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# Expression of Kif5b protein is significantly associated with the progression, recurrence and prognosis of oral squamous cell carcinoma

Y.-J. LUAN[1,2], Y. XU[1,2,3], J. CAI[3], Y. DOU[1], W.-J. YU[2,4], K.-T. WANG[1], S.-H. LIU[1], P.-S. YANG[5], X. QU[1,2], F.-C. WEI[1]

[1]Department of Stomatology, Qilu Hospital and Institute of Stomatology, Shandong University, Jinan, China
[2]Institute of Basic Medical Sciences and Key Laboratory of Cardiovascular Proteomics in Shandong Province, Qilu Hospital, Shandong University, Jinan, China
[3]Jinan Stomalogic Hospital, Jinan, China
[4]Department of Oncology, Yantai Affiliated Hospital of Binzhou Medical University, Yantai, China
[5]School of Stomatology, Shandong University, Jinan, China

*Yijun Luan and Yan Xu contributed equally to this work*

**Abstract. – OBJECTIVE: Kinesin family member 5b (Kif5b), a conventional kinesin, mainly participates in lysosome and mitochondria transportation. Some studies have indicated that Kif5b may be associated with the development of a variety of tumors. However, the role Kif5b plays in oral squamous cell carcinoma (OSCC) has yet to be determined. Our study aimed at investigating the expression level of Kif5b in primary OSCC and discussing its clinical significance in patients' outcomes.**

**PATIENTS AND METHODS: We measured Kif5b expression in 82 OSCC tissue samples with immunohistochemistry. The associations between the expression level of Kif5b and clinicopathological characteristics as well as patients' survival were statistically assessed.**

**RESULTS: Kif5b level was significantly associated with tumor size ($p$=0.034), histological differentiation ($p$=0.028), disease recurrence ($p$=0.018), surrounding tissue invasion ($p$=0.045), recurrence time ($p$=0.036) and survival status ($p$=0.030). Kaplan-Meier cumulative survival analyses indicated that high expression of Kif5b was linked to worse overall survival ($p$=0.0112) and disease-free survival ($p$=0.0085). The univariate and multivariate Cox proportional hazard analysis further identified the expression status of Kif5b as an independent variable that correlated with patients' survival and recurrence. Furthermore, in 54 early-stage, clinically node negative OSCC patients, Kif5b expression were correlated with histological differentiation ($p$=0.034), disease recurrence ($p$=0.038) and surrounding tissue invasion ($p$=0.029). Univariate and multivariable logistic regression results showed that only Kif5b expression level could influence the probability of recurrence.**

**CONCLUSIONS: Our results reveal that Kif5b expression is associated with poor clinical outcome in OSCC and even in early-stage, clinically node negative OSCC and may be a potential target for OSCC treatment.**

Key Words
Kinesin family member 5b (Kif5b), Oral squamous cell carcinoma (OSCC), Prognosis, Immunohistochemistry.

## Introduction

Oral cavity cancer is one of the most frequently diagnosed cancers in the world, and oral squamous cell carcinoma (OSCC) is one of the most common tumors of the head and neck[1,2]. Despite recent advances in surgery, radiotherapy and chemotherapy, the 5-year survival rate for patients with OSCC has remained at 50% for the past 30 years[3]. Although Tumor-Node-Metastasis (TMN) classification-based staging is an important prognostic factor in OSCC patients, the prognosis is not satisfactory even in early-stage and high-risk patients who are Stage I/II OSCC[4]. Nowadays, researchers are looking for novel factors that can identify the subpopulation of OSCC patients who are at high risk of tumor relapse, which aid to the improvement in the efficacy of treatment for OSCC, and to provide new insights into a treatment strategy to improve survival[5,6].

Kinesin superfamily proteins (KIFs) are a conserved class of microtubule dependent molecular

*Corresponding Author:* Xun Qu, MD; e-mail: quxun@sdu.edu.cn
Fengcai Wei, MD; e-mail: weifengcai@yahoo.cn

motor proteins. They have adenosine triphosphatase (ATPase) activity and motion characteristics[7]. The active movement of kinesins supports several cellular functions, such as mitosis, meiosis, and the transport of macromolecules[8]. There is indication that the abnormal expression and function of kinesins have many important connections with the development or progression of many kinds of human cancers[9]. Some studies[10-14] have been confirmed that Kif5b, a member of the kinesins, was upregulated in several types of cancer tissues, including cancers of neurofibromatosis, stomach, bladder, skin and breast. In addition, Kif5b was found to play a significant role in growth and survival of HeLa cells by regulating lysosomal leakage[15]. The results revealed that Kif5b protein is closely related with the incidence of tumors and suggested that Kif5b protein might be a promising target in the control of the cancers.

Although Kif5b is related to malignant lesions, it has not been established yet in OSCC. Considering this, our study was conducted to evaluate the immunohistochemical expression and distribution of Kif5b in OSCC and to investigate the relationship between Kif5b level and clinicopathological features as well as patients' prognosis. Thus, the current study aimed to assess the expression of Kif5b in OSCC, and to investigate the possible correlation of Kif5b expression with tumor evaluation, including prognosis.

## Patients and Methods

### Patients and Tissue Specimens

This study was conducted in Qilu Hospital, Shandong University from 2006 to 2015 and was approved by the local Ethics Committee. A total of 82 patients with OSCC were treated surgically and all surgical margins were clear from tumor cells. None of the patients had received any form of tumor-specific therapy before the total surgical excision of the lesion. After surgery, tumor samples were paraffin-embedded and stored at room temperature. The diagnosis was all performed by senior specialists of Pathology and patients' clinical pathological characteristics were obtained from the Department of Pathology in Qilu Hospital. The follow-up period was defined from the date of diagnosis until the last visit to the hospital, or the date of death. Two researchers previously calibrated performed this process. Essential information of patients was collected, including age, sex, smoking and alcohol consumption, tumor size, lymph node metastasis, histological differentiation, clinical stage, disease recurrence, surrounding tissue invasion, survival status and 5-year survival rate.

### Immunohistochemistry

Immunohistochemical staining for Kif5b was performed on 4 μm-thick sections from formalin-fixed paraffin-embedded clinical samples. These tissue slides were heated to 60°C for 1 h, dewaxed in xylene and rehydrated through graded series of ethanol. Antigen retrieval was performed with 0.01 M citrate buffer at pH 6.0 at 95°C. Then, the tissue slides were blocked using 3% hydrogen peroxide.

Immunohistochemical staining was performed on the OSCC slides using primary antibody against Kif5b (ab167429, Abcam, Cambridge, MA, USA; 1:200 dilution) in a moist chamber at 4°C overnight. After primary antibody incubation, the slides were washed three times in phosphate-buffered saline (PBS). The sections were incubated with horseradish peroxidase (HRP)-conjugated secondary antibody (Zhongshan Golden BridgeBiotech, Beijing, China) for 30 min at 37°C. Following this incubation, the slides were washed three times in PBS. Finally, diaminobenzidine (DAB) was used to visualize the signal development. Slides were counterstained with Harris hematoxylin, dehydrated and mounted. Omission of primary antibodies served as a negative control. A human endometrial cancer sample was used as positive control.

### Evaluation of Immunoreactivity

Expression levels for Kif5b were scored based on staining intensity and distribution using the immunoreactive score[16]: immunoreactive score=intensity score × proportion score. The intensity score was defined as (0) negative; (1) weak; (2) moderate; or (3) strong, and the proportion score was defined as (0) negative; (1) <10%; (2) 11- 50%; (3) 51-80%; or (4) >80% positive cells. The immunoreactivity was divided into three groups on the basis of the final score: negative immunoreactivity was defined as a total score of 0, low immunoreactivity was defined as a total score of 1-4, and high immunoreactivity was defined as a total score >4[16,17]. The slides were scored blindly with respect to clinical patient data.

### Statistical Analysis

All statistical analyses were performed using IBM SPSS (Statistical Product and Service Solutions) statistical software, version 20.0 (IBM, Armonk, NY, USA) and the Graphpad Prism 5 (La Jolla, CA, USA). The $x^2$-test was used to analyze the correlation between Kif5b

expression and clinicopathological parameters. The overall survival rates were estimated using Kaplan-Meier method and compared with Log-rank test. The univariate and multivariate Cox regression analysis were applied to assess the impact of various clinicopathological parameters on overall survival and recurrence of OSCC patients. Univariate logistic regressions were used to evaluate the predictive effect of each factor for T1-2N0M0 OSCC recurrence. Furthermore, some factors in univariate logistic regression were included in the multivariable logistic regression model. *p*-values less than 0.05 were considered statistically significant.

## Results

### *The Kif5b Expression Correlated with Clinicopathological Parameters in OSCC Patients*

A total of 82 cases of OSCC were analyzed, 43 negative/low expression of Kif5b (51%) and 39 high expression (49%). Immunohistochemical analyses revealed that Kif5b was observed mainly in the cytoplasm and it could be found in both non-tumor squamous cells and carcinoma cells (Figure 1A-1F). Low expression of Kif5b could be observed in well-differentiated OSCC samples (Figure 1G, 1H) and high expression of

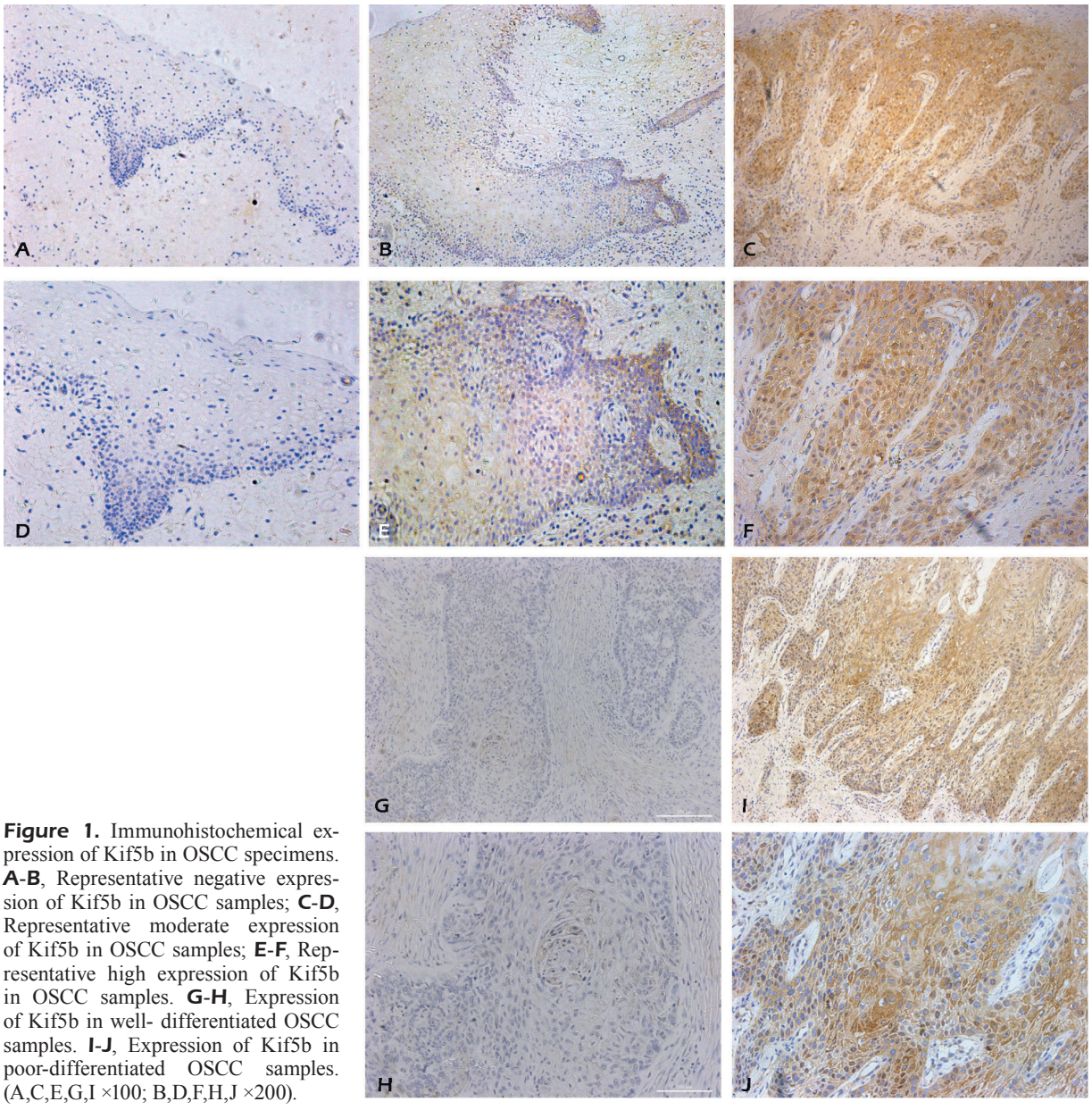


**Figure 1.** Immunohistochemical expression of Kif5b in OSCC specimens. **A-B**, Representative negative expression of Kif5b in OSCC samples; **C-D**, Representative moderate expression of Kif5b in OSCC samples; **E-F**, Representative high expression of Kif5b in OSCC samples. **G-H**, Expression of Kif5b in well- differentiated OSCC samples. **I-J**, Expression of Kif5b in poor-differentiated OSCC samples. (A,C,E,G,I ×100; B,D,F,H,J ×200).

Kif5b was showed in poor-differentiated samples (Figure 1I, 1J).

The main clinicopathological data of the patients analyzed in this study are listed in Table I. To explore the clinicopathological significance of Kif5b expression in patients with OSCC, we analyzed the associations between Kif5b expression status and multiple clinicopathological parameters (Table I). Notably, high-level expression of Kif5b was significantly correlated with larger tumor size ($p$=0.034), worse histological differentiation ($p$=0.028), more disease recurrence ($p$=0.018) and surrounding tissue invasion ($p$=0.045), earlier recurrence time ($p$=0.036) and

**Table I.** Correlation between KIF5b expression and clinicopathological parameters in OSCCs.

| Kif5b | No. patients | Clinicopathological parameters cases | | *p*-value |
|---|---|---|---|---|
| | | Negative/Low | High | |
| ***Age at surgery (years)*** | | | | |
| <60 | 42 | 26 | 16 | |
| ≥60 | 40 | 17 | 23 | 0.079 |
| ***Gende*** | | | | |
| Male | 51 | 26 | 25 | |
| Female | 31 | 17 | 14 | 0.734 |
| ***Smoking*** | | | | |
| Yes | 39 | 20 | 19 | |
| No | 43 | 23 | 20 | 0.842 |
| ***Drinking*** | | | | |
| Yes | 31 | 18 | 13 | |
| No | 51 | 25 | 26 | 0.426 |
| ***Both Smoking and Drinking*** | | | | |
| Yes | 29 | 16 | 13 | |
| No | 53 | 27 | 26 | 0.714 |
| ***Tumor size*** | | | | |
| T1+T2 | 71 | 41 | 30 | |
| T3+T4 | 11 | 2 | 9 | 0.034 |
| ***Lymph node metastasis*** | | | | |
| N0 | 61 | 35 | 26 | |
| N+ | 21 | 8 | 13 | 0.127 |
| ***Histological differentiation*** | | | | |
| Well | 42 | 27 | 15 | |
| Moderate/Poor | 40 | 16 | 24 | 0.028 |
| ***Clinical stage*** | | | | |
| I+II | 54 | 32 | 22 | |
| III+IV | 28 | 11 | 17 | 0.086 |
| ***Disease recurrence*** | | | | |
| Yes | 18 | 5 | 13 | |
| No | 64 | 38 | 26 | 0.018 |
| ***Surrounding issue invasion*** | | | | |
| Yes | 13 | 3 | 10 | |
| No | 69 | 40 | 29 | 0.045 |
| ***Recurrence time*** | | | | |
| ≤24moth | 8 | 0 | 8 | |
| >24moth | 10 | 5 | 5 | 0.036 |
| ***Survival status*** | | | | |
| Yes | 66 | 39 | 27 | |
| No | 16 | 4 | 12 | 0.030 |
| ***Five-year survival*** | | | | |
| Yes | 19 | 12 | 7 | |
| No | 63 | 31 | 32 | 0.286 |

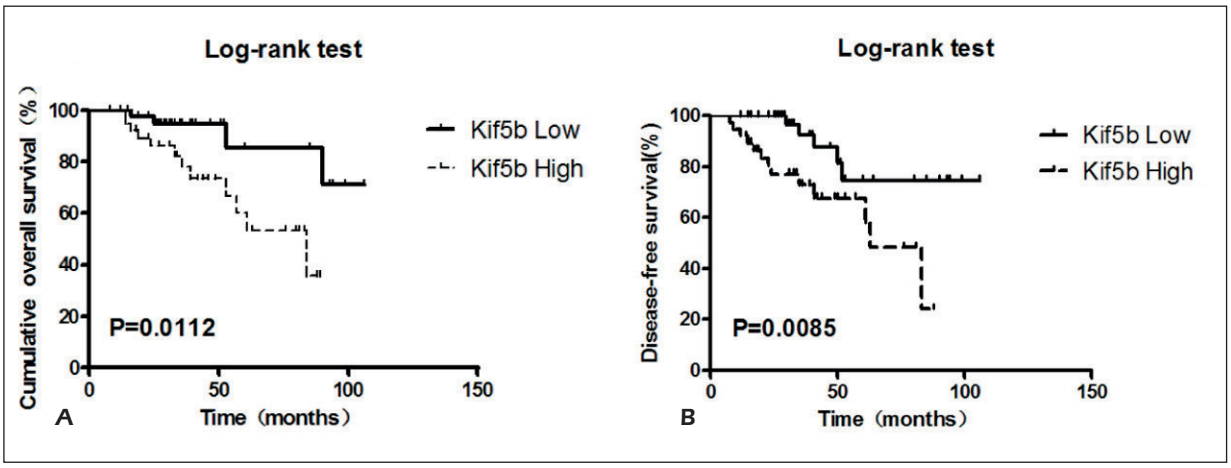


**Figure 2.** The expression of Kif5b associated with prognosis of 82 OSCC patients. Kaplan-Meier survival analysis of overall survival (**A**) and disease-free survival (**B**) in patients with OSCC was generated according to Kif5b protein expression. The log-rank test was applied to calculate *p*-value.

worse survival status ($p$=0.030). There was no correlation between Kif5b expression and age ($p$=0.079), gender ($p$=0.734), smoking ($p$=0.842), drinking ($p$=0.426), lymph node metastasis ($p$=0.127), clinical stage ($p$=0.086), or five-year survival ($p$=0.286).

### *The Expression of Kif5b is an Independent Variable Factor of Overall Survival Time in OSCC Patients*

To reveal potential prognostic value of Kif5b level in 82 OSCC patients, we tried to identify possible association between its level and patients' survival. Until the last follow-up, 58 of 82 (70.7%) patients remained alive without local recurrence and lymph node or distant metastasis, 8 (9.8%) still alive but with local recurrences and/or lymph node metastases, whereas 16 (19.5%) died due to post-surgical relapse, metastasis or other diseases. As showed in Figure 2, Kaplan-Meier survival analysis and log-rank test implied that patients with high expression of Kif5b seemed to suffer lower possibility of overall survival ($p$=0.0112) and lower possibility of disease-free survival ($p$=0.0085). The inter-relationship between possible prognostic factors with overall survival was further analyzed by univariate Cox regression analysis. As shown in Table II, lymph node metastasis ($p$=0.043), histological differentiation (Well/ Moderate, Poor) ($p$=0.024), clinical stage (I,II/III,IV) ($p$=0.000), disease recurrence ($p$=0.000) and Kif5b expression status (hazard ratio (HR), 5.793; 95% confidence interval (95% CI), 1.588-21.134; $p$=0.008) significantly affected the overall survival of the OSCC patients. Moreover, multivariate survival analyses revealed that

**Table II.** Univariate Cox proportional hazard analysis of prognostic factors for survival of 82 patients with OSCC.

| Variable | Hazard ratio | 95% CI | *p*-value |
|---|---|---|---|
| Gender (male vs. female) | 1.476 | 0.512-4.257 | 0.471 |
| Age (<60, ≥60) | 1.918 | 0.696-5.282 | 0.208 |
| Smoking (yes/no) | 1.511 | 0.548-4.169 | 0.425 |
| Drinking (yes/no) | 0.959 | 0.347-2.649 | 0.936 |
| Tumor size (T3 + T4 vs. T1+T2) | 3.322 | 0.700-15.756 | 0.131 |
| Lymph node metastasis(N+ vs. N0) | 2.874 | 1.032-8.007 | 0.043 |
| Histological differentiation (Well/Moderate, Poor) | 3.553 | 1.284-10.663 | 0.024 |
| Clinical stage(I,II/III,IV) | 11.123 | 3.057-40.475 | 0.000 |
| Disease recurrence(Yes/No) | 7.115 | 2.421-20.909 | 0.000 |
| Surrounding tissue invasion (Yes/No) | 1.767 | 0.496-5.292 | 0.379 |
| Kif5B status (Negative vs. Positive) | 5.793 | 1.588-21.134 | 0.008 |

CI, confidence interval.

**Table III.** Multivariate Cox proportional hazard analysis of prognostic factors for survival of 82 patients with OSCC.

| Variable | Hazard ratio | 95% CI | *p*-value |
|---|---|---|---|
| Histological differentiation (Well/Moderate, Poor) | 2.601 | 1.124-6.020 | 0.026 |
| Clinical stage (I,II/III,IV) | 2.468 | 1.365-4.463 | 0.003 |
| Disease recurrence (Yes/No) | 5.304 | 1.582-18.013 | 0.007 |
| Kif5B status (Negative vs. Positive) | 7.506 | 1.675-33.639 | 0.008 |

CI, confidence interval.

**Table IV.** Univariate Cox proportional hazard analysis of prognostic factors for disease recurrence of 82 patients with OSCC.

| Variable | Hazard ratio | 95% CI | *p*-value |
|---|---|---|---|
| Gender (male vs. female) | 1.826 | 0.650-5.131 | 0.253 |
| Age (<60, ≥60) | 1.462 | 0.575-3.715 | 0.425 |
| Smoking (yes/no) | 1.314 | 0.509-3.395 | 0.573 |
| Drinking (yes/no) | 0.811 | 0.303-2.173 | 0.677 |
| Tumor size (T3 + T4 vs. T1+T2) | 1.151 | 0.145-9.145 | 0.894 |
| lymph node metastasis (N+ vs. N0) | 2.415 | 0.879-6.638 | 0.087 |
| Histological differentiation (Well/Moderate, Poor) | 1.028 | 0.403-2.620 | 0.954 |
| Clinical stage (I,II/III,IV) | 3.563 | 1.243-10.211 | 0.018 |
| Surrounding tissue invasion (Yes/No) | 1.535 | 0.440-5.357 | 0.502 |
| Kif5B status (Negative vs. Positive) | 3.619 | 1.280-10.229 | 0.015 |

CI, confidence interval.

histological differentiation (Well/Moderate, Poor) ($p$=0.026), clinical stage (I,II/III,IV) ($p$=0.003), disease recurrence ($p$=0.007) and Kif5b expression status (HR,7.506; 95% CI, 1.675-33.639; $p$=0.008) were independent prognostic factors for OSCC patients' overall survival (Table III).

### The Expression of Kif5b is an Independent Prognostic Factor of Disease Recurrence in OSCC Patients

Univariate Cox regression analysis is shown in Table IV. Kif5b expression status (HR, 3.619; 95% CI, 1.280-10.229; $p$=0.015) and clinical stage (I,II/III,IV) ($p$=0.018), significantly affected the disease recurrence of the OSCC patients. Moreover, multivariate Cox regression analyses revealed that Kif5b expression status (HR, 3.913; 95% CI, 1.355-11.297; $p$=0.012) and clinical stage (I,II/III,IV) were significantly independent prognostic factors for OSCC patients' recurrence (Table V). Together, these data reveal that Kif5b expression can serve as an important prognostic factor for OSCC.

### The Expression of Kif5b is Significantly Associated with Disease Recurrence in T1-2N0M0 OSCC Patients

In order to reveal Kif5b relations with early stage, clinically node negative OSCC, we tried to analyzed possible association between its level and clinicopathological parameters of 54 T1-2N0M0 OSCC patients. Kif5b expression was significantly correlated with histological differentiation (Well/Moderate, Poor) ($p$=0.034), disease recurrence ($p$=0.038) and surrounding tissue invasion ($p$=0.029) in T1-2N0M0 OSCC patients (Table VI). The potential factors influencing the probability of recurrence were included in uni-

**Table V.** Multivariate Cox proportional hazard analysis of prognostic factors for disease recurrence of 82 patients with OSCC.

| Variable | Hazard ratio | 95% CI | *p*-value |
|---|---|---|---|
| Clinical stage (I,II/III,IV) | 4.314 | 1.314-14.160 | 0.016 |
| Kif5B status (Negative vs. Positive) | 3.913 | 1.355-11.297 | 0.012 |

CI, confidence interval.

**Table VI.** Correlation between KIF5b expression and Clinicopathological parameters in 54 T1-2N0M0 OSCC.

| Kif5b | No. patients | Clinicopathological parameters cases | | *p*-value |
|---|---|---|---|---|
| | | Negative/Low | High | |
| ***Age at surgery (years)*** | | | | |
| <60 | 27 | 15 | 12 | |
| ≥60 | 27 | 16 | 11 | 0.783 |
| ***Gender*** | | | | |
| Male | 31 | 18 | 13 | |
| Female | 23 | 14 | 9 | 0.836 |
| ***Smoking*** | | | | |
| Yes | 23 | 14 | 9 | |
| No | 31 | 18 | 13 | 0.836 |
| ***Drinking*** | | | | |
| Yes | 18 | 13 | 5 | |
| No | 36 | 19 | 17 | 0.170 |
| ***Histological differentiation*** | | | | |
| Well | 29 | 21 | 8 | |
| Moderate/Poor | 25 | 11 | 14 | 0.034 |
| ***Disease recurrence*** | | | | |
| Yes | 43 | 29 | 14 | |
| No | 11 | 3 | 8 | 0.038 |
| ***Surrounding issue invasion*** | | | | |
| Yes | 7 | 1 | 6 | |
| No | 37 | 31 | 16 | 0.029 |
| ***Five-year survival*** | | | | |
| Yes | 17 | 10 | 7 | |
| No | 37 | 22 | 15 | 0.965 |

variate logistic regression analysis (Table VII). Two factors from the univariate logistic regression, including surrounding tissue invasion and Kif5b expression status, were analyzed in the multivariable step-wise logistic regression model. The result showed that only Kif5b expression level (odds ratio (OR), 4.617; 95% CI, 1.069-21.708; $p$=0.041) could significantly influence the probability of recurrence in 54 T1-2N0M0 OSCC patients (Table VIII).

## Discussion

Kif5b is a N-kinesin (Plus-end motor) belonging to the superfamily of kinesin-1 molecular motor proteins. Together with cytoplasmic dynein, Kif5b is responsible for microtubule-dependent transport of cargo in eukaryotic cells[18]. A few studies[11-15] have found that Kif5b has an important connection with the occurrence and development of many tumors. In this research, we assessed

**Table VII.** Univariate logistic regression analysis of influencing factors for recurrence in T1-2N0M0 patients with OSCC.

| Variable | OR | 95% CI | *p*-value |
|---|---|---|---|
| Gender (male vs. female) | 1.385 | 0.353-5.441 | 0.640 |
| Age (<60, ≥60) | 0.795 | 0.211-3.004 | 0.736 |
| Smoking (yes/no) | 1.157 | 0.305-4.387 | 0.830 |
| Drinking (yes/no) | 0.375 | 0.072-1.957 | 0.245 |
| Histological differentiation (Well/Moderate, Poor) | 1.516 | 0.401-5.735 | 0.540 |
| Surrounding tissue invasion (Yes/No) | 3.656 | 0.682-19.601 | 0.130 |
| Kif5B status (Negative vs. Positive) | 5.524 | 1.267-24.078 | 0.023 |

OR, odds ratio

**Table VIII.** Multivariate logistic regression analysis of influencing factors of recurrence in T1-2N0M0 patients with OSCC.

| Variable | OR | 95% CI | *p*-value |
|---|---|---|---|
| Surrounding tissue invasion (Yes/No) | 2.394 | 0.400-14.321 | 0.339 |
| Kif5B status (Negative vs. Positive) | 4.617 | 1.069-21.708 | 0.041 |

OR, odds ratio

Kif5b protein expression in 82 OSCC patients using immunohistochemistry to reveal relationship of Kif5b expression with clinicopathological parameters and prognosis in OSCC. The results showed that the high expression of Kif5b was significantly associated with tumor size, histological differentiation, disease recurrence, surrounding tissue invasion, earlier recurrence and survival status. Recurrence is one of the main causes of treatment failure of OSCC, and contributes significantly to the relatively low survival rates of this cancer. Our study showed that the elevated Kif5b expression had a significant association with the probability of recurrence in OSCC. Furthermore, survival analysis showed that increased Kif5b expression was significantly associated with lower survival time. Kif5b expression status was identified as an independent factor affecting patients' survival and recurrence. These findings suggest that Kif5b expression may have both diagnostic and prognostic values for OSCC.

All tumors were staged according to the TNM classification of the AJCC eighth edition[19], and the degree of differentiation was determined according to the grade classification of the World Health Organization[20]. However, 14% to 45% of patients with OSCC show occult neck metastases and progress to a fatal outcome despite being classified as low-risk by the TNM classification[21]. In patients with early-stage, clinically node negative OSCC, there are survival and recurrence differences[22].

To explore the clinicopathological significance of Kif5b expression in patients with early-stage, clinically node negative OSCC, we analyzed the clinicopathological parameters of 54 T1-2N0M0 patients with OSCC. This study found that high Kif5b expression may be linked to high probability of recurrence rate and more surrounding tissue invasion in 54 T1-2N0M0 patients with OSCC. Patients with a high Kif5b expression showed poorer prognosis on univariate analysis and multivariate analysis also demonstrated that Kif5b status was an independent prognostic factor. Taken together, Kif5b may help identify individuals with a poor prognosis in patients with T1-2N0M0.

## Conclusions

We found that an increased Kif5b expression was significantly associated with poor clinical outcome in OSCC and even in early-stage, clinically node negative OSCC. Therefore, it might be represent a candidate prediction of prognosis, and a potentially target for OSCC treatment.

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### Conflict of interest

The authors declared no conflict of interest.

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