Journal of Cardiothoracic Surgery

RESEARCH

Open Access

Nomogram model for the preoperative prediction of spread through air spaces in sub-centimeter non-small cell lung cancer

Xiao Wang[1], Jingwei Shi[2*] and Zhengcheng Liu[1*]

Abstract

Introduction To construct and validate a nomogram risk prediction model based on clinical characteristics and radiological features to predict spread through air spaces (STAS) of stage IA sub-centimeter non-small cell lung cancer.

Methods 112 patients who underwent surgical treatment in Nanjing Drum Tower Hospital with pathologically diagnosed stage IA sub-centimeter non-small cell lung cancer were retrospectively collected. The training cohort and the validation cohort were chosen in a 7:3 ratio. Based on the presence or absence of STAS in pathology results, they were divided into STAS positive and STAS negative groups. The independent risk predictors of STAS in clinical characteristics and radiological features were selected by univariate and multivariate logistic regression analysis and then used to construct a nomogram. The sensitivity and specificity were calculated based on the Youden index, area under the curve (AUC), calibration curves and decision curve analysis (DCA) were used to evaluate the performance of the model.

Results The incidence of STAS in the training cohort was 17.9%. Univariate logistic regression analysis showed that male, anti-GAGE7 antibody positive and mean CT value were associated with the occurrence of STAS; multivariate logistic regression analysis showed that male (OR = 7.900, 95%CI: 1.502–41.545), anti-GAGE7 antibody positive (OR = 10.065, 95%CI: 1.256–80.659) and mean CT value (OR = 1.009, 95%CI: 1.004–1.014) were independent predictors for STAS. The nomogram based on the above factors achieved good predictive performance for STAS with AUC was 0.897 (sensitivity was 0.929, specificity was 0.781) in the training cohort and 0.860 in the validation cohort. The calibration curve and DCA validated the good performance of the model.

Conclusion The nomogram model established in this study had good predictive performance for STAS status of sub-centimeter lung cancer, and provide reference significance for preoperative planning of patients.

Keywords Sub-centimeter lung cancer, Spread through air spaces, Nomogram, Prediction model

*Correspondence:
Jingwei Shi
shijingwei555@126.com
Zhengcheng Liu
zhengcheng.liu@njglyy.com
[1]Department of Thoracic Surgery, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing 211166, China
[2]Department of Thoracic Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, China

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Introduction

Lung cancer is still the malignant tumor with the greatest incidence and death rate in China, and its occurrence is rising annually around the world [1, 2]. Recent years have seen an increase in the diagnosis rate of early lung cancer, including sub-centimeter lung cancer, thanks to the widespread use of low-dose spiral CT scanning and increased public awareness of health examinations [3]. The outcomes of the clinical trials JCOG0804, JCOG0802, and CALGB140503 have demonstrated that sublobar resection is anticipated to replace lobectomy as the conventional procedure for peripheral early non-small cell lung cancer with a diameter of up to 2 cm [4–6]. Although the prognosis for sub-centimeter lung cancer is generally favorable, some individuals may still experience metastasis or recurrence [7]. An separate kind of lung cancer transmission known as spread through air spaces (STAS) refers to the air diffusion of tumor cells to the alveolar space outside the original tumor's margin in the form of solid nests, micropapillary clusters, or single cells [8]. In addition to adenocarcinoma, STAS is also present in other forms of lung cancer such as neuroendocrine tumors, squamous cell carcinoma and carcinoid carcinoma [9, 10]. Whether early non-small cell lung cancer with STAS positive status is suitable for sublobar resection is a research hotspot in the field of thoracic surgery. According to a meta-analysis of 10,883 individuals with stage I non-small cell lung cancer, sublobar resection was associated with a greater 5-year risk of recurrence (HR = 3.44, 95%CI: 2.49–4.76) and mortality in STAS-positive patients (HR = 3.40, 95%CI: 2.05–5.64) [11]. In a retrospective study of 555 patients with stage IA non-small cell lung cancer, Ikeda et al. found that wedge resection was an independent risk factor for poor recurrence free survival (RFS) and overall survival (OS) in STAS positive patients [12]. Therefore, knowledge of whether the tumor is accompanied by STAS before and during the operation is of great significance to guide surgeons to choose the surgical procedure.

For the diagnosis of STAS, intraoperative rapid pathology has a high specificity but a low sensitivity [13, 14]. Thus, the preoperative clinical and radiological features have become increasingly important in the prediction of STAS in recent years. Studies have demonstrated the tight relationship between STAS and clinical factors such as gender, carcinoembryonic antigen (CEA), as well as radiological aspects such as consolidation tumor ratio (CTR), nodule type, lobulation, and spiculation [15, 16]. Liao et al. created a prediction model with a sensitivity of 82% and a specificity of 80% to predict STAS in stage I lung adenocarcinoma by merging radiomics technology [17]. According to Wang et al.'s analysis of the clinical imaging features of 241 lung adenocarcinoma patients, the generated nomogram's area under the curve (AUC) was 0.860 in the training set and 0.919 in the validation set [18].

The studies mentioned above cover a wider range of case stages, and there is limited clinical value in predicting middle and advanced stage lung cancer with STAS. Additionally, radiomics technology is complex and not easily adapted for clinical promotion, the prediction model that solely relies on radiological features is moderate, and similarly little research has been done on using lung cancer autoantibodies to forecast the STAS. Furthermore, no STAS model exists for sub-centimeter lung cancer. Yearly increases in the number of patients with sub-centimeter lung cancer are seen; while most lesions were found early and the prognosis is generally good overall, a small percentage of lesions are still quite aggressive, and some even come with STAS. The study aims to investigate the association between clinical and imaging features and STAS, as well as to develop a nomogram model based on preoperative clinical and imaging data for predicting STAS in stage IA sub-centimeter non-small cell lung cancer patients.

Materials and methods

Patients

A retrospective analysis identified 4,667 consecutive patients who underwent surgical resection of lung nodules or masses with histopathological diagnosis of non-small cell lung cancer in Nanjing Drum Tower Hospital from January 2022 to October 2023. The training cohort and the validation cohort were chosen in a 7:3 ratio. Pathological staging was performed according to the International Association for the Study of Lung Cancer (IASLC). The 2021 World Health Organization (WHO) classification of thoracic tumors clearly proposed that microinvasive adenocarcinoma was the exclusion criteria for STAS [19]. Therefore, patients with microinvasive adenocarcinoma were excluded from this study. The inclusion criteria were as follows: (1) pathological diagnosis of primary lung cancer; (2) thoracic CT examination performed before the surgery less than one month; (3) stage IA sub-centimeter non-small cell lung cancer. The exclusion criteria were as follows: (1) Microinvasive adenocarcinoma; (2) Neoadjuvant chemotherapy before surgery; (3) Presence of multiple lung cancer; (4) Lack of lung cancer autoantibody detection after the hospitalization. The selection process for patients in this study is displayed in Fig. 1.

CT imaging acquisition and interpretation

The patient underwent a preoperative thoracic CT examination, which was performed using two types of CT machines: the Dutch Philips IQon-Spectral 128-row CT machine and the Dutch Philips iCT 256-row CT machine. The parameters were set as follows: tube

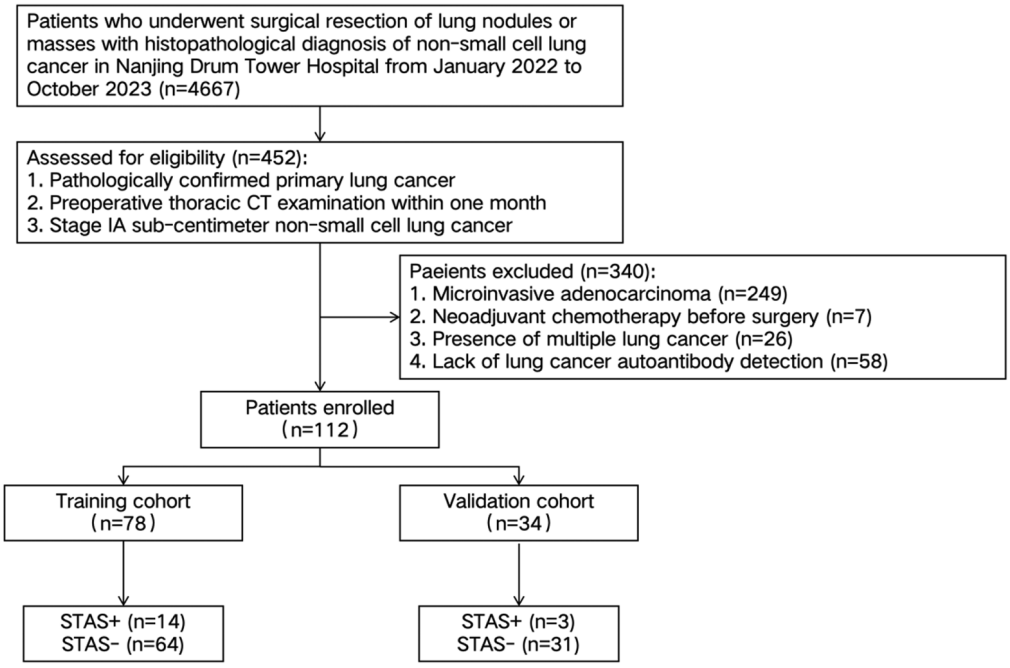

Fig. 1 Patient selection process

voltage 120kVp; automatic tube current regulation; detector collimation 0.625 mm. Lung window observation was reconstructed using lung algorithm, section thickness was 1.0–2.0 mm, gap was 1.0–1.5 mm (window level, -600HU; window width, 1500 HU). Soft tissue observation was reconstructed using standard algorithm, layer thickness was 3.0 mm, gap was 3.0 mm (window level, 40HU; window width, 250HU).

CT imaging analysis was conducted on the Picture Archiving and Communication System (PACS) using lung window and soft tissue window. Two residents with over 2 years of experience in thoracic imaging diagnosis each independently analyzed the radiological features, including lesion location, lobulation, spiculation, and mean CT value. Prior to reading, they were blinded to analyzing the STAS results from the pathology department. The mean CT value was measured using the lung window setting in the maximum transverse section of the nodule to minimize interference from small pulmonary vessels, small bronchi, and calcification foci as much as possible. The intraclass correlation coefficients (ICC) were used to evaluate the consistency between the two readers. Any discrepancies were resolved by two associate chief physicians.

Histopathological evaluation

Tumor specimens were fixed in a 10% neutral formalin solution for 12–48 h prior to sampling, paraffin embedding, sectioning, hematoxylin/eosin staining, and observation by light microscopy. Postoperative lung resection specimens were assessed by two experienced pathologists in accordance with the WHO definition. Consensus was reached for cases with inconsistent results after discussion. STAS was defined as the airborne diffusion of tumor cells in the form of micropapillary clusters, solid nests, or individual cells into the alveolar space outside the margin of the primary tumor. Immunohistochemical staining was utilized to differentiate lung alveolar macrophages from bona fide STAS.

Lung cancer autoantibodies detection

Venous blood (about 4 ml) was collected from the patient on an empty stomach before the pulmonary operation. The serum was separated by a serum coagulant tube of 3500r/min and centrifuged for 10 min. The serum was stored in a refrigerator at -80 °C. Serum concentrations of seven kinds of tumor-associated autoantibodies (TAABs) were measured by enzyme linked immunosorbent assay (ELISA), and anti-p53, PGP9.5, SOX2, GAGE7, GBU4-5, MAGEA1 and CAGE antibodies were detected. The normal reference intervals for the 7 TAABs were obtained from the kit instructions and verified by the laboratory.

Statistical analysis

SPSS 29.0 software and R statistical software (R version 4.2.3) were used for statistical analysis. Measurement data were tested for normality using the Shapiro-Wilk test. If the normal distribution is followed, the mean ± standard deviation and the independent sample *t*-test, otherwise the median (interquartile range) and the Mann-Whitney *U* test were used for group comparison. The counting data were statistically described by

frequency and percentage, and statistical inference was performed by chi-square test. Independent predictors of predicting STAS in clinical and radiographic features were screened by univariate and multivariate logistic regression. The variance inflation factor (VIF) is used to assess whether there is multicollinearity between the independent variables. VIF < 5 suggests no collinearity interference between the independent variables. The "rms" package builds the nomogram model based on independent predictors, and the model was evaluated by drawing calibration curve, receiver operating characteristic (ROC) curve and decision curve analysis (DCA). The Bootstrap method repeated sampling 1000 times for internal verification to reduce the overfitting bias of the model. Two-sided test was used, and $P < 0.05$ was considered a statistically significant difference.

Results

Patient clinical characteristics and radiological features

A total of 78 patients of stage IA sub-centimeter non-small cell lung cancer were enrolled in the training cohort of this study, including 14 patients with STAS positive rate (17.9%); there were 64 STAS negative patients, accounting for 82.1% of the total population. The majority (98.7%) of patients exhibited the pathological type of invasive adenocarcinoma, with only one patient diagnosed with carcinoid. STAS positive patients were mostly male, and most of them had clinical characteristics of anti-CAGE7 antibody positive. In terms of radiological features, most STAS positive patients, the mean CT value was higher than that of STAS negative patients, while other radiological features were not correlated with STAS. The specific clinical characteristics and radiological features are shown in Table 1.

Table 1 Clinical characteristics and radiological features in the training cohort

Variable	All patients (*n* = 78)	Positive for STAS(*n* = 14)	Negative for STAS(*n* = 64)	*P* value
Age/year[a]	56.9 ± 10.5	57.3 ± 9.8	56.8 ± 10.7	0.868
Gender				0.038
Male	31 (39.7)	9 (64.3)	22 (34.4)	
Female	47 (60.3)	5 (35.7)	42 (65.6)	
Hypertension				0.627
Absent	49 (62.8)	8 (57.1)	41 (64.1)	
Present	29 (37.2)	6 (42.9)	23 (35.9)	
Diabetes mellitus				0.795
Absent	68 (87.2)	13 (92.9)	55 (85.9)	
Present	10 (12.8)	1 (7.1)	9 (14.1)	
Anti-TP53				1.000
Negative	76 (97.4)	14 (100.0)	62 (96.9)	
Positive	2 (2.6)	0 (0.0)	2 (3.1)	
Anti-GAGE7				0.007
Negative	72 (92.3)	10 (71.4)	62 (96.9)	
Positive	6 (7.7)	4 (28.6)	2 (3.1)	
Anti-PGP9.5				-
Negative	78 (100.0)	14 (100.0)	64 (100.0)	
Positive	0 (0.0)	0 (0.0)	0 (0.0)	
Anti-CAGE				-
Negative	78 (100.0)	14 (100.0)	64 (100.0)	
Positive	0 (0.0)	0 (0.0)	0 (0.0)	
Anti-MAGEA1				-
Negative	78 (100.0)	14 (100.0)	64 (100.0)	
Positive	0 (0.0)	0 (0.0)	0 (0.0)	
Anti-SOX2				0.792
Negative	76 (97.4)	13 (92.9)	63 (98.4)	
Positive	2 (2.6)	1 (7.1)	1 (1.6)	
Anti-GBU4-5				0.953
Negative	75 (96.2)	14 (100.0)	61 (95.3)	
Positive	3 (3.8)	0 (0.0)	3 (4.7)	
Surgical procedure				0.272
WR	18 (23.1)	2 (14.3)	16 (25.0)	
Segmentectomy	35 (44.9)	5 (35.7)	30 (46.9)	
Lobectomy	25 (32.1)	7 (50.0)	18 (28.1)	
Tumor location				0.363
Upper and middle lobe	42 (53.8)	6 (42.9)	36 (56.3)	
Lower lobe	36 (46.2)	8 (57.1)	28 (43.8)	
Lobulation				0.089
Absent	23 (29.5)	1 (7.1)	22 (34.4)	
Present	55 (70.5)	13 (92.9)	42 (65.6)	
Spiculation				0.127
Absent	64 (82.1)	9 (64.3)	55 (85.9)	

Analysis of clinical characteristics and radiological features associated with STAS

In this study, univariate and multivariate logistic regression analysis was used to determine which parameters could be used as independent predictors of STAS. Univariate regression analysis showed that male, anti-GAGE7 antibody positive and mean CT value were associated with STAS positivity in stage IA sub-centimeter non-small cell lung cancer. Multivariate regression analysis showed that male (OR = 7.900, 95%CI: 1.502–41.545), anti-GAGE7 antibody positive (OR = 10.065, 95%CI: 1.256–80.659) and mean CT value (OR = 1.009, 95%CI: 1.004–1.014) were independent predictors of STAS positivity. The rest were non-independent predictors (Table 2). A collinearity analysis was conducted on the three factors mentioned above, and the results showed that the VIF values were 1.018, 1.045, and 1.053, all less than 5, indicating that there is no collinearity relationship between the three factors mentioned above.

Table 1 (continued)

Variable	All patients (*n* = 78)	Positive for STAS(*n* = 14)	Negative for STAS(*n* = 64)	*P* value
Present	14 (17.9)	5 (35.7)	9 (14.1)	
Mean CT value[b]	-243.6 (-384.1, -43.5)	31.4 (-112.8, 112.2)	-282.3 (-425.0, -106.6)	< 0.001

WR = Wedge resection; STAS = Spread through air spaces

[a]Normally distributed measurement data were presented as the mean ± standard deviation

[b]Skewedly distributed measurement data were presented as the median (interquartile range)

Construction and validation of the nomogram prediction model

Based on the independent predictors (male, anti-GAGE7 antibody positive, mean CT value), the nomogram model predicting STAS was constructed using R statistical software (Fig. 2A). As can be seen from Fig. 2A, each variable has a different range of values, and the size of the score value is related to the OR value of the regression analysis. Each patient can be scored according to their own risk factors, and the total score is projected into the probability column to obtain the probability of positive STAS.

Area under the curve (AUC) of the nomogram was 0.897 (sensitivity was 92.9%, specificity was 78.1%) in the training cohort and 0.860 in the validation cohort (Fig. 2C-D). The calibration curve showed good agreement relative to the postoperative pathology findings, indicating the preoperative stability of nomogram in predicting STAS in early lung cancer (Fig. 2B). C-index was 0.897 (95%CI: 0.773–0.981), suggesting that this model has a good prediction effect. The optimal cut-off value of the model was 73.00. Using this cut-off value as a reference, the typical image analysis for the validation group was presented in Fig. 3.

Clinical use

The DCA plot shows that the threshold probability range of the model for predicting STAS is 0–84% and 88%-97%, the patient had a good net benefit with clinical utility (Fig. 4).

Discussion

To our knowledge, this is the first time that a Nomogram prediction model has been developed and validated to predict STAS status in sub-centimeter stage IA non-small cell lung cancer to weigh the feasibility of limited resection. The majority of thoracic surgeons and lung cancer patients agree that surgical resection is the preferred method to treat early-stage lung cancer, and sublobar resection has emerged as a standard clinical surgical approach. Additionally, the clinical studies JCOG0804, JCOG0802, and CALGB140503 offer strong evidence-based medical evidence [4–6]. WHO officially introduced the concept of STAS in 2015, recognizing it as a novel lung cancer invasion mechanism. STAS is an independent risk factor that influences the prognosis of patients with early-stage non-small cell lung cancer [8, 19]. Numerous investigations have revealed that STAS significantly worsens the prognosis of patients receiving limited resection, particularly wedge resection [11, 12]. Thus, for a thorough assessment of the surgical approach, the preoperative and intraoperative prediction of STAS in early lung cancer is crucial.

Although some researchers have suggested using rapid intraoperative pathological examination to identify STAS, this approach is less sensitive than using conventional pathological Sects. [13, 14]. Research has also suggested using preoperative biopsies to assess STAS. In 111 patients with lung adenocarcinoma, Cao et al. retrospectively examined preoperative percutaneous transthoracic needle biopsies and postoperative resection specimens. They discovered that desmoplasia, intratumoral budding, and micropapillary/solid histologic subtype were independently linked to STAS [20]. Promoting invasive operations in patients with early-stage lung cancer is challenging, unfortunately.

Jia et al. observed that CTR was linearly linked with STAS in the correlation analysis of CTR and STAS through the generalized additive model. The multivariable regression model based on CTR revealed OR value of 1.24 and P value of 0.015 [21]. However, the study used a propensity score matching method, because of the selection bias, which affected the generalization of the model. Liao et al. used radiomics technology to build a model to predict STAS [17]. Despite the model's high predictive effectiveness, radiomics technology operates in a complex way, making it challenging to mainstream in clinical practice. Wang et al. used clinical and imaging characteristics to create a nomogram model that predicted STAS [18]. However, the stage of enrolled cases was not restricted to the early stage, the clinical significance of determining whether advanced lung cancer is associated with STAS was restricted.

Previous studies on the predictive significance of serology for STAS were often limited to CEA and ignored the potential value of lung cancer autoantibodies. Furthermore, no STAS model exists for lung cancer that is less than one centimeter in size. Adenocarcinoma in situ and microinvasive adenocarcinoma are the most common lesions found in patients with sub-centimeter lung cancer; overall prognosis is good following surgical treatment; however, a small percentage of lesions still have high malignancy, and developed into invasive adenocarcinoma based on sub-centimeter size, and even develop STAS. A total of 112 stage IA sub-centimeter non-small cell lung cancer were included in this study,

Table 2 Univariate and multivariate logistic regression analysis of factors in the training cohort

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age/year	1.005	0.950–1.062	0.866			
Gender (Male VS Female)	3.436	1.026–11.510	0.045	7.900	1.502–41.545	0.015
Hypertension	1.337	0.413–4.330	0.628			
Diabetes mellitus	0.470	0.055–4.046	0.492			
Anti-TP53	-	-	-			
Anti-GAGE7	12.400	2.001–76.842	0.007	10.065	1.256–80.659	0.030
Anti-PGP9.5	-	-	-			
Anti-CAGE	-	-	-			
Anti-MAGEA1	-	-	-			
Anti-SOX2	4.846	0.284–82.563	0.275			
Anti-GBU4-5	-	-	-			
Surgical procedure (Segmentectomy VS WR)	1.333	0.232–7.661	0.747			
Surgical procedure (Lobectomy VS WR)	3.111	0.563–17.196	0.193			
Tumor location (Upper and middle lobe VS Lower lobe)	1.714	0.533–5.513	0.366			
Lobulation	6.810	0.835–55.515	0.073			
Spiculation	3.395	0.925–12.466	0.065			
Mean CT value	1.008	1.003–1.012	< 0.001	1.009	1.004–1.014	< 0.001

CI: Confidence interval; OR: Odds ratio; STAS = Spread through air spaces; WR = Wedge resection

and univariate regression analysis suggested that clinical features including male, anti-GAGE 7 antibody positive were associated with STAS, and mean CT value in the imaging features were associated with STAS. Multivariate regression analysis showed that male, anti-GAGE 7 antibody positive, and mean CT value were independent predictors of STAS.

The incidence of STAS is higher in the male population than in females, which has been confirmed in a large number of literatures [12, 15, 22, 23]. However, the underlying reasons remain unclear. We hypothesize that this may be related to higher smoking rates among men and genetic heterogeneity between genders. Smoking significantly increases lung cancer risk, and the pulmonary microenvironment of smokers is more conducive to cancer cell dissemination. Thus, there is a correlation between smoking history and STAS, potentially contributing to its higher incidence in male patients. In terms of genes, numerous studies have explored the relationship between STAS and lung cancer gene status, particularly with regard to the epidermal growth factor receptor (EGFR) [24, 25]. EGFR mutations are the most common genetic alterations in NSCLC, affecting 45–50% of Asian adenocarcinoma patients and 15–20% of those in Western countries [26]. These mutations primarily occur in exons 18–21 of the kinase domain, leading to sustained activation of downstream EGFR signaling, promoting cell proliferation and tumor development. A global prospective study on EGFR mutations in NSCLC patients indicated a significant correlation between female gender and increased likelihood of EGFR mutations [27]. Additionally, patients with STAS tend to have a lower frequency of EGFR mutations, often presenting with EGFR wild-type [24]. Therefore, the gender differences in genetic mutations may be another reason for the higher prevalence of STAS in male patients.

GAGE7 belongs to the tumor/testicular antigen gene family, and its expression product belongs to tumor rejection antigen, which is only expressed in malignant tumors and testicular tissue. While anti-GAGE7 antibody is primarily used for early screening in lung cancer patients, there are no reports on their predictive capability for STAS. In this study, anti-GAGE7 antibody indicate limited diagnostic value. However, when combined with two variables—gender and mean CT value—the diagnostic performance of the model significantly improved, with VIF values for all three variables remaining below 5, indicating no multicollinearity. This research suggests that TAABs may possess potential clinical value in diagnosing STAS. Furthermore, this represents a new serological approach to explore STAS, following CEA and inflammatory markers. Future studies could further investigate the molecular mechanisms underlying GAGE7 and its role in patient prognosis.

Mean CT value is an important medical radiological parameter, mainly used to evaluate the density of the tissue and the nature of the lesion. Tumor cell invasion into alveolar tissue leads to thickening of the alveolar septa, collapse of some alveoli, and increased capillary density. Consequently, as the tumor progresses, the CT value of the lesion gradually increases [28]. Patients in the STAS positive group had a considerably higher mean CT value than those in the STAS negative group, which may be explained by the fact that STAS is a novel form of lung

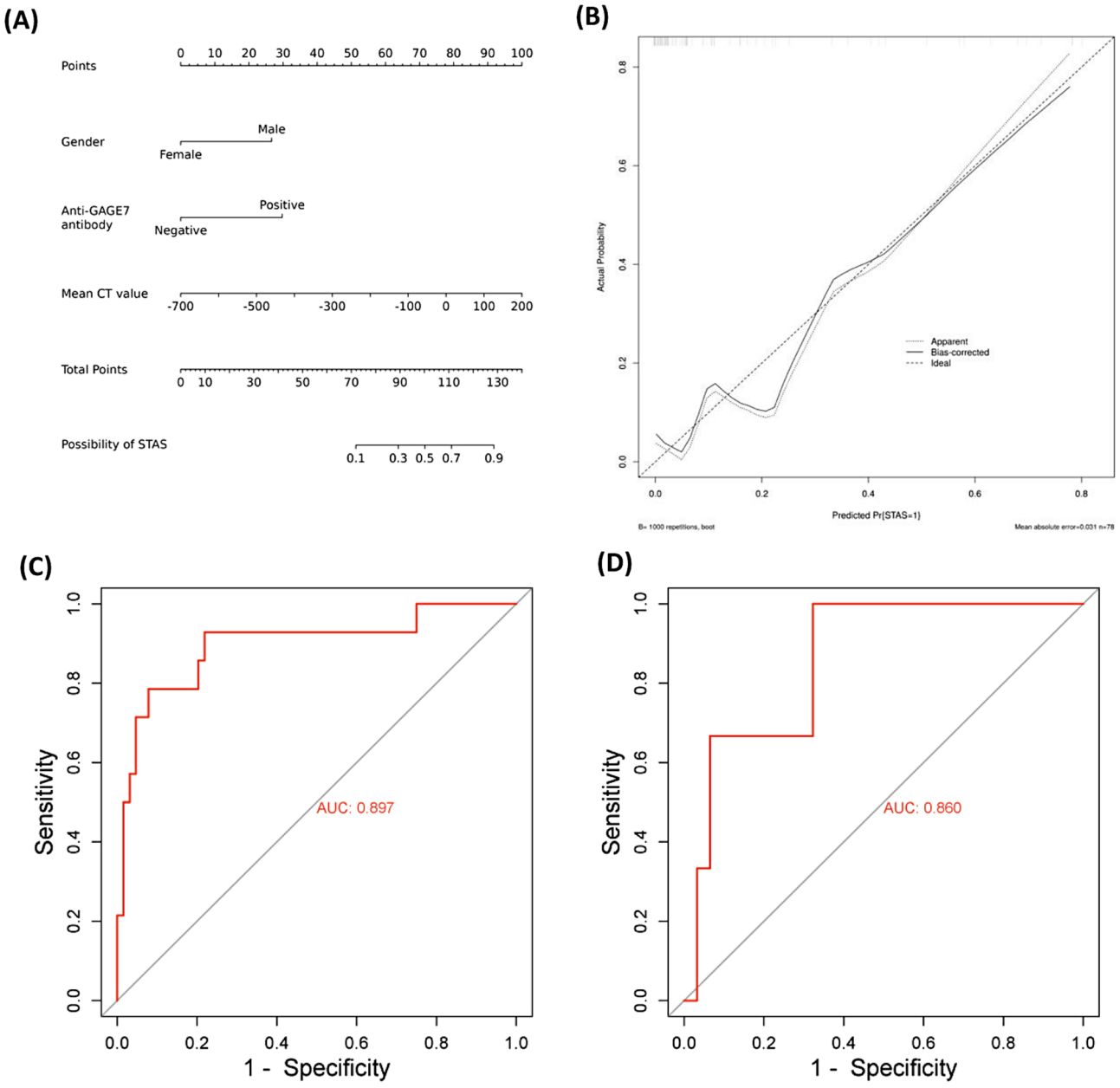

Fig. 2 Preoperative prediction model for STAS in stage IA sub-centimeter non-small cell lung cancer. (**A**) Nomogram for predicting the incidence of STAS. (**B**) The calibration curve of the nomogram. (**C**) The ROC curve of the nomogram in the training cohort. (**D**) The ROC curve of the nomogram in the validation cohort

cancer invasion and an indication of high tumor invasion. Yamamoto et al. pointed out that mean CT value was an independent risk factor for predicting STAS, with mean CT value greater than − 251.8Hu was more likely to have STAS, AUC was 0.738 (sensitivity was 80.5%, specificity was 65.4%) [29]. Our study, however, found that the optimal cut-off value of mean CT value was − 43.00Hu. The discrepancy may be due to different patient inclusion criteria between the two studies. The subjects included by Yamamoto et al. were lung adenocarcinoma patients at clinical stage N0, whose tumor diameter varied widely, and malignancy was generally higher than that of sub-centimeter lung cancer, potentially leading to differences in the optimal cut-off value for the mean CT value.

We built the nomogram model using the three independent predictors mentioned above, and it had a good predictive accuracy with an AUC of 0.897 (sensitivity 92.9%, specificity 78.1%) for predicting STAS of stage IA sub-centimeter non-small cell lung cancer. Currently, the number of patients with sub-centimeter lung cancer is steadily increasing, and the choice of surgical methods may impact the prognosis of patients with STAS. The

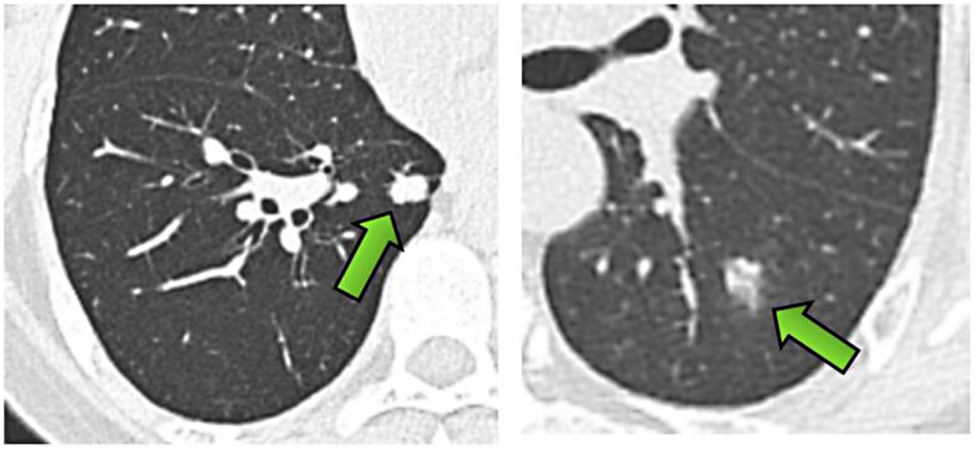

Fig. 3 A 48-year-old woman (left) with lung adenocarcinoma of the right lower lobe, STAS(+). Solid nodule (green arrow), anti-CAGE7 antibody (-), mean CT value: 166.53Hu, nomoscore: 90.73 > 73.00. A 55-year-old woman (right) with lung adenocarcinoma of the left lower lobe, STAS(-). Mixed ground glass nodule (green arrow), anti-CAGE7 antibody (-), mean CT value: -109.97Hu, nomoscore: 65.56 < 73.00

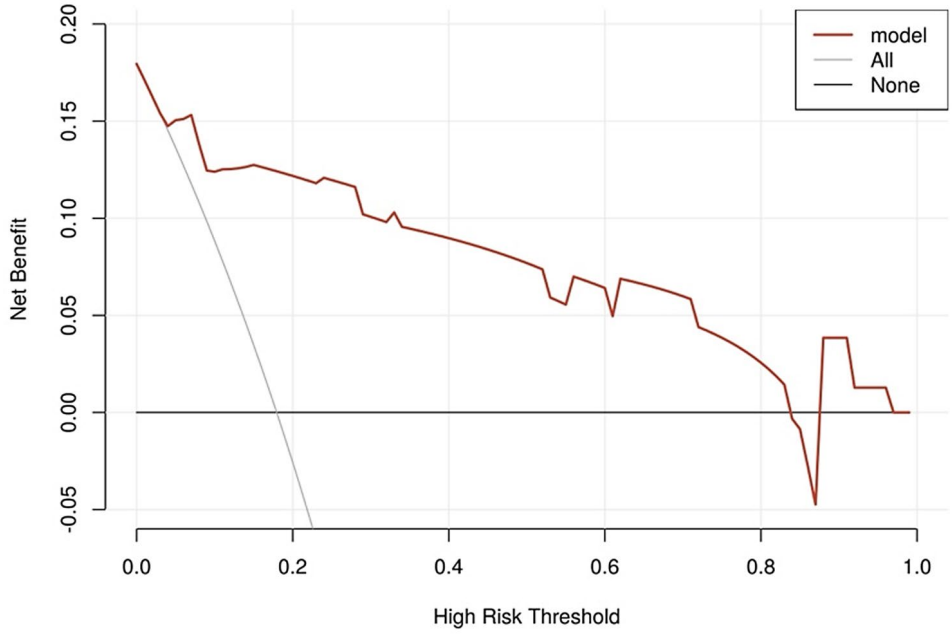

Fig. 4 DCA plot of the prediction model in the training cohort

prediction model designed in this study can well meet the clinical needs. Additionally, the nomogram model offers the advantages of visualization and ease of popularization, aligning well with clinical practice.

This study has a few limitations: firstly, this study is a single-center retrospective study, with inevitable bias in data collection; secondly, the study only includes a small number of patients, particularly those who are STAS positive, the study results may be affected. In addition, different CT devices may affect image review. Future prospective multicenter trials are required for additional validation.

Conclusion

In conclusion, we constructed a nomogram model to predict STAS based on preoperative clinical characteristics combined with radiological features, and concluded that this model had high predictive accuracy through validation. This model solves the difficulty of the preoperative diagnosis of STAS status; it is convenient for the surgeon to comprehensively evaluate and develop an appropriate surgical strategy.

Acknowledgements

We would like to express our gratitude to Dr. Rusong Yang from Department of Thoracic surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital

of Nanjing University Medical School for his valuable advice and thorough review of all the statistical analysis.

Author contributions
Xiao Wang and Jingwei Shi were responsible for the conception and design of the study. Data collection was conducted by Xiao Wang. Data analysis was performed by Zhengcheng Liu and Xiao Wang. Xiao Wang drafted the initial manuscript, and all authors contributed to revising it. All authors read and approved the final manuscript.

Funding
Fengyang County Science and Technology Plan Project, 2024SF-01.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
This retrospective study was approved by the Institutional Ethics Committee of Nanjing Drum Tower Hospital. Written informed consent was waived due to the retrospective nature of this study.

Conflict of interest
The authors declare that they have no conflicts of interest.

Received: 5 October 2024 / Accepted: 6 April 2025
Published online: 23 April 2025

References

1. Han B, Zheng R, Zeng H, et al. Cancer incidence and mortality in China, 2022 [J]. J Natl Cancer Cent. 2024;4(1):47–53.
2. Siegel R L, Giaquinto A N Jemala. Cancer statistics, 2024 [J]. CA Cancer J Clin. 2024;74(1):12–49.
3. Hui H, Yin H T, Wang T, et al. Computed tomography-guided core needle biopsy for sub-centimeter pulmonary nodules [J]. Kardiochir Torakochirurgia Pol. 2022;19(2):65–9.
4. Suzuki K, Watanabe S I, Wakabayashi M, et al. A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer [J]. J Thorac Cardiovasc Surg. 2022;163(1):289–e3012.
5. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial [J]. Lancet. 2022;399(10335):1607–17.
6. Altorki N, Wang X. Lobar or sublobar resection for peripheral stage IA Non-Small-Cell lung cancer [J]. N Engl J Med. 2023;388(6):489–98.
7. Kawaguchi T, Yoshikawa D, Nakai T, et al. Outcome of resected lung cancers with subcentimeter solid component on computed tomography [J]. Thorac Cardiovasc Surg. 2023;71(3):214–21.
8. Kadota K, Nitadori J I, Sima C S, 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]. J Thorac Oncol. 2015;10(5):806–14.
9. Dagher S, Sulaiman A, Bayle-bleuez S et al. Spread through air spaces (STAS) is an independent prognostic factor in resected lung squamous cell carcinoma [J]. Cancers (Basel), 2022, 14(9).
10. Aly R G, Rekhtman N, Li X, et al. Spread through air spaces (STAS) is prognostic in atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma of the lung [J]. J Thorac Oncol. 2019;14(9):1583–93.
11. Nurmamat A, Hu Y, Mamatabdulla M, et al. [The effect of tumor spread through air spaces on the prognosis of patients with stage I non-small cell lung cancer: a meta-analysis] [J]. Zhonghua Yi Xue Za Zhi. 2023;103(45):3683–90.
12. Ikeda T, Kadota K, Go T, et al. Segmentectomy provides comparable outcomes to lobectomy for stage IA Non-small cell lung cancer with spread through air spaces [J]. Semin Thorac Cardiovasc Surg. 2023;35(1):156–63.
13. Zhou F, Villalba J A, Sayo T M S, et al. Assessment of the feasibility of frozen sections for the detection of spread through air spaces (STAS) in pulmonary adenocarcinoma [J]. Mod Pathol. 2022;35(2):210–7.
14. Villalba JA, Shih A R, Sayo T M S, et al. Accuracy and reproducibility of intraoperative assessment on tumor spread through air spaces in stage 1 lung adenocarcinomas [J]. J Thorac Oncol. 2021;16(4):619–29.
15. Wang Y, Lyu D. Hu L, CT-Based intratumoral and peritumoral radiomics nomograms for the preoperative prediction of spread through air spaces in clinical stage IA Non-small cell lung cancer [J]. J Imaging Inf Med, 2024.
16. Chen Y, Jiang C, Kang W, et al. Development and validation of a CT-based nomogram to predict spread through air space (STAS) in peripheral stage IA lung adenocarcinoma [J]. Jpn J Radiol. 2022;40(6):586–94.
17. Liao G, Huang L, Wu S, et al. Preoperative CT-based peritumoral and tumoral radiomic features prediction for tumor spread through air spaces in clinical stage I lung adenocarcinoma [J]. Lung Cancer. 2022;163:87–95.
18. Wang J, Yao Y, Tang D, et al. An individualized nomogram for predicting and validating spread through air space (STAS) in surgically resected lung adenocarcinoma: a single center retrospective analysis [J]. J Cardiothorac Surg. 2023;18(1):337.
19. Nicholson A G, Tsao M S, Beasley M B, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015 [J]. J Thorac Oncol. 2022;17(3):362–87.
20. Cao L, Jia M, Sun Pl, et al. Histopathologic features from preoperative biopsies to predict spread through air spaces in early-stage lung adenocarcinoma: a retrospective study [J]. BMC Cancer. 2021;21(1):913.
21. Jia C, Jiang H C, Liu C, et al. The correlation between tumor radiological features and spread through air spaces in peripheral stage IA lung adenocarcinoma: a propensity score-matched analysis [J]. J Cardiothorac Surg. 2024;19(1):19.
22. Khalil Ha, Shi W. Analysis of recurrence in lung adenocarcinoma with spread through air spaces [J]. J Thorac Cardiovasc Surg. 2023;166(5):1317–e284.
23. Tasnim S, Raja S, Mukhopadhyay S, et al. Preoperative predictors of spread through air spaces in lung cancer [J]. J Thorac Cardiovasc Surg. 2024;168(3):660–e94.
24. Ye R, Yu Y, Zhao R, et al. Comprehensive molecular characterizations of stage I-III lung adenocarcinoma with tumor spread through air spaces [J]. Front Genet. 2023;14:1101443.
25. Xu K, Lv Y, Chen T, et al. Evaluation of the novel international association for the study of lung cancer grading system in adenocarcinoma with spread through air space [J]. Transl Lung Cancer Res. 2024;13(8):1862–76.
26. Borgeaud M, Parikh K, Banna GL, et al. Unveiling the landscape of uncommon EGFR mutations in NSCLC-A systematic review [J]. J Thorac Oncol. 2024;19(7):973–83.
27. Soo R A, Reungwetwattana T, Perroud H A, et al. Prevalence of EGFR mutations in patients with resected stages I to III NSCLC: results from the EARLY-EGFR study [J]. J Thorac Oncol. 2024;19(10):1449–59.
28. He S, Chen C, Wang Z, et al. The use of the mean computed-tomography value to predict the invasiveness of ground-glass nodules: A meta-analysis [J]. Asian J Surg. 2023;46(2):677–82.
29. Yamamoto M, Tamura M, Miyazaki R, et al. Mean computed tomography value to predict spread through air spaces in clinical N0 lung adenocarcinoma [J]. J Cardiothorac Surg. 2024;19(1):260.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.