



To explore the prognostic value of spread through air spaces and develop a nomogram combined with spread through air spaces in lung squamous cell carcinoma

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Background: Spread through air spaces (STAS), as a new pattern of invasion, was officially proposed by the World Health Organization (WHO) in 2015, and its importance was reiterated in 2021. Since it was proposed, numerous studies have confirmed that STAS is associated with poor prognosis, but there are relatively few studies related to the prognosis of postoperative patients with lung squamous cell carcinoma. By synthesizing different predictive variables, nomogram can obtain the individual digital probability of clinical events succinctly and intuitively, which can meet our needs for personalized medicine. In this study, our goal is to explore the prognostic value of STAS in lung squamous cell carcinoma and establish a prognostic prediction model.

Methods: Under six inclusion criteria, 540 postoperative patients were enrolled in the study. STAS was re-evaluated by pathologists at Ningbo Clinicopathological Diagnosis Center. Progression-free survival (PFS) referred to the time from randomization to the first occurrence of disease progression or death of any cause. Recurrences were confirmed by clinical, radiological or pathological assessment. The survival information was collected by telephone and outpatient follow-up. A total of 540 patients were randomly divided into groups in a 6:4 ratio for survival analysis to determine the correlation between STAS and prognosis. Cox regression was used for univariate and multivariate analysis, so as to establish a predictive model. The assessment of the nomogram was carried out by receiver operating characteristic (ROC) curve analysis, calibration curve analysis and decision curve analysis (DCA).

Results: The overall 5-year survival rate was 70.35% in STAS-negative patients and 42.35% in STAS-positive patients. In all cohorts, STAS-negative patients had longer 5-year PFS than STAS-positive patients ($P < 0.001$). Multivariate analysis showed that stage [stage II $P = 0.008$, hazard ratio (HR) = 1.792; stage III $P < 0.001$, HR = 3.148], tumor differentiation (well-differentiation $P = 0.021$, HR = 0.436), and STAS ($P = 0.026$, HR = 1.470) were independent predictors of PFS. The area under the curve (AUC) of model 5 in discovery cohort is 0.720, while the AUC of model 5 in validation cohort is 0.693.

Conclusions: The nomogram combined with STAS can provide a personalized visual survival probability prediction map for postoperative patients with lung squamous cell carcinoma, so as to aid in the pursuit of personalized medicine to a certain extent.

Keywords: Lung squamous cell carcinoma; spread through air spaces (STAS); prognosis

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Introduction

GLOBOCAN 2020 (1) showed that although female breast cancer has surpassed lung cancer as the most common cancer worldwide, lung cancer is still the leading cause of cancer death. Despite many new advances in treatment, the prognosis of non-small cell lung cancer (NSCLC) remains poor. Schegoleva *et al.* (2) demonstrated that even if NSCLC is diagnosed at stage I and II, nearly 1/4 of patients will have postoperative recurrence. Recently, new immunophenotypes or molecular markers have emerged in NSCLC that have related prognostic and predictive functions, including previously underestimated morphological parameters which are considered to affect prognosis. These include improved staging criteria (3) as well as tumor distance to the resection margin, tumor budding, single-cell invasion around the tumor, and spread through air spaces (STAS). In 2015, STAS was identified as a new invasive pattern in the classification of lung tumors proposed by the World Health Organization (WHO). The definition (4) is as follows: “*STAS consists of micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma*”. Moreover, STAS is not included in the percentage measurement of subtype patterns in comprehensive histological typing or in the measurement of invasive size. It is an invasion pattern similar to pleural invasion and vascular invasion. In the updated classification of thoracic tumors in 2021 (5), the WHO reiterated that as a histological feature, STAS has important prognostic significance. Since STAS can be accurately observed in pathological sections, it is controversial whether sublobectomy should be performed as a treatment for small lung cancers (less than 2 cm in diameter). R0 resection did not completely remove part of the alveolar cavity of STAS. On conventional hematoxylin-eosin (H&E)-stained sections, clusters of small or large tumor cells were lined by STAS in the alveoli surrounding the main tumor. Many retrospective studies have shown that STAS is closely related to the prognosis of lung cancer (6-10). According to some studies published in the past 2 years, the incidence of STAS in NSCLC is 15.7% to 48.1% (7-9,11-16). In a prognostic model of invasive lung adenocarcinoma based on pathological features (17), STAS is a significant prognostic factor for regression-free survival (RFS) and OS. However, TNM stage and related clinical features were not included in the model. STAS was initially recognized in lung adenocarcinoma, and subsequent studies in lung adenocarcinoma have emerged one after another,

while there are few studies on STAS in lung squamous cell carcinoma. Therefore, in this study, we determined the pathological features and survival of 540 patients with lung squamous cell carcinoma to explore the value of STAS in predicting the prognosis of postoperative patients with lung squamous cell carcinoma. And we sought to investigate whether a prognostic model including STAS combined with clinical characteristics could significantly predict PFS in lung squamous cell carcinomas. We hope that by adding the factor of STAS, the prediction accuracy of prognosis can be improved. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1065/rc>).

Methods

Patients and samples

From January 2011 to December 2015, a total of 2302 patients underwent lung cancer surgery in The Affiliated Lihuili Hospital, Ningbo University. Under the inclusion criteria: (I) initial diagnosis is lung squamous cell carcinoma; (II) no intraoperative metastasis was observed; (III) no induction therapy; (IV) patients diagnosed the disease as a solitary disease; (V) negative surgical margin; (VI) the follow-up data is relatively complete. A total of 540 patients were enrolled in this retrospective study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Ningbo Medical Center Lihuili Hospital (The Affiliated Lihuili Hospital, Ningbo University) (No. KY2019PJ058) and individual consent for this retrospective analysis was waived. The clinical staging of patients was determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging criteria. STAS was re-evaluated by pathologists at Ningbo Clinicopathological Diagnosis Center. Progression-free survival (PFS) referred to the time from randomization to the first occurrence of disease progression or death of any cause. Recurrences were confirmed by clinical, radiological or pathological assessment. We obtained the survival information (including survival or death, tumor recurrence) of patients by telephone follow-up and outpatient follow-up. For the first 3 years, follow-up was conducted every 6 months. After 3 years, patients with stage I were followed up every year, and patients with stage II and III were followed up every 6 months. PFS referred to the time from randomization to the first occurrence of disease progression

or death of any cause. The assessment of recurrence was confirmed by clinical, radiological or pathological information. In this study, patients were randomly divided into the discovery cohort (n=324) and validation cohort (n=216) according to the proportion of 6:4.

Statistical analysis

We carried out the *t*-test for continuous variables and chi-square test for categorical variables to compare differences between the two groups. The survival time of STAS-positive/negative patients was estimated by Kaplan-Meier survival analysis and the log-rank test. We used receiver operating characteristic (ROC) curves to study the predictive performance of STAS. The 'pROC' package was applied to perform the ROC curve analysis. Univariate and multivariate Cox regression analysis were applied to analyze the independent prognostic effect of STAS. In multivariate analysis, AJCC stage, tumor differentiation and STAS were independent predictors of PFS. Cox regression coefficients were used to construct a nomogram for predicting the probability of PFS. Calibration plots were derived based on the regression analysis. We assessed the clinical utility of the nomogram by decision curve analysis (DCA). The nomogram and calibration plots were generated using the 'rms' R package. Statistical analysis was performed with R software (version 3.0.1) and statistical levels were two-sided. Statistical significance was set at 0.05.

Results

Clinical characteristics of patients

All patients in the cohort (540 patients) underwent surgical resection, and 196 (36.3%) patients were reported to be STAS positive. The clinical staging of patients was determined according to the 8th edition of the AJCC TNM staging criteria. The clinical information of the patients were obtained from medical records and pathological reports. *Table 1* presents information on the discovery cohort (n=324) and validation cohort (n=216).

Evaluation of the status of STAS

According to the definition of STAS given by the WHO in the classification of lung tumors in 2021: "STAS consists of micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung

parenchyma" (5). STAS status was confirmed in all 540 patients. STAS mainly presents as 3 morphological patterns (18): (I) micropapillary structures consisting of papillary structures without central fibrovascular cores which occasionally form ring-like structures within air spaces; (II) solid nests or tumor islands consisting of solid collections of tumor cells filling air spaces; and (III) single cells consisting of scattered discohesive single cells. The artifacts identified with STAS mentioned in related research (18,19) mainly focus on the following categories: (I) mechanically induced tumor floaters are often randomly located at the edges or planes of tissue sections; (II) alveolar macrophages; (III) jagged edges of tumor cell clusters, suggesting tumor fragmentation or edges cut by a knife during specimen handling; (IV) linear tumor cells detached from alveolar walls; (V) benign epithelial cells, such as hyperplastic alveolar parietal cells or bronchial epithelial cells; (VI) solitary tumor clusters distant from the tumor, not spreading continuously from the edge of the tumor.

The correlation between STAS and PFS

There was a significant difference in survival time among patients who were grouped according to their STAS status. The 324 patients in the discovery cohort were further divided into a STAS-negative group and STAS-positive group. Patients who were STAS negative typically had longer 5-year PFS than patients who were STAS positive ($P < 0.001$; *Figure 1A*). The same analysis was performed in the validation cohort (n=216). According to the pathological results, these patients were also divided into a STAS-negative group and STAS-positive group. The 5-year PFS in the STAS-negative group was also better than that in the STAS-positive group ($P < 0.001$; *Figure 1B*). In the comprehensive analysis of 540 patients according to negative/positive STAS status, there was still a similar difference in 5-year PFS between the two groups ($P < 0.001$; *Figure 1C*).

Prediction accuracy of STAS

In the univariate analysis, smoking status, vascular invasion, neural invasion, pleural invasion, AJCC stage, degree of differentiation, and STAS were significant prognostic factors, while there was no significant difference in other clinicopathological factors (*Table 2*). Multivariate analysis showed that AJCC stage, differentiation, and STAS were still independent predictors of PFS (*Table 2*). We used ROC

Table 1 Clinical information of 540 postoperative patients with lung squamous cell carcinoma

Variables	Discovery cohort (n=324)		Validation cohort (n=216)	
	STAS (-)	STAS (+)	STAS (-)	STAS (+)
Gender				
Male	196	110	127	77
Female	14	4	7	5
Age				
≥60 years	138	77	91	52
<60 years	72	37	43	30
Smoker				
No	79	33	43	25
Former + current	131	81	91	57
Differentiation				
Low	69	53	55	32
Moderately	122	49	59	38
Well	19	12	20	12
Invasion*				
Vessel (+)	27	36	18	19
Neural (+)	27	19	13	5
Pleural (+)	23	29	12	11
TNM stage				
I	115	28	76	25
II	53	37	34	18
III	42	49	24	39

*, the negative data are not included. STAS, spread through air spaces; TNM, tumor, node, metastasis.

curve analysis to evaluate the predictive performance of each model. The area under the curve (AUC) is measured on a scale of 0.5 (no better than chance) to 1 (perfect discrimination). A good prognostic prediction model will have an AUC value closer to 1. The results showed that the AUC of the STAS model was 0.612, the AUC of the AJCC staging model was 0.693, the AUC of the combined STAS and AJCC staging model was 0.713, and the AUC of the combined STAS, AJCC staging, and tumor differentiation status model was 0.720 (*Figure 2*). The graph intuitively showed that although STAS had a certain diagnostic value, the value of AJCC staging was better than STAS. The AUC of the combination of STAS and AJCC staging was higher than that of AJCC staging alone (using the DeLong's test method, $P=0.018$). Therefore, we believe that when

AJCC staging is combined with STAS, higher predictive performance can be obtained, that is, the prognostic value of AJCC staging in predicting the risk of recurrence and survival is increased. Also, we used ROC curve analysis to evaluate the predictive performance of model 5 in validation cohort with the AUC of 0.693 (*Figure 2*).

Establishment and clinical application of the nomogram

To provide a clinically useful tool for predicting prognosis, we constructed a nomogram integrating multiple clinicopathological risk factors associated with PFS, including STAS, AJCC staging, and tumor differentiation (*Figure 3*). Nomograms, also known as alignment diagrams, are a commonly used tool for estimating prognosis in

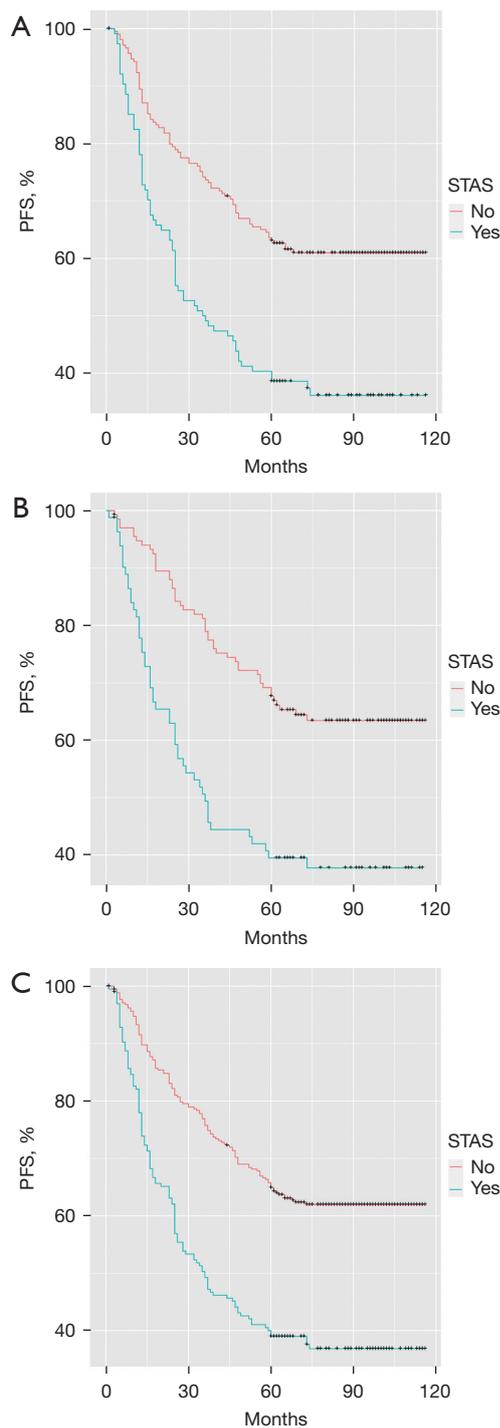


Figure 1 Results of Kaplan-Meier survival analysis of the discovery cohort (A), validation cohort (B), and total cohort (C). PFS, progression-free survival; STAS, spread through air spaces.

oncology and medicine. Based on the results of the multivariate analysis, multiple predictive indexes are integrated, distributed according to a certain proportion, and the relationship between outcome predictions is visualized among variables in the form of graphics. At the same time, the length of the line can be used to express the impact of different variables on the outcome, as well as the impact of different values of variables on the outcome, so as to advance the pursuit of personalized medicine. The calibration curve showed that the nomogram performed well, and the predicted 3- or 5-year PFS from the nomogram was in good agreement with the Kaplan-Meier prediction (Figure 4). DCA was used to evaluate the clinical potential of the predictive models by quantifying the net benefit. We evaluated the clinical utility of the above seven models (Figure 2) using DCA. The threshold probability for a patient to choose a treatment suggests how the patient weighs the relative harms of false-positive and false-negative predictions. The net benefit was calculated by subtracting the proportion of all false-positive patients from the proportion of true-positive patients (20). Through DCA, it was found that the clinical application potential of AJCC staging combined with STAS was higher than that of AJCC staging alone. When tumor differentiation was included, the model showed higher potential for clinical application, as the threshold probability range for 3- or 5-year PFS compared to full- or no-treatment regimens ensured a better net gain (Figure 5).

Discussion

The concept of STAS was clearly pointed out by the WHO in the pathological classification of lung cancer in 2015 as a new tumor invasion mode (4). Previously, Onozato *et al.* (21) had found this phenomenon in their study as an isolated, massive collection of tumor cells with vague micropapillary structures that exist in the alveolar air spaces, called tumor islands. Tumor islands are located around the lesion, separated from the main tumor by at least a few alveoli, and are seen in lung adenocarcinomas. Kadota *et al.* (18) later described the components of STAS in detail: “Single cells are defined as single tumor cells without cohesion in the alveolar space; micropapillary clusters are defined as the absence of a central fibrovascular core in the papillary structure;

Table 2 Results of Cox regression analysis of the discovery cohort

Variables	Univariate		Multivariate	
	P value	P value	HR	95% CI
Age	0.818	–	–	–
Smoker	0.0118	0.054	1.426	0.994–2.046
Gender	0.643	–	–	–
Vascular invasion	0.0006	0.272	1.256	0.836–1.886
Neural invasion	0.0388	0.240	1.306	0.837–2.037
Pleural invasion	0.0016	0.659	1.094	0.733–1.633
Differentiation				
Low	–	–	–	–
Moderate	0.4616	0.289	0.834	0.595–1.167
Well	0.0319	0.021	0.436	0.215–0.882
STAS	<0.001	0.026	1.470	1.046–2.066
Stage				
I	–	–	–	–
II	0.0011	0.008	1.792	1.165–2.758
III	<0.001	<0.001	3.148	2.056–4.819

HR, hazard ratio; CI, confidence interval; STAS, spread through air spaces.

solid cell nests are defined as collections of tumor cells filling the alveolar spaces". Morphologically, these tumor cells are located in the alveolar space, such as micropapillary clusters, solid cell nests, or individual tumor cells, as opposed to adherent growth in which tumor cells grow linearly along the alveolar wall surface. The degree of packing varies from massive cellular infiltration to inconspicuous single cells or micropapillary clusters that are sometimes difficult to distinguish from alveolar macrophages. In lung squamous cell carcinoma, Lu *et al.* (22) found that all STAS lesions consist of solid cell nests. STAS was initially identified in lung adenocarcinoma, but with subsequent extensive studies, STAS has also been found in other histological types of lung cancer, including lung squamous cell carcinoma, pleomorphic carcinoma, invasive mucinous adenocarcinoma, neuroendocrine tumor, and lymphoepithelioma-like carcinoma, among others. Chae *et al.* (23) found that the positive rate of STAS in neuroendocrine tumors (54/77, of which STAS was most common in small cell carcinoma) was higher than that of other previously reported tumors. At present, most studies focus on lung adenocarcinoma with a higher incidence, and studies related to STAS have

reported that STAS is closely related to poor prognosis. As for research on the relationship between lung squamous cell carcinoma and STAS, only a small number of English studies have directly investigated STAS and lung squamous cell carcinoma (22,24,25) since 2015. According to the 2020 Global Cancer Center Annual work report (26), the 5-year relative survival rate of primary lung cancer was extremely low, only about 19.7%, which was about 3% higher than 10 years ago. The correlation between STAS and prognosis has been mentioned in many meta-analyses. An analysis of 8 studies before April 2018 included by Wang *et al.* (27) showed that STAS was associated with poor RFS and OS. An analysis of 14 studies before August 2018 included by Chen *et al.* (28) showed that STAS was also associated with poor RFS and OS in NSCLC. The analysis of 12 studies from 2015 to 2018 included by Liu *et al.* (29) showed that STAS was related to the decline of 5-year RFS. Yang *et al.* (30) included 11 studies involving patients with stage I lung adenocarcinoma before December 2020, and the analysis showed that STAS was an independent prognostic risk factor, and its high expression could lead to a high 5-year recurrence rate. Li *et al.* (31) included 13 studies

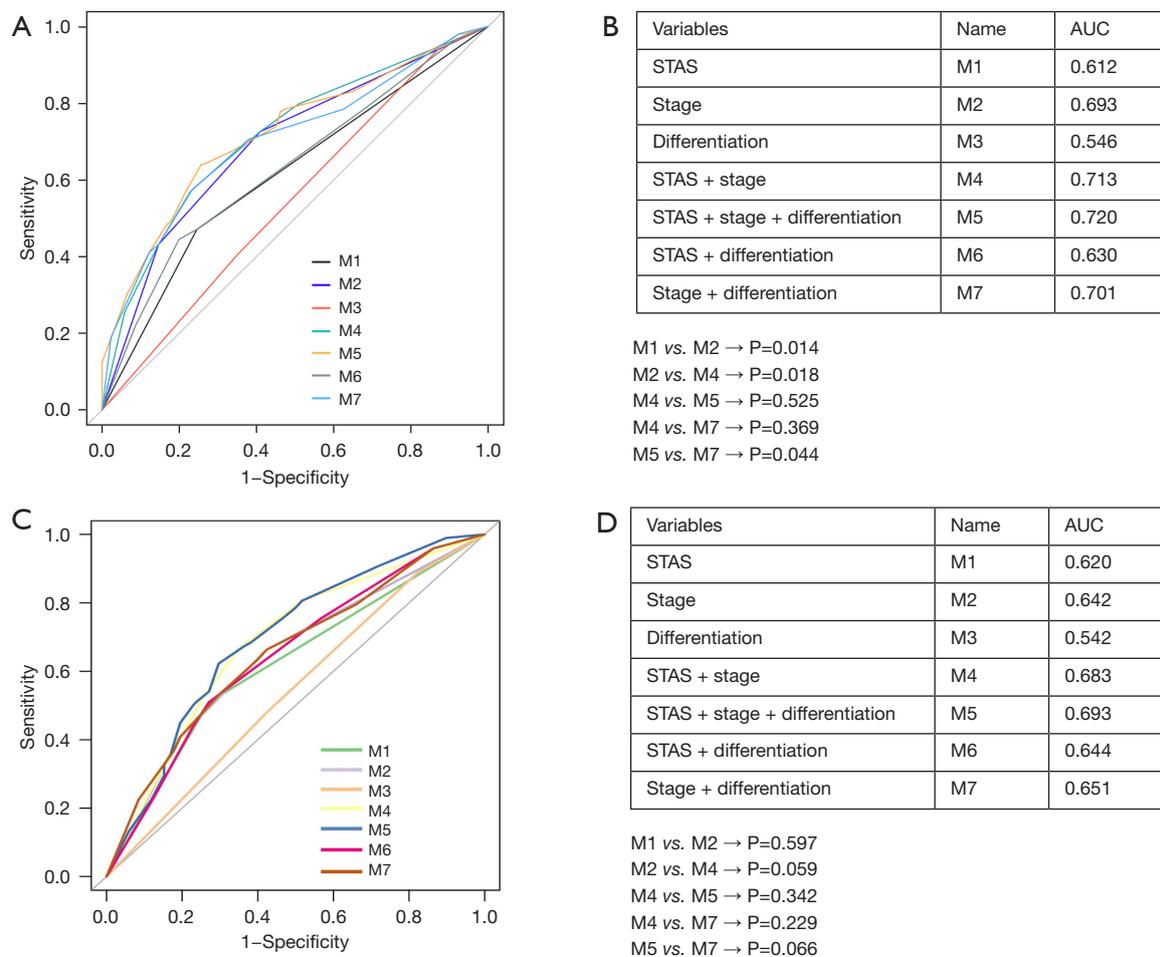


Figure 2 Results of ROC curve analysis. (A) In the discovery cohort, ROC curve analysis comparing the prognostic value of the seven models. (B) In the discovery cohort, description and the AUC of the seven models. (C) In the validation cohort, ROC curve analysis comparing the prognostic value of the seven models. (D) In the validation cohort, description and the AUC of the seven models. AUC, area under the curve; STAS, spread through air spaces; ROC, receiver operating characteristic.

of stage I NSCLC involving surgical procedures before March 2021, and the analysis showed that there was a significant correlation between STAS and RFS. In order to better assist clinical decision-making and individualized medical treatment, we analyzed a group of postoperative patients with lung squamous cell carcinoma to study STAS, and developed a nomogram that integrates STAS, AJCC staging, and other clinicopathological risk factors related to PFS to evaluate 3- and 5-year PFS in postoperative patients with lung squamous cell carcinoma. In this study, we divided the discovery and validation cohorts into STAS-negative/positive groups based on the description of STAS mentioned above. In the discovery cohort, patients in the STAS-negative group had significantly higher 5-year

PFS than the STAS-positive group. Similar results were also observed in the validation cohort. Furthermore, we validated the potential value of STAS in predicting patient outcomes in the validation cohort. Multivariate analysis showed that STAS was an independent prognostic factor for PFS after adjustment for clinicopathological variables. This is consistent with the findings of Lu *et al.* (22) that STAS is an independent prognostic factor for recurrence and survival in postoperative patients with lung squamous cell carcinoma in North America, and that STAS is associated with poor prognosis in Japanese patients with postoperative lung squamous cell carcinoma as shown by Kadota *et al.* (25). Yanagawa *et al.* (24) further studied the correlation between STAS and lung cancer stage. Multivariate analysis showed

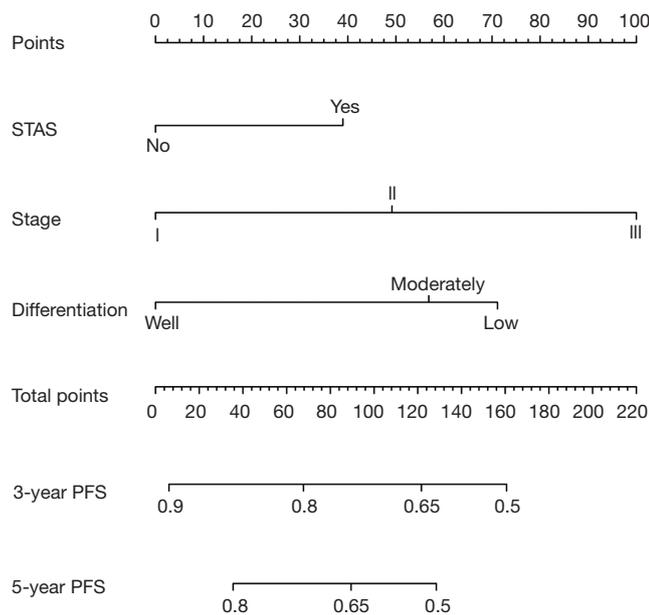


Figure 3 Nomogram. STAS, spread through air spaces; PFS, progression-free survival.

that the presence of STAS was an independent predictor of recurrence in stage I lung squamous cell carcinoma, but not in stage II and stage III. In this study, the prediction of PFS by combining AJCC staging and STAS was better than using the AJCC staging system alone. The calibration curve showed that there was a good correlation between the predicted survival time and the actual survival time. DCA showed that the nomogram had high potential for clinical application.

A previous study has proposed that “*STAS is an artificial product produced by knife face diffusion*” (32). Part of the reason for the artifact comes from the unique anatomical structure of lung specimens, including the collapse of lung tissue caused by surgery and the contraction of smooth muscle *ex vivo*, which is inevitable, though other reasons are worthy of further attention. In the process of tumor section processing, tissue fragments and individual cells may spread with the cutting of the knife face. The concept of spreading through a knife surface (STAKS) was first proposed by Thunnissen *et al.* (32). They believe that artifacts from knife

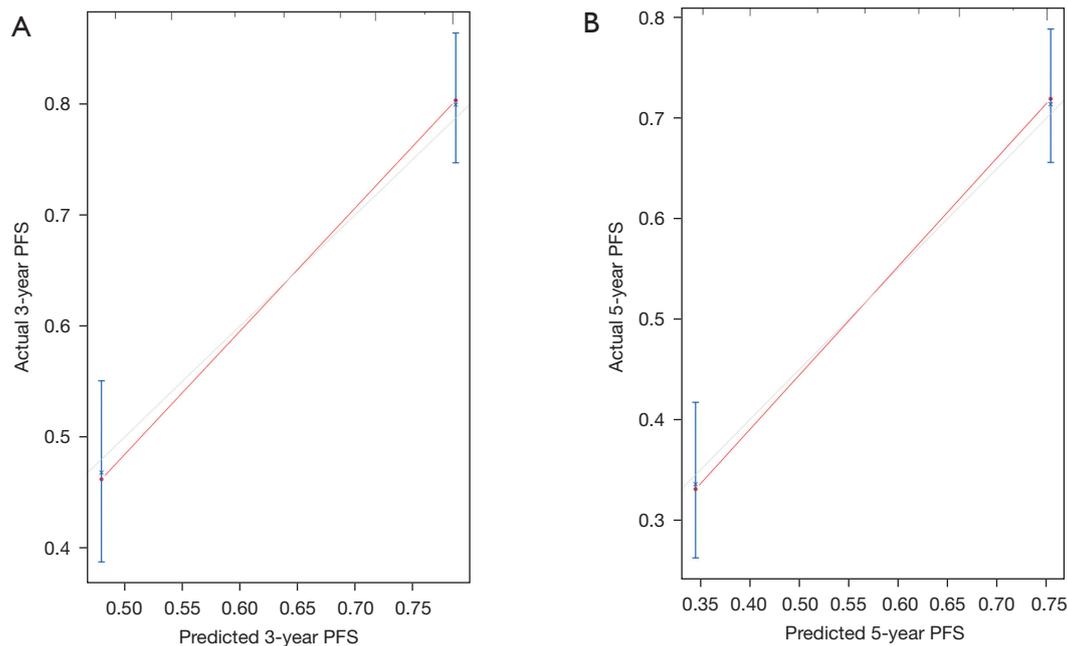


Figure 4 Calibration curves. (A) Evaluation of nomogram using 3-year nomogram calibration curves. Dashed line represents an ideal evaluation, whereas the red line represents the performance of the nomogram. (B) Evaluation of nomogram using 5-year nomogram calibration curves. Dashed line represents an ideal evaluation, whereas the red line represents the performance of the nomogram. PFS, progression-free survival.

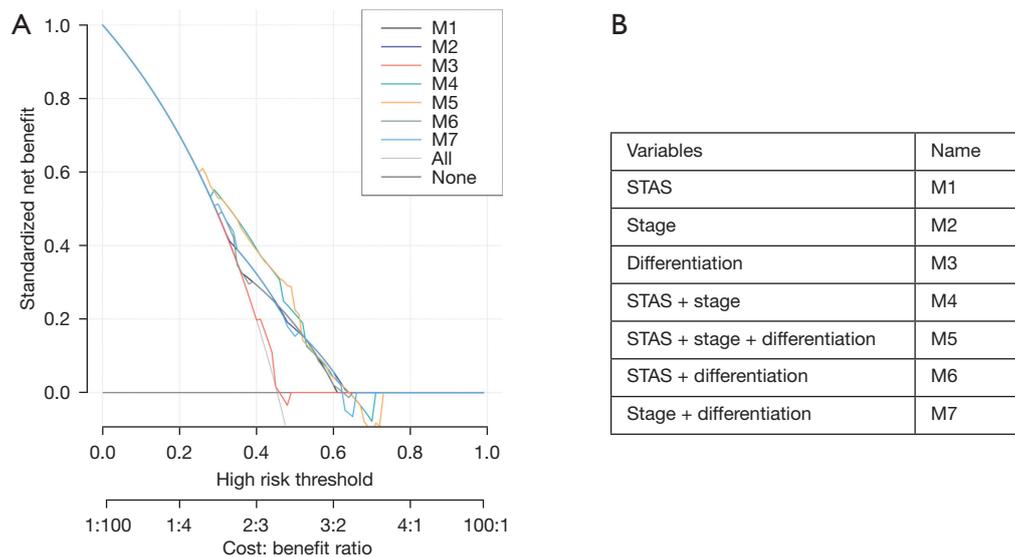


Figure 5 Decision curve analysis. (A) Decision curve analysis to evaluate the clinical utility of the nomogram. (B) Description of the seven models. STAS, spread through air spaces.

cutting are real, and that each continuous cut increases the mass of free-floating tumors. STAKS's explanation for the association between STAS and histological types with poor prognosis is that tumor cells tend to separate. They suggest that about half of the reported lung adenocarcinomas have a frequency of STAS exactly in line with the possible frequency of STAKS. Blaauwgeers *et al.* (33) proposed that a typical cutter or scalpel blade is 30 times wider than a human cell, which may cause the cell to move along the knife path during the cutting process. Through a prospective study, they proved that the existence of free cells in lung cancer specimens is an induced and reproducible phenomenon, that is, the floating tumor cell mass is entirely caused by mechanical force. The spread of benign and malignant cells in the lung is likely to be caused by the mechanical force exerted on the tissue during surgery and/or dissection of the specimen. Since the lung tissue is mainly composed of air, it is highly likely that displaced cells will exist in the air cavity. This may also explain the relatively low frequency of intravascular and endobronchial fragments compared with intra-alveolar fragments. However, Lu *et al.* (22) proposed that in STAS, tumor cell nests have a smooth boundary and can be seen in a continuous pattern from the edge of the tumor to the farthest location. Artifacts are more likely to show jagged edges and random distribution on sections, such as isolated tumor fragments on tissue sections. In addition, in specimens of lung adenocarcinoma with STAS as the main histological

pattern, it was observed that the area of floating tumor mass of STAS was not the area while the knife cutting through the main tumor. After Gross *et al.* (34) found STAS in the first surgical resection (R0 resection), several tumor cell clusters could still be found in the air cavity of the normal lung tissue resected in the subsequent second surgery. Metovic *et al.* (35) confirmed through a prospective study that there was no significant difference in the incidence of STAS between fresh tissues and formalin-fixed tissues, and there was no obvious dominant distribution of STAS in the air cavity of the lung parenchyma before and after the knife cut through the tumor. The results of these two studies strongly refute that STAS is a man-made event related to the operating procedure of pathologists.

In their review, Ikeda *et al.* (36) proposed other issues related to STAS recognition, such as the possibility of STAS recognition on frozen sections, and morphological and molecular properties of STAS. For preoperative prediction, ground glass opacity (37), solid component (38,39), and metabolic tumor volume (MTV)/computed tomography volume (CTV) >1 on 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) (40) is associated with STAS. The prediction models (41-44) established by radiomics signatures can effectively predict STAS. With regard to intraoperative prediction, the diagnostic performance of frozen sections (45,46) is unfavorable due to their low sensitivity. With respect to morphological properties, micropapillary-

predominant pattern (38,47-49) and solid-predominant pattern (47,48) are common in STAS. Nakajima *et al.* (50) found that cribriform pattern was also related to STAS. At the genetic level (47), epidermal growth factor receptor (*EGFR*), tumor protein p53 (*TP53*), Kirsten rat sarcoma viral oncogene (*KRAS*), anaplastic lymphoma kinase (*ALK*), and ROS proto-oncogene 1 (*ROS1*) are the 5 most common changes in STAS-positive lung adenocarcinoma. Other related studies on CD68⁺ tumor-associated macrophages (TAMs) (51) and epithelial-mesenchymal transition (EMT) (52) have also revealed their close relationship with STAS.

Although the nomogram combined with STAS had certain accuracy in predicting the survival of postoperative patients with lung squamous cell carcinoma, our current study still has some limitations. Firstly, this was a retrospective study, which may have a selection bias in population selection, and further prospective studies are needed to verify the findings. Secondly, the nomogram was verified internally, and subsequent verification should be performed in an external independent cohort. Furthermore, pathologists doubt whether the detection rate of STAS is affected by extensive sampling of peritumoral lung parenchyma. Since there is no consensus (8,23,53,54) on the definition of the degree of STAS, we did not conduct a graded study of STAS.

Conclusions

In summary, we developed and verified a nomogram that combines STAS and clinicopathological features, which can accurately predict the prognosis of postoperative patients with lung squamous cell carcinoma to a certain extent. Using an accurate prognostic model to predict patients' survival will be of great help in choosing the best treatment strategy and individualizing patient treatment.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1065/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Ningbo Medical Center Lihuili Hospital (The Affiliated Lihuili Hospital, Ningbo University) (No. KY2019PJ058) and individual consent for this retrospective analysis was waived.

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