono S, Yanagawa N. Spread through air spaces is a predictive factor of recurrence and a prognostic factor in stage I lung adenocarcinoma. Interact CardioVasc Thorac Surg 2016;23:567–72.
[5] Ren Y, Xie H, Dai C, She Y, Su H, Xie D *et al.* Prognostic impact of tumor spread through air spaces in sublobar resection for 1A lung adenocarcinoma patients. Ann Surg Oncol 2019;26:1901–8.
[6] Mino-Kenudson M. Significance of tumor spread through air spaces (STAS) in lung cancer from the pathologist perspective. Transl Lung Cancer Res 2020;9:847–59.
[7] Blaauwgeers H, Flieder D, Warth A, Harms A, Monkhorst K, Witte B *et al.* A prospective study of loose tissue fragments in non-small cell lung cancer resection specimens: an alternative view to "spread through air spaces". Am J Surg Pathol 2017;41:1226–30.
[8] Kadota K, Nitadori JI, Sima CS, Ujiie H, Rizk NP, Jones DR *et al.* Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. J Thorac Oncol 2015;10: 806–14.

[9] Kadota K, Kushida Y, Kagawa S, Ishikawa R, Ibuki E, Inoue K *et al.* Limited resection is associated with a higher risk of locoregional recurrence than lobectomy in stage I lung adenocarcinoma with tumor spread through air spaces. Am J Surg Pathol 2019;43:1033–41.
[10] Chen D, Wang X, Zhang F, Han R, Ding Q, Xu X *et al.* Could tumor spread through air spaces benefit from adjuvant chemotherapy in stage I lung adenocarcinoma? A multi-institutional study. Ther Adv Med Oncol 2020;12:1758835920978147.
[11] Toyokawa G, Yamada Y, Tagawa T, Kozuma Y, Matsubara T, Haratake N *et al.* Significance of spread through air spaces in resected pathological stage I lung adenocarcinoma. Ann Thorac Surg 2018;105:1655–63.
[12] Metovic J, Falco EC, Vissio E, Santoro F, Delsedime L, Massa F *et al.* Gross specimen handling procedures do not impact the occurrence of spread through air spaces (STAS) in lung cancer. Am J Surg Pathol 2021;45: 215–22.
[13] Gross DJ, Hsieh M-S, Li Y, Dux J, Rekhtman N, Jones DR *et al.* Spread through air spaces (STAS) in non-small cell lung carcinoma: evidence supportive of an in vivo phenomenon. Am J Surg Pathol 2021;45:1509–15.
[14] Warth A, Muley T, Kossakowski CA, Goeppert B, Schirmacher P, Dienemann H *et al.* Prognostic impact of intra-alveolar tumor spread in pulmonary adenocarcinoma. Am J Surg Pathol 2015;39:793–801.
[15] Medina MA, Onken AM, de Margerie-Mellon C, Heidingger BH, Chen Y, Bankier AA *et al.* Preoperative bronchial cytology for the assessment of tumor spread through air spaces in lung adenocarcinoma resection specimens. Cancer Cytopathol 2020;128:278–86.
[16] Eguchi T, Kameda K, Lu S, Bott M, Tan KS, Montecalvo J *et al.* Lobectomy is associated with better outcomes than sublobar resection in spread through air spaces (STAS)-positive T1 lung adenocarcinoma: a propensity score-matched analysis. J Thorac Oncol 2019;14:87–98.
[17] Walts AE, Marchevsky AM. Current evidence does not warrant frozen section evaluation for the presence of tumor spread through alveolar spaces. Arch Pathol Lab Med 2018;142:59–63.
[18] Morimoto J, Nakajima T, Suzuki H, Nagato K, Iwata T, Yoshida S *et al.* Impact of free tumor clusters on prognosis after resection of pulmonary adenocarcinoma. J Thorac Cardiovasc Surg 2016;152:64–72.e1.
[19] Toki MI, Harrington K, Syrigos KN. The role of spread through air spaces (STAS) in lung adenocarcinoma prognosis and therapeutic decision-making. Lung Cancer 2020;146:127–33.
[20] Shiono S, Endo M, Suzuki K, Hayasaka K, Yanagawa N. Spread through air spaces in lung cancer patients is a risk factor for pulmonary metastasis after surgery. J Thorac Dis 2019;11:177–87.
[21] Uruga H, Fujii T, Fujimori S, Kohno T, Kishi K. Semiquantitative assessment of tumor spread through air spaces (STAS) in early-stage lung adenocarcinomas. J Thorac Oncol 2017;12:1046–51.
[22] de Margerie-Mellon C, Onken A, Heidinger BH, VanderLaan PA, Bankier AA. CT manifestations of tumor spread through airspaces in pulmonary adenocarcinomas presenting as subsolid nodules. J Thorac Imaging 2018;33:402–8.
[23] Kim SK, Kim TJ, Chung MJ, Kim TS, Lee KS, Zo JI *et al.* Lung adenocarcinoma: CT features associated with spread through air spaces. Radiology 2018;289:831–40.
[24] Yin Q, Wang H, Cui H, Wang W, Yang G, Qie P *et al.* Meta-analysis of association between CT-based features and tumor spread through air spaces in lung adenocarcinoma. J Cardiothorac Surg 2020;15:243.
[25] Zhong Y, Xu Y, Deng J, Wang T, Sun X, Chen D *et al.* Prognostic impact of tumour spread through air space in radiological subsolid and pure solid lung adenocarcinoma. Eur J Cardiothorac Surg 2021;59:624–32.