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Low IGSF10 Protein Expression Is Associated with Advanced NSCLC Stage and Histological Heterogeneity

Huaxue Xing[1], Bo Ling[1,2], Yun Zhao[1], Lianyu Cheng[1], Beibei Ma[1]

[1]School of Basic Medical Sciences, Youjiang Medical University for Nationalities, Baise, China
[2]College of Pharmacy, Youjiang Medical University for Nationalities, Baise, China
Email: xinghuaxue0603@163.com

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Abstract

Objective: To investigate the protein expression profile of immunoglobulin superfamily member 10 (IGSF10) in non-small cell lung cancer (NSCLC) tissues and its association with clinicopathological characteristics. **Methods**: Tissue samples were collected from 112 patients with pathologically confirmed NSCLC, including 59 cases of lung adenocarcinoma and 53 cases of lung squamous cell carcinoma. Tissue microarrays were constructed using tumor tissues and paired adjacent non-tumor tissues. IGSF10 protein expression was detected by immunohistochemistry and quantified using the H-score system. Statistical analyses were performed to evaluate the associations between IGSF10 expression and T/N/M stage, clinical stage, and histological subtype. **Results**: IGSF10 expression was significantly higher in adjacent non-tumor tissues than in tumor tissues ($p = 0.004$). In tumor tissues, IGSF10 expression decreased with tumor progression. The H-scores were lower in patients with T2 - T4 disease, M1 disease, and clinical stage II - IV disease than in those with T1 disease, M0 disease, and clinical stage I disease, respectively. Low IGSF10 expression was also associated with advanced N stage. Histological comparison showed that IGSF10 expression was significantly lower in lung squamous cell carcinoma than in lung adenocarcinoma ($p < 0.001$). Multivariable analysis further indicated that histological subtype was consistently associated with low IGSF10 expression, and both clinical stage II - IV disease and lung squamous cell carcinoma were independently associated with reduced IGSF10 expression. **Conclusion**: IGSF10 protein expression is downregulated in NSCLC tumor tissues and is associated with T/N/M stage, clinical stage, and the lung squamous cell carcinoma phenotype. These findings suggest that reduced IGSF10 expression may be involved in NSCLC progression and may serve as a candidate histological marker reflecting tumor advancement.

Keywords

Non-Small Cell Lung Cancer, IGSF10, Tissue Microarray, Clinical Stage, Immunohistochemistry

1. Introduction

Lung cancer is one of the most representative high-burden diseases in modern oncology. GLOBOCAN 2022 estimated approximately 2.48 million new lung cancer cases and 1.817 million deaths worldwide, placing lung cancer among the leading causes of cancer death [1]. Non-small cell lung cancer (NSCLC) accounts for most lung cancers and mainly comprises two common histological subtypes: lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) [2] [3]. Over the past two decades, molecular targets such as EGFR, ALK, ROS1, BRAF, MET, RET, and KRAS, together with PD-1/PD-L1 immune-checkpoint therapy, have substantially changed the clinical management of NSCLC. Molecular testing has become an important component of treatment decision-making for advanced and some early resectable NSCLC [3]-[5]. At the same time, histopathology, TNM stage, and immunohistochemical markers remain the basic framework for risk stratification, treatment selection, and prognostic assessment [3] [4].

NSCLC is not a homogeneous disease. LUAD and LUSC differ markedly in anatomical site, smoking association, molecular driver events, immune microenvironment, treatment strategy, and patterns of recurrence and metastasis [6]. The 2021 WHO classification of lung tumors continues to emphasize morphology-first diagnosis, immunohistochemical support, and molecular testing as a complement, while further incorporating advances in molecular pathology into the classification of lung tumors [6]. The IASLC Lung Cancer Staging Project has also continued to update its global database to inform revisions for the ninth edition of the TNM classification [7]. These developments indicate that a central priority is to understand how morphological type, anatomical stage, molecular alterations, and protein expression together form an interpretable map of tumor progression.

Immunoglobulin superfamily proteins contain immunoglobulin-like domains and participate in cell adhesion, migration, signal transduction, immune recognition, and tissue development. IGSF10 was initially studied in developmental biology and neuroendocrine migration and was later found to be potentially involved in the development and progression of multiple tumors [8]. Recent lung cancer studies suggest that IGSF10 may suppress tumor progression in LUAD. Bioinformatic and *in vitro* studies have found that IGSF10 expression is decreased in lung cancer or LUAD tissues and is associated with prognosis [9] [10]. Ling *et al.* reported that miR-106b-5p can affect LUAD cell growth and progression by regulating IGSF10, suggesting that IGSF10 is part of a non-coding RNA regulatory network [10]. Further experimental work showed that IGSF10 suppresses LUAD metastasis through the Spi-B/Integrin-beta1 signaling pathway [11]. In 2025,

Cheng *et al.* further suggested that high IGSF10 expression inhibits LUAD progression through p53-related ferroptosis and epithelial-mesenchymal transition (EMT) regulation [12]. Another study showed that IGSF10 knockdown promotes proliferation, migration, and invasion of A549 cells, accompanied by upregulation of Snail, Slug, and N-cadherin and downregulation of E-cadherin [13]. Together, these findings support a potential tumor-suppressive role of IGSF10 in lung adenocarcinoma [9]-[13].

Although existing studies have reported several findings on the relationship between IGSF10 and LUAD, much of the evidence comes from public databases, cell models, or a single LUAD subtype [9]-[13]. Direct detection of IGSF10 protein expression in real-world clinicopathological tissues remains relatively limited. In addition, the relationship between IGSF10 and pathological stage in NSCLC has not been systematically presented, especially across the T, N, and M dimensions. Whether IGSF10 differs histologically between LUAD and LUSC also remains unclear.

On this basis, we sought to advance IGSF10 from a single molecular functional clue to a progression-related candidate marker that can be validated in pathological cohorts. Although targeted therapy and immunotherapy have made substantial progress in recent years, most patients are still diagnosed at an advanced stage, and prognosis remains unsatisfactory [1]-[4]. Therefore, identifying new molecular markers associated with tumor initiation and progression is important for improving lung cancer diagnosis and treatment. In this context, the clinicopathological value of IGSF10 warrants renewed evaluation.

2. Materials and Methods

2.1. Study Subjects

A total of 112 pathologically confirmed NSCLC tumor tissues and adjacent normal tissues were collected from the Department of Pathology, Affiliated Hospital of Youjiang Medical University for Nationalities. Staging was based on the eighth edition of the AJCC staging system, and all cases were reviewed by two pathologists.

This study was approved by the Ethics Committee of Youjiang Medical University for Nationalities and its Affiliated Hospital.

2.2. Immunohistochemistry (IHC) Analysis

Immunohistochemical staining was performed according to the manufacturer's instructions (UltraSensitive SP; MXB). IGSF10 staining was performed using an anti-IGSF10 antibody (1:100 dilution, ab197671, Abcam). All tissues were paraffin-embedded, sectioned, and stained by immunohistochemistry. H-score = ∑(pi × i) = (percentage of weak intensity × 1) + (percentage of moderate intensity × 2) + (percentage of strong intensity × 3). where pi represents the proportion of positive signal pixel area or positive cells, and i represents staining intensity. H-scores ranged from 0 to 300, with higher values indicating stronger overall positive stain-

ing intensity.

2.3. Statistical Analysis

Tumor tissues were divided into high- and low-expression groups according to the median score. Continuous H-scores were expressed as medians with interquartile ranges or other appropriate descriptive statistics. Tumor tissues and paired adjacent non-tumor tissues were compared using the paired Wilcoxon signed-rank test. Tumor H-scores between two independent groups were compared using the Wilcoxon rank-sum test. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Univariate models were used to evaluate the relationships between tumor H-score and T stage, N stage, M stage, clinical stage, and histological type. Multivariable logistic models were then constructed to evaluate the independent associations of staging variables and histological type. Results are reported as values and percentages, and $p < 0.05$ was considered statistically significant. The clinicopathological characteristics of the study cohort are shown in Table 1.

3. Results

3.1. Differences in IGSF10 Expression between Tumor and Adjacent Non-Tumor Tissues

Immunohistochemical (IHC) staining was performed to assess IGSF10 protein expression in LUAD and LUSC tissues and their matched adjacent normal tissues. Representative IHC staining images of IGSF10 protein expression in these tissue types are presented in Figure 1. Paired comparison of tumor and adjacent non-tumor tissues showed that IGSF10 H-scores were overall higher in adjacent non-tumor tissues than in tumor tissues in Figure 2(A). Although some individual cases showed higher expression in tumor tissue than in adjacent non-tumor tissue, the overall trend was decreased expression in tumor tissue. This finding indicates that, after controlling for genetic background and some environmental factors within the same patient, IGSF10 protein expression remains significantly reduced in tumor tissue. This decrease is consistent with previous LUAD transcriptomic and functional studies. Prior studies have suggested that IGSF10 is downregulated in LUAD and is associated with tumor progression, migration, and metastatic capacity. Thus, the present study provides histopathological evidence supporting the potential tumor-suppressive relevance of IGSF10 in NSCLC.

Table 1. Correlation between IGSF10 expression and clinicopatho-logical characteristics of patients.

Characteristics	Total (N)	IGSF10 expression Median (IQR)	*p* value
Age	112		0.062
<=60	54 (48.2%)	1.737 (1.075 - 2.425)	
>60	58 (51.8%)	1.011 (0.252 - 2.882)	

Continued

Gender	112		0.164
Male	81 (72.3%)	1.341 (0.320 - 2.313)	
Female	31 (27.7%)	1.763 (0.977 - 4.034)	
T stage	112		**0.015**
T1	41 (36.6%)	1.974 (0.891 - 4.547)	
T2 - T4	71 (63.4%)	1.254 (0.297 - 2.182)	
N stage	112		0.058
N0	81 (72.3%)	1.725 (0.511 - 3.766)	
N1 - N3	31 (27.7%)	1.117 (0.297 - 1.841)	
M stage	112		**0.034**
M0	93 (83.0%)	1.687 (0.511 - 3.310)	
M1	19 (17.0%)	0.977 (0.273 - 1.777)	
Pathologic stage	112		**<0.001**
Stage I	60 (53.6%)	1.990 (0.874 - 4.494)	
Stage II - IV	52 (46.4%)	1.054 (0.253 - 1.928)	
Pathological type	112		**<0.001**
LUAD	59 (52.7%)	1.974 (1.072 - 4.357)	
LUSC	53 (47.3%)	0.833 (0.253 - 1.713)	

3.2. IGSF10 Is Associated with T-Stage Progression

T stage reflects primary tumor size, the extent of local invasion, and involvement of adjacent structures, and is a core dimension of anatomical staging in NSCLC. The results shown in Figure 2(B) indicated that IGSF10 protein expression scores were significantly lower in patients with T2 - T4 disease, which indicates a greater primary tumor burden, than in patients with early T1 disease.

After further stratification into high- and low-expression groups, the proportion of high IGSF10 expression was lower in the T2 - T4 group than in the T1 group. This pattern suggests that low tumor IGSF10 expression is reflected not only by reduced continuous H-scores but also by enrichment of low expression at the categorical level (Table 1).In the univariate continuous H-score model in Table 2, the OR for the T2 - T4 group relative to the T1 group was 0.87 (95% CI, 0.77 - 0.99; $p = 0.032$), indicating an association with lower IGSF10 expression. In the multivariable model including both T and N stage (Figure 5(B)), the association for T2 - T4 showed a borderline trend (OR, 2.06; 95% CI, 0.91 - 4.65; $p = 0.084$). When T stage and M stage were entered into the same model, T2 - T4 remained statistically significant (OR, 2.44; 95% CI, 1.09 - 5.46; $p = 0.030$). These results suggest a stable association between local primary tumor progression and decreased IGSF10 protein expression, although this association may be influenced by other staging dimensions.

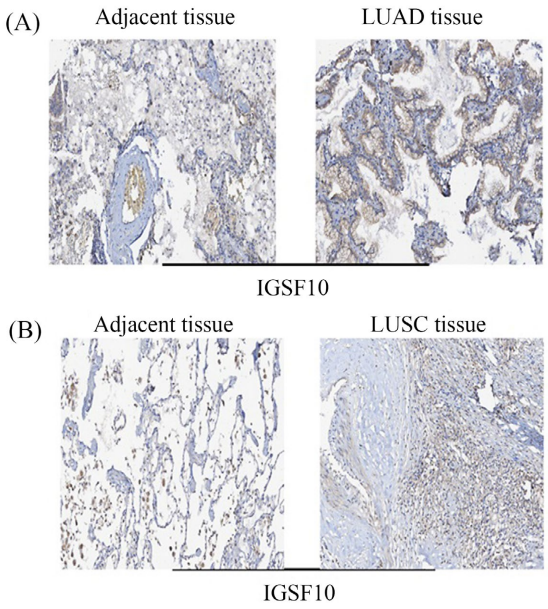

Figure 1. Differential expression of IGSF10 in lung adenocarcinoma and lung squamous cell carcinoma. (A) IHC images of IGSF10 protein in lung adenocarcinoma. (B) IHC images of IGSF10 protein in lung squamous cell carcinoma.

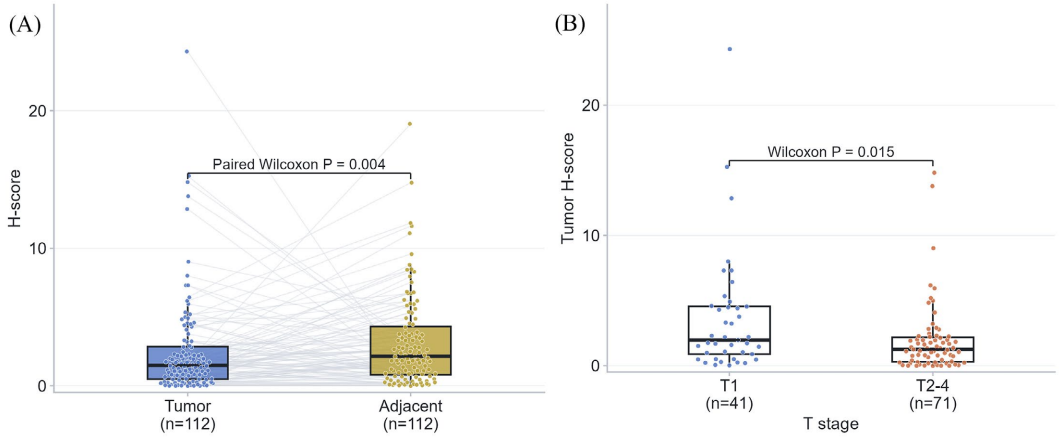

Figure 2. Comparison of immunohistochemical H-scores of IGSF10 in lung cancer tissues stratified by clinicopathological characteristics. (A) Distribution of IGSF10 scores in tumor tissues and corresponding adjacent normal tissues. (B) Relationship between tumor IGSF10 score and T stage.

Table 2. Univariate binary logistic regression analysis of the association between continuous IGSF10 H-score and clinicopathological characteristics in lung cancer.

Variable	B	SE	Wald	OR	95% CI	*p* Value
T stage (T1 = 0, T2 - T4 = 1)	−0.138	0.065	4.603	0.871	(0.767 - 0.988)	0.032
N stage (N0 = 0, N1 - N3 = 1)	−0.241	0.122	3.882	0.786	(0.619 - 0.999)	0.049
M stage (M0 = 0, M1 = 1)	−0.382	0.197	3.746	0.683	(0.464 - 1.005)	0.053
Pathologic stage (I = 0, II - IV = 1)	−0.312	0.110	8.009	0.732	(0.590 - 0.909)	0.005
Pathological Type (LUAD = 0, LUSC = 1)	−0.266	0.1	7.046	0.766	(0.630 - 0.933)	0.008

3.3. IGSF10 Expression Is Associated with Lymph Node Metastasis

Lymph node metastasis is one of the most important factors in NSCLC staging and treatment decision-making. The results of study in **Figure 3(A)** depicted that patients without lymph node metastasis (N0) showed overall higher IGSF10 immunohistochemical scores than patients with lymph node metastasis, and the continuous-variable comparison reached borderline significance ($p = 0.058$).

The univariate model showed that the OR for the lymph node metastasis group relative to the non-metastasis group was 0.79 (95% CI, 0.62 - 1.00; $p = 0.049$), suggesting an association between low IGSF10 expression and lymph node metastasis. In multivariable models, the association for N stage was attenuated after N stage was entered together with T stage, M stage, or histological type, Most results showed borderline trends or did not reach significance (**Figure 5(A)**, **Figure 5(B)**). This finding may indicate that the relationship between N stage and IGSF10 expression is jointly affected by sample size, histological type, and other staging factors.

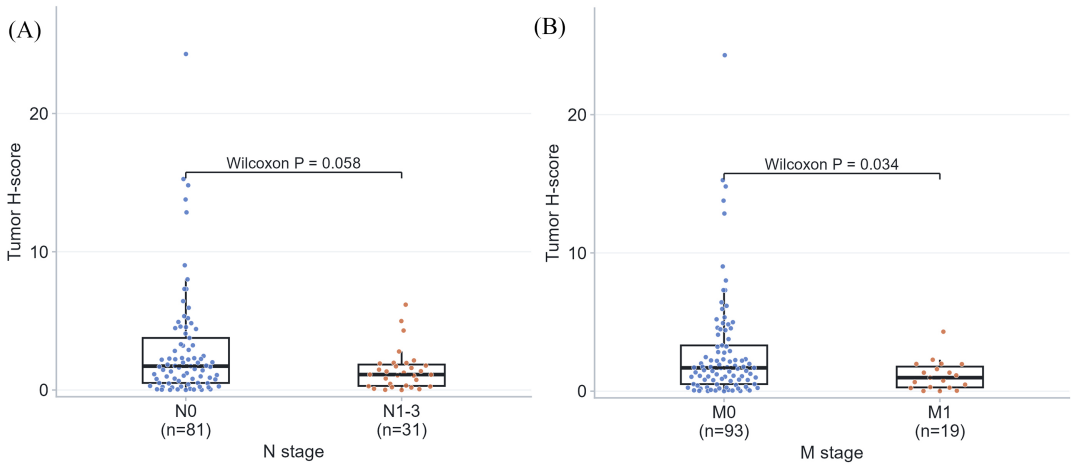

Figure 3. Comparison of immunohistochemical H-scores of IGSF10 in lung cancer tissues stratified by clinicopathological characteristics. (A) Comparison of IGSF10 H-score between N0 and N1 - N3 groups. (B) Comparison of IGSF10 H-score between M0 and M1 groups.

3.4. IGSF10 Is Associated with Distant Metastasis Status

M stage reflects distant metastasis and is a decisive factor for prognosis and treatment pathways in NSCLC. The present analysis showed that tumor IGSF10 immunohistochemical scores were lower in the distant metastasis group than in the non-distant-metastasis group (**Figure 3(B)**), with a statistically significant difference ($p = 0.034$). Although the number of M1 cases was small, the overall score distribution was lower, suggesting an association between reduced IGSF10 protein expression and distant metastasis status. After stratification into high- and low-expression groups, the proportion of high IGSF10 expression was lower in the distant metastasis group than in the non-distant-metastasis group. In the univari-

ate continuous H-score model, the OR for distant metastasis relative to no distant metastasis was 0.68 (95% CI, 0.46 - 1.00; $p = 0.053$), showing a borderline trend. In multivariable models, the comparison of M1 with M0 yielded p values of approximately 0.075 - 0.077 after M stage was entered together with T or N stage (Figure 5(B)).

Distant metastasis is a complex process influenced by vascular invasion, immune escape, tumor clonal evolution, and treatment selection. Whether IGSF10 participates in metastatic initiation, survival in circulation, organ colonization, or only serves as a concomitant marker of metastatic tumor status requires validation through functional experiments and longitudinal cohorts.

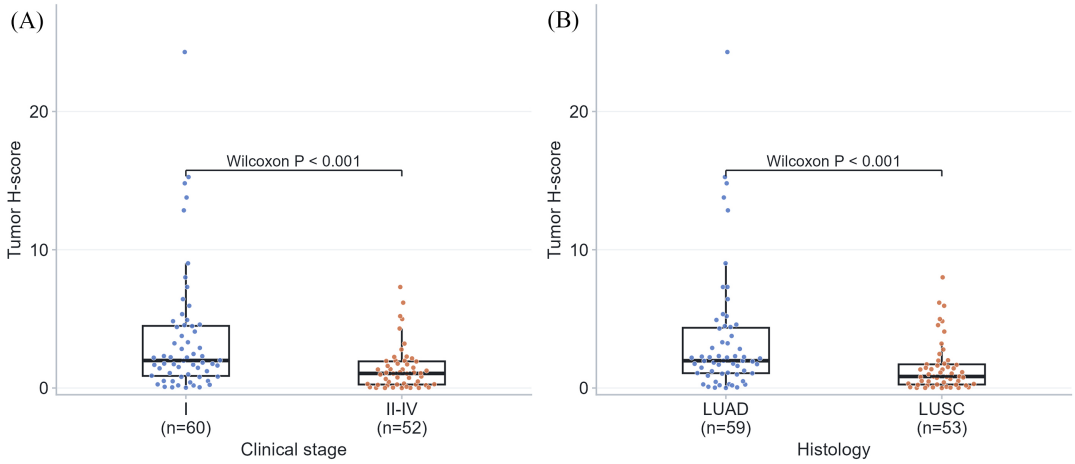

Figure 4. Comparison of immunohistochemical H-scores of IGSF10 in lung cancer tissues stratified by clinicopathological characteristics. (A) Comparison of IGSF10 H-score between clinical stage I and stages II - IV groups. (B) Comparison of IGSF10 H-score between LUAD and LUSC.

3.5. IGSF10 Decreases with Increasing Clinical Stage

Clinical stage integrates T, N, and M information and is a higher-level variable for clinical treatment decision-making and prognostic assessment. In Figure 4(A), Tumor IGSF10 H-scores were significantly lower in the intermediate-to-advanced stage group (stages II, III, and IV) than in the early-stage group (stage I) ($p < 0.001$). High- and low-expression analysis also showed that the proportion of high IGSF10 expression was lower in the intermediate-to-advanced stage group than in the early-stage group. In the univariate continuous H-score model (Figure 5(A)), the OR for intermediate-to-advanced stage relative to early stage was 0.73 (95% CI, 0.59 - 0.91; $p = 0.005$), suggesting an association between clinically advanced disease and lower IGSF10 expression.

In the multivariable model including both clinical stage and histological type, intermediate-to-advanced stage remained significantly associated with low IGSF10 expression (OR, 3.54; 95% CI, 1.55 - 8.09; $p = 0.003$). This result indicates that low IGSF10 expression is not explained solely by differences in the proportions of LUAD and LUSC, and that clinical stage itself may contribute independent information (Figure 5(B)). The decrease in IGSF10 expression in intermediate-to-advanced

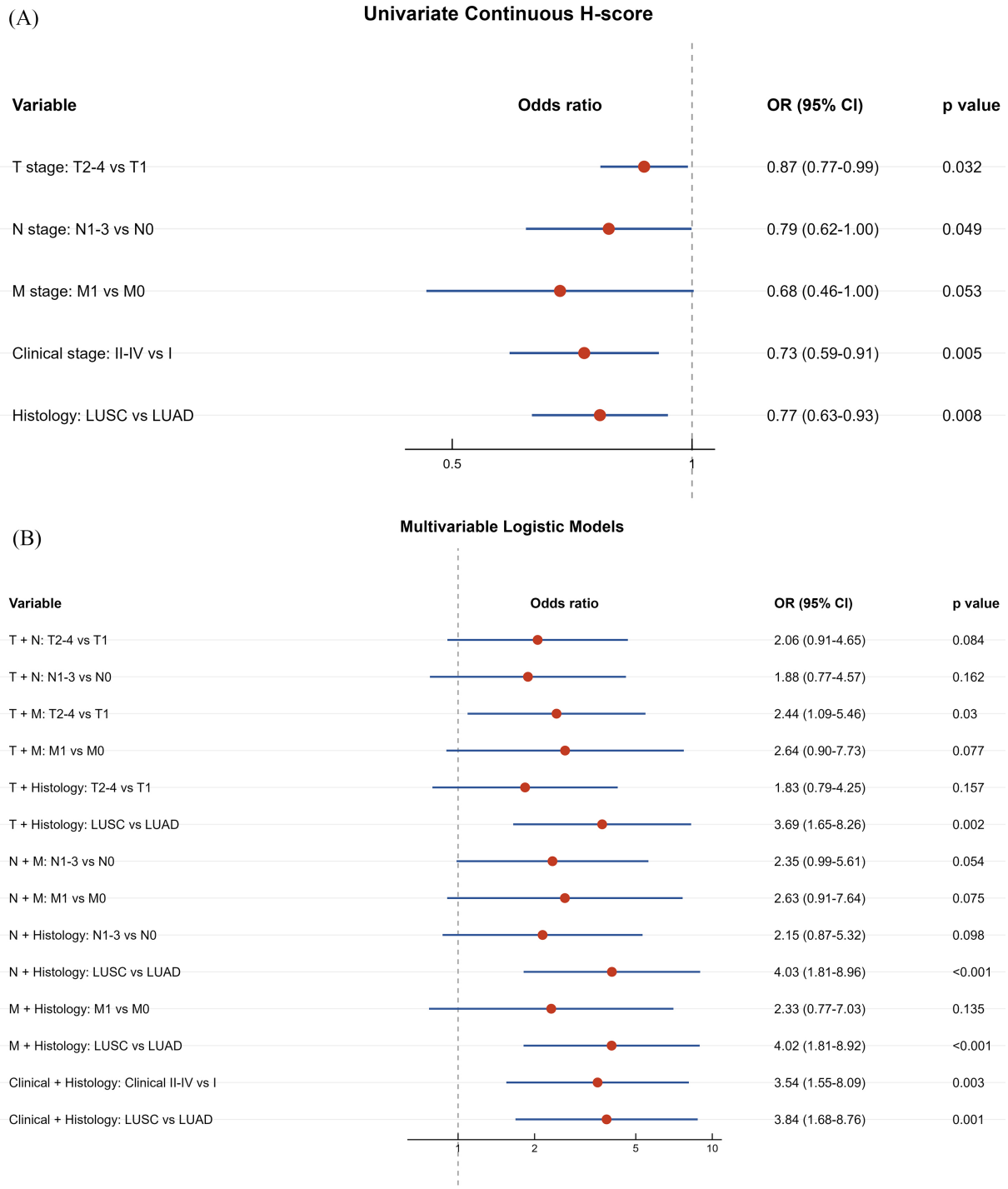

Figure 5. Forest plots of logistic regression analyses showing the association between IGSF10 H-score and clinicopathological characteristics in lung cancer. (A) Univariate binary logistic regression analyses were performed using T stage, N stage, M stage, clinical stage, and histological type as binary dependent variables, with continuous IGSF10 H-score as the independent variable. Variable coding was defined as follows: T1 = 0 and T2 - T4 = 1; N0 = 0 and N1 - N3 = 1; M0 = 0 and M1 = 1; stage I = 0 and stages II - IV = 1; LUAD = 0 and LUSC = 1. (B) Multivariable logistic regression models were constructed using dichotomized IGSF10 expression status as the dependent variable. IGSF10 expression status was defined according to the median H-score of 112 lung cancer tissues. Different combinations of clinicopathological variables were included to evaluate their associations with low IGSF10 expression. $p < 0.05$ was considered statistically significant.

disease suggests that this expression change may be consistent with the overall progression state of NSCLC rather than being limited to a single staging dimension. In other words, loss of IGSF10 protein may not be an incidental local tissue phenomenon. Instead, it may be a molecular pathological feature accompanying the transition from early localized disease to advanced disease.

3.6. IGSF10 Expression Is Significantly Lower in Lung Squamous Cell Carcinoma than in Lung Adenocarcinoma

Comparison by histological type showed that tumor IGSF10 immunohistochemical scores were significantly lower in the LUSC group than in the LUAD group ($p < 0.001$). High- and low-expression analysis also showed that the proportion of high IGSF10 expression was lower in LUSC than in LUAD (**Figure 4(B)**).

In the univariate continuous H-score model (**Figure 5(A)**), the OR for LUSC relative to LUAD was 0.77 (95% CI, 0.63 - 0.93; $p = 0.008$), indicating that LUSC was associated with lower IGSF10 expression. More importantly, multivariable logistic models showed that histological type remained robustly associated across different adjustment models (**Figure 5(B)**). When entered with T stage, the OR for LUSC versus LUAD was 3.69 (95% CI, 1.65 - 8.26; $p = 0.002$). When entered with N stage, the OR was 4.03 (95% CI, 1.81 - 8.96; $p < 0.001$). When entered with M stage, the OR was 4.02 (95% CI, 1.81 - 8.92; $p < 0.001$). When entered with clinical stage, the OR was 3.84 (95% CI, 1.68 - 8.76; $p = 0.001$). Interpreted according to the model event definition, these results support an independent and stable relationship between LUSC and low IGSF10 expression.

3.7. Univariate and Multivariable Models Support an Overall Link between Low IGSF10 Expression and Progression Phenotypes

Univariate analysis using immunohistochemical score as a continuous variable showed that T2 - T4 stage (**Figure 5(A)**), lymph node metastasis, intermediate-to-advanced clinical stage, and LUSC were all associated with lower IGSF10 expression, Distant metastasis also showed a borderline trend. This pattern was broadly consistent with the boxplot results and formed an evidence chain from individual clinicopathological variables to the overall progression phenotype. In particular, T stage, clinical stage, and histological type were statistically significant in both continuous-variable comparisons and model analyses, indicating that these relationships were relatively stable.

Multivariable logistic models further showed that histological type was the most robust associated factor (**Figure 5(B)**). Whether entered into models with T, N, M, or clinical stage, LUSC remained significantly associated with low IGSF10 expression relative to LUAD. When clinical stage and histological type were included together, stages II - IV also retained an independent association. T stage remained significant when modeled with M stage, but its association was attenuated when modeled with N stage or histological type. N stage and M stage mainly showed borderline trends in multivariable models.

4. Discussion

As a member of the immunoglobulin superfamily, IGSF10 has potential roles in cell recognition, migration, and tissue structural regulation. Cell migration is a fundamental event in development and a core basis of tumor invasion and metastasis [14] [15]. In recent years, IGSF10 has been increasingly studied in LUAD. In 2020, Ling *et al.* used bioinformatic analysis and *in vitro* experiments to screen prognostic markers in lung cancer and suggested that IGSF10 may have biological relevance in lung cancer [9]. In 2021, the same group further reported that miR-106b-5p affects LUAD cell growth and progression by regulating IGSF10 [10]. A 2024 study showed that IGSF10 suppresses LUAD metastasis through the Spi-B/Integrin-beta1 pathway [11]. In 2025, Cheng *et al.* reported that high IGSF10 expression triggers ferroptosis through p53 and inhibits EMT, thereby suppressing LUAD progression [12]. Although these studies differ in the specific pathways they emphasize, they collectively point to an association between IGSF10 and reduced LUAD aggressiveness [9]-[12].

The significance of the present study is that it advances these mechanistic clues to the level of clinicopathological tissue. Unlike mRNA expression in public databases, immunohistochemical scores directly reflect protein expression within tissue architecture and are closer to an assay format that can be implemented in pathology departments. In recent years, H-score has remained widely used in immunohistochemical biomarker studies, and digital pathology and algorithmic scoring have also helped improve its reproducibility [15] [16]. We observed that IGSF10 was lower in tumor tissues than in paired adjacent non-tumor tissues and was further decreased in higher T stage, higher clinical stage, distant metastasis, and LUSC. This pattern of decrease during malignant transformation and further decrease during progression gives IGSF10 the basic features of a candidate histological marker. It is not merely a single between-group difference, but a change that shows a consistent direction along clinicopathological risk gradients.

From a cellular functional perspective, reduced IGSF10 may affect cell adhesion, migration restraint, and tissue-structure stability. IGSF10 knockdown in LUAD models promotes migration, invasion, and EMT-related changes [13], and studies on IGSF10-mediated inhibition of metastasis also involve adhesion and migration pathways such as Integrin-beta1/FAK/AKT [11]. These mechanisms are consistent with the decrease in IGSF10 observed in tumor tissues. If IGSF10 participates in maintaining epithelial structure and limiting abnormal migration in normal or adjacent lung tissue, its reduction may allow tumor cells to escape tissue constraints more readily and acquire invasive potential [11]-[13].

TNM staging is the core language of NSCLC clinical management. The T, N, and M dimensions correspond to local tumor burden, regional lymph node spread, and distant metastatic capacity, respectively. Continuous updates of the IASLC staging database also indicate that anatomical staging remains the most stable foundation for lung cancer prognostic stratification [7]. The present study showed an interpretable connection between IGSF10 and this classical anatomical

staging system.

The T-stage results most directly reflect local progression of the primary tumor. Immunohistochemical Scores were lower in the T2 - T4 group than in the T1 group, suggesting that IGSF10 reduction may accompany tumor enlargement and enhanced local invasion. The N-stage results were more complex. The continuous H-score comparison was only borderline significant, but high- and low-expression grouping and the univariate model suggested enrichment of low expression in cases with lymph node metastasis. This may imply a threshold effect between IGSF10 and lymph node metastasis, or it may be influenced by the relatively small sample size. The M-stage results showed lower scores in cases with distant metastasis, but independence was insufficient in multivariable models, indicating that the association with distant metastasis requires validation in larger samples [15] [17].

These findings again highlight the biological complexity of tumor progression. Local invasion, lymph node metastasis, and distant metastasis do not form a linear single-pathway process. Instead, they are jointly shaped by intrinsic tumor-cell states, stromal interactions, vascular and lymphatic routes, immune pressure, and treatment selection [14] [15]. If IGSF10 participates in the regulation of cell migration and adhesion, its reduced expression may have effects at multiple steps [11]-[13]. However, the statistical significance of each step will be influenced by sample size, case composition, and confounding factors. Therefore, low IGSF10 expression may be associated with the progression phenotype of NSCLC.

This study also has limitations. For example, survival data are required to assess the independent prognostic value of IGSF10. Moreover, key covariates, including tumor differentiation, smoking status, and molecular alterations, are crucial for establishing the clinical relevance of this protein.

5. Conclusion

This study shows that IGSF10 protein expression is significantly lower in NSCLC tumor tissues than in paired adjacent non-tumor tissues and that low expression is associated with T/N/M-stage progression, higher clinical stage, and LUSC histology.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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