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# Prognostic role of Rab27A and Rab27B expression in patients with non-small cell lung carcinoma

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**Keywords**
Carcinoma; non-small cell; prognosis; Rab27A; Rab27B.

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## Abstract

**Background:** Rab27A and Rab27B are the major components of vesicle fusion and trafficking in exosome secretion and play important roles in tumor progression and metastasis. In addition, Rab27A and Rab27B are associated with tumor prognosis. This study investigated the prognostic roles of Rab27A and Rab27B expression in patients with non-small cell lung cancer (NSCLC).

**Methods:** Rab27A and Rab27B expression was assessed in 133 cases of NSCLC by immunohistochemistry. We evaluated the correlations between Rab27A and Rab27B expression and clinicopathological data and determined their prognostic role in NSCLC.

**Results:** Rab27A and Rab27B expression were significantly related to patient gender ($P = 0.007$ and 0.002, respectively) and histologic type ($P = 0.009$ and $< 0.001$, respectively), but not to patient age, smoking history, surgical method, or tumor node metastasis stage. The multivariate Cox proportional hazards regression model verified that high Rab27B expression is a prognostic factor for unfavorable disease-specific survival (hazard ratio 2.680, 95% confidence interval 1.116–6.437; $P = 0.027$) in squamous cell carcinoma (SQCC). Kaplan–Meier analysis revealed significantly poorer prognosis in SQCC patients with high Rab27B expression compared to patients with low Rab27B expression ($P = 0.030$).

**Conclusion:** High Rab27B expression could be an unfavorable prognostic factor in patients with SQCC of the lung.

## Introduction

Lung cancer is one of the most common causes of cancer-related death.[1] The majority of lung cancers are non-small cell lung cancer (NSCLC).[2] A large number of patients with NSCLC experience recurrence and unfavorable prognosis, even after surgery and chemotherapy.[3,4] Therefore, the identification of factors associated with relapse has become an important issue for early treatment and improved patient survival.[4]

Rab proteins belong to the Ras family of small GTPases and play a role in the activation of the GTP-binding enzymatic cycle, anchor to the vesicular membrane, and interact with effectors in the posttranscriptional process.[5,6] Rab27A and Rab27B are Rab proteins that are expressed in many types of secretory epithelial cells, although Rab27B is much more restricted than Rab27A.[7] More importantly, Rab27A and Rab27B are the major regulators of vesicle fusion and trafficking in the exosome secretion process.[8,9] Studies have shown that exosome secretion plays an important role in tumor progression and metastasis by modulating the tumor microenvironment.[9–11] Li *et al.* reported that Rab27A controls exosome secretion in lung adenocarcinoma (ADC) cells.[12] Furthermore, some reports have demonstrated that Rab27A and Rab27B are associated with tumor progression and have been used as a prognostic factor in hepatocellular carcinoma; glioma; and pancreatic, ovarian, and colorectal cancers.[6,7,9,13,14]

  

To our knowledge, no study has investigated the prognostic roles of Rab27A and Rab27B in NSCLC. Therefore, this study evaluated Rab27A and Rab27B expression, their correlation with clinicopathological data, and their prognostic significance in NSCLC.

## Methods

### Patients and clinicopathological data

We enrolled 133 consecutive patients who underwent surgical resection for NSCLC between January 2002 and December 2009 at Gyeongsang National University Hospital (Jinju, Korea). The tumors were staged according to the eighth edition of the American Joint Committee on Cancer Tumor Node Metastasis (TNM) Classification of Malignant Tumors. The tumor histological type and differentiation grade were established according to the fourth edition of the World Health Organization classification system. Clinical and survival data were obtained from electronic medical and National Statistical Office (Seoul, South Korea) records. Disease-free survival (DFS) was defined as the period from the date of surgery to the date of cancer recurrence, while disease-specific survival (DSS) was defined as the period from the date of surgery to the date of death, which was mostly a result of NSCLC.[15] Smoking history was defined as either non-smoker (< 100 lifetime cigarettes) or smoker (including current and ex-smokers). This study was approved by the Institutional Review Board of Gyeongsang National University Hospital and informed consent was waived (2018-07-029-001).

### Tissue microarray construction and immunohistochemistry

Hematoxylin and eosin-stained slides were examined, and a core (3 mm in diameter) of the most representative tumor focus was made from each formalin-fixed paraffin block based on major differentiation in the invasive area. Immunohistochemical staining was conducted using an automated immunostainer (Benchmark Ultra, Ventana Medical Systems Inc., Tucson, AZ, USA) with a monoclonal anti-RAB27A antibody at a dilution of 1:50 (ab55667, Abcam, Cambridge, UK) and polyclonal anti-RAB27B antibody at a dilution of 1:250 (PA5-54096, Thermo Fisher Scientific, Waltham, MA, USA). The positive controls for RAB27A and RAB27B were prostatic glandular epithelial cells and urothelial cells, respectively. The primary antibody was omitted for the negative control.

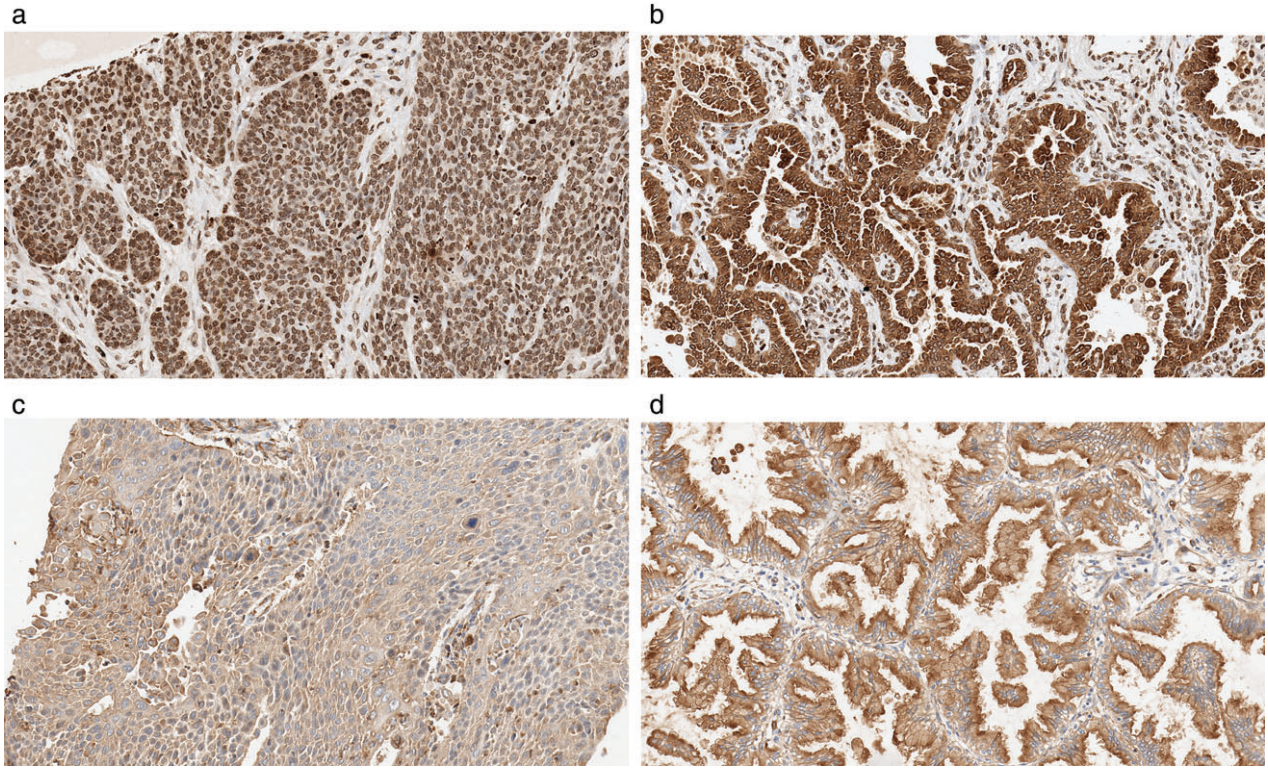


**Figure 1** Rab27A and Rab27B expression in non-small cell lung cancer. High expression of (**a**,**b**) Rab27A and (**c**,**d**) Rab27B in squamous cell carcinoma and adenocarcinoma, respectively (original magnification: 200×).

 

### Rab27A and Rab27B expression

Immunohistochemical staining of the tumor cells was evaluated in both the nucleus and cytoplasm for Rab27A and in the cytoplasm and membrane for Rab27B (Fig 1). The intensity of the stained tumor cells was graded as either high or low expression. High expression was classified as > 30% of tumor cells stained and with stronger staining than tumor-infiltrating immune cells, while the others were classified as low expression. If the tumor cells showed heterogeneous expression in the same core, the representative value was determined according to the majority of tumor cells. To confirm reproducibility, all samples were individually reviewed by two pathologists.

### Statistical analysis

Correlations between Rab27A and Rab27B expression and clinicopathological data were evaluated by Pearson's chi-square test. DFS and DSS were analyzed using the Kaplan–Meier method with log-rank tests between groups. The prognostic significance of clinicopathological data for DFS and DSS was investigated using a Cox proportional hazard regression model. $P$ values < 0.05 were considered statistically significant. The analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

## Results

### Clinicopathological patient data

The clinicopathological data of the patients are summarized in Table 1. The median age was 66 years (range: 31–77 years). The histologic types of the tumors included: 96 (72.2%) squamous cell carcinoma (SQCC) cases, primarily moderately differentiated (59, 61.4%); and 37 (27.8%) ADC cases, with an acinar pattern the most prevalent (15, 40.5%). Among the enrolled patients, 116 (87.2%) underwent lobectomy, including all ADC cases and the remaining 17 (12.8%) underwent bilobectomy, sleeve lobectomy, or pneumonectomy. Regarding the TNM stage, 57 tumors (42.8%) were stage I, 54 (40.6%) were stage II, 19 (14.3%) were stage III, and three (2.3%) were stage IV.

**Table 1** Clinicopathological patient data

| Data | Number (%) ($n$ = 133) |
|---|---|
| Median age (years) | 66 |
| Male gender | 111 (83.5) |
| Smoking history† | 86 (64.7) |
| Surgical procedure | |
| Lobectomy | 116 (87.2) |
| Bilobectomy or sleeve lobectomy | 3 (2.3) |
| Pneumonectomy | 14 (10.5) |
| Histologic type | |
| Squamous cell carcinoma | 96 (72.2) |
| Well-differentiated | 15 |
| Moderately-differentiated | 59 |
| Poorly-differentiated | 22 |
| Adenocarcinoma | 37 (27.8) |
| Acinar | 15 |
| Solid | 6 |
| Papillary | 8 |
| Micropapillary | 3 |
| Lepidic | 3 |
| Mucinous | 2 |
| Tumor stage | |
| T1 | 45 (33.8) |
| T2 | 56 (42.1) |
| T3 | 21 (15.8) |
| T4 | 11 (8.3) |
| Lymph node metastasis | |
| N0 | 90 (67.7) |
| N1 | 40 (30.0) |
| N2 | 3 (2.3) |
| Distant metastasis | |
| M0 | 130 (97.7) |
| M1a | 3 (2.3) |
| Tumor node metastasis stage | |
| I | 57 (42.8) |
| II | 54 (40.6) |
| III | 19 (14.3) |
| IV | 3 (2.3) |
| Median survival (months) | 40 |

†Smoking history was defined as ex-smokers and current smokers.

### Correlations between Rab27A and Rab27B expression and clinicopathological data

The correlations between Rab27A and Rab27B expression and clinicopathological data are shown in Table 2. Rab27A and Rab27B expression was significantly correlated with patient gender ($P$ = 0.007 and 0.002, respectively) and histologic type ($P$ = 0.009 and < 0.001, respectively) but not with patient age, smoking history, surgical method, tumor stage, lymph node metastasis, distant metastasis, or TNM stage. Rab27A and Rab27B expression was more frequent in women than in men and in patients with ADC than in those with SQCC.

Tumors with distant metastasis showed a higher percentage of Rab27A and Rab27B expression. In addition, tumor differentiation did not show any significant association with Rab27A and Rab27B expression in SQCC (well and moderately differentiated vs. poorly differentiated; Rab27A, $P$ = 0.377; Rab27B, $P$ = 0.701) and in ADC (others vs. solid and micropapillary; Rab27A, $P$ = 0.327; Rab27B, $P$ = 0.900).

We also evaluated the relationship between Rab27A expression patterns and clinicopathological data. Positive

  

nuclear Rab27A expression was significantly associated with distant metastasis ($P = 0.015$), while positive cytoplasmic Rab27A expression was significantly correlated with patient gender ($P < 0.001$), histologic type ($P < 0.001$), and smoking history ($P = 0.044$). Positive nuclear Rab27A expression was more frequent in tumors without distant metastasis than in those with distant metastasis, and positive cytoplasmic Rab27A expression was more prevalent in women than in men, in non-smokers than in smokers, and in patients with ADC than in those with SQCC.

## Rab27A and Rab27B expression and survival analysis

Among patients with SQCC, 54.2% ($n = 52$) developed recurrence and 46.9% ($n = 45$) died as a result of the disease. The DSS rate was significantly lower in the group with high Rab27B expression ($n = 43$, 53.1%) than in the group with low Rab27B expression ($n = 1$, 2.3%) ($P = 0.049$). Moreover, Kaplan–Meier analysis revealed that high Rab27B expression was significantly associated with an unfavorable DSS ($P = 0.030$) (Fig 2a). Furthermore, a multivariate Cox proportional hazard test showed that high Rab27B expression was an independent factor for poor DSS (hazard ratio 2.680; 95% confidence interval 1.116–6.437; $P = 0.027$) in SQCC (Table 3). However, statistical analysis did not reveal any significant differences in DFS between the groups with high or low Rab27B expression (Table 3, Fig 2b). In addition, DSS and DFS did not differ significantly between the groups with high or low Rab27A expression.

Among patients with ADC, 32.4% ($n = 12$) developed recurrence and 21.6% ($n = 8$) died as a result of the disease. The DFS and DSS did not differ significantly between groups with Rab27A and Rab27B expression. Finally, statistical analysis showed that neither Rab27A nor Rab27B expression had a prognostic effect in ADC (Table 3).

We additionally performed survival analysis between groups with different Rab27A expression patterns. However, there were no significant differences between groups with nuclear and cytoplasmic Rab27A expression.

**Table 2** Correlation of RAB27A and RAB27B expression with clinicopathological data

| | RAB27A expression | | | RAB27B expression | | |
|---|---|---|---|---|---|---|
| Data | Low expression | High expression | *P* | Low expression | High expression | *P* |
| Age | | | 0.360 | | | 0.906 |
| < 65 | 25 (43.9) | 32 (56.1) | | 44 (83.0) | 9 (17.0) | |
| ≥ 65 | 27 (36.0) | 48 (64.0) | | 57 (83.8) | 11 (16.2) | |
| Gender | | | 0.007 | | | 0.002 |
| Male | 49 (44.5) | 61 (55.5) | | 89 (88.1) | 12 (11.9) | |
| Female | 3 (13.6) | 19 (86.4) | | 12 (60.0) | 8 (40.0) | |
| Smoking | | | 0.637 | | | 0.218 |
| Non-smoker | 17 (37.0) | 29 (63.0) | | 33 (78.6) | 9 (21.4) | |
| Smoker | 35 (41.2) | 50 (58.8) | | 68 (87.2) | 10 (12.8) | |
| Surgery | | | 0.711 | | | 0.568 |
| Lobectomy | 46 (40.0) | 69 (60.0) | | 86 (82.7) | 18 (17.3) | |
| Other† | 6 (35.3) | 11 (64.7) | | 15 (88.2) | 2 (11.8) | |
| Histologic type | | | 0.009 | | | < 0.001 |
| SQCC | 44 (46.3) | 51 (53.7) | | 81 (92.0) | 7 (8.0) | |
| ADC | 8 (21.6) | 29 (78.4) | | 20 (60.6) | 13 (39.4) | |
| Tumor stage | | | 0.320 | | | 0.981 |
| T1,T2 | 37 (37.0) | 63 (63.0) | | 76 (83.5) | 15 (16.5) | |
| T3,T4 | 15 (46.9) | 17 (53.1) | | 25 (83.3) | 5 (16.7) | |
| Lymph node metastasis | | | 0.687 | | | 0.882 |
| Absent | 34 (38.2) | 55 (61.8) | | 69 (83.1) | 14 (16.9) | |
| Present | 18 (41.9) | 25 (58.1) | | 32 (84.2) | 6 (15.8) | |
| Distant metastasis | | | 0.158 | | | 0.199 |
| Absent | 52 (40.3) | 77 (59.7) | | 100 (84.0) | 19 (16.0) | |
| Present | 0 (0.0) | 3 (100.0) | | 1 (50.0) | 1 (50.0) | |
| TNM stage | | | 0.111 | | | 0.647 |
| I, II | 40 (36.4) | 70 (63.6) | | 85 (84.2) | 16 (15.8) | |
| III, IV | 12 (54.5) | 10 (45.5) | | 16 (80.0) | 4 (20.0) | |

†Other includes bilobectomy or sleeve lobectomy and pneumonectomy. Values are presented as numbers (%). ADC, adenocarcinoma; SQCC, squamous cell carcinoma; TNM, tumor node metastasis.

 

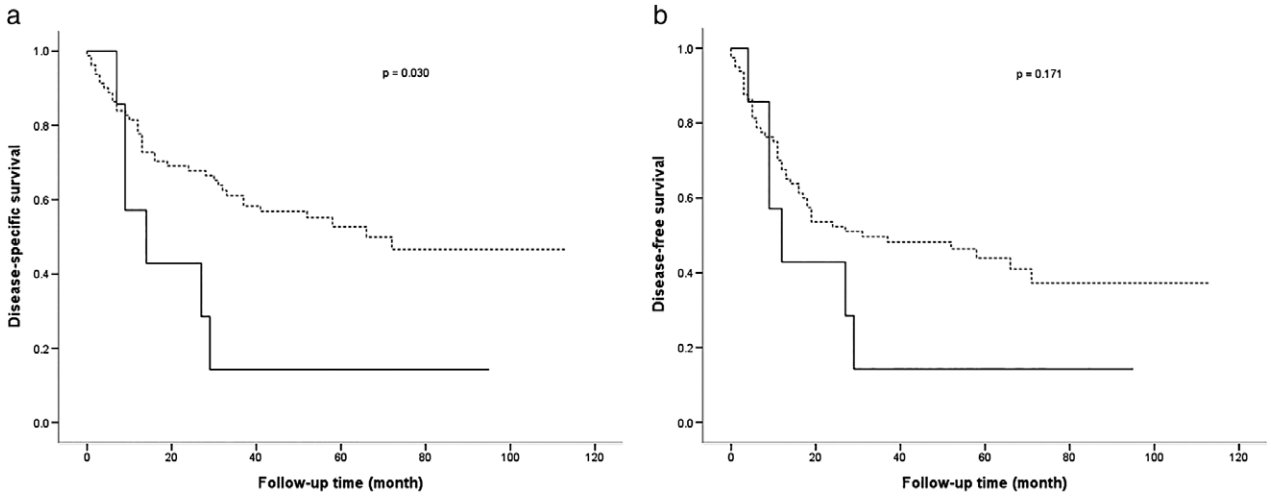


**Figure 2** Kaplan-Meier survival analysis based on Rab27B expression in patients with squamous cell carcinoma (SQCC). The high-expression group shows (**a**) significantly lower disease-specific survival and (**b**) a tendency toward decreased disease-free survival compared to those in the low-expression group. (⎽⎽⌋‾⌉) low expression ($n$ = 81), and (⎽⎽⌋⎽⌉) high expression ($n$ = 7).

## Discussion

Recent studies reported that Rab27A and Rab27B are located on the lipid bilayer of multivesicular endosomes that are released to exosomes and regulate exosome secretion involving the docking multivesicular endosomes.[16,17] Exosomes are well-known vesicles that interact with the tumor microenvironment and result in tumor invasion and metastasis.[10,16] Consequently, there is little doubt that Rab27A and Rab27B are associated with prognosis in cancer patients, and thus, more research is warranted to determine their exact mechanisms in exosome release to control tumor invasion and metastasis.[17]

Our results show that high Rab27B expression is an independent factor associated with unfavorable DSS in patients with SQCC. Among all enrolled patients with SQCC, only seven had high Rab27B expression. The clinicopathological data of these patients are summarized in Table 4.

Six patients had a lower DSS compared to patients at the same TNM stage. Therefore, SQCC patients with high

**Table 3** Cox proportional hazards regression model of DFS and DSS in NSCLC patients ($n$ = 133)

| | Univariate analysis | | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | DFS | | DSS | | DFS | | DSS | |
| Characteristic | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| SQCC | | | | | | | | |
| Age (< 65 vs. ≥ 65) | 1.402 (0.784–2.506) | 0.255 | 1.170 (0.635–2.157) | 0.614 | | | | |
| Gender (male vs. female) | 0.824 (0.200–3.391) | 0.789 | 0.398 (0.055–2.895) | 0.363 | | | | |
| Smoking (non-smoker vs. smoker) | 0.644 (0.356–1.164) | 0.145 | 0.671 (0.355–1.266) | 0.218 | | | | |
| TNM stage (I–II vs. III–IV) | 2.325 (1.208–4.476) | 0.012 | 2.060 (1.016–4.176) | 0.045 | 2.175 (1.124–4.208) | 0.021 | 1.968 (0.965–4.013) | 0.063 |
| Rab27B expression (low vs. high) | 1.789 (0.761–4.204) | 0.182 | 2.513 (1.053–6.000) | 0.038 | 1.909 (0.809–4.505) | 0.140 | 2.680 (1.116–6.437) | 0.027 |
| ADC | | | | | | | | |
| Age (<65 vs. ≥65) | 0.934 (0.296–2.945) | 0.907 | 0.818 (0.195–3.428) | 0.784 | | | | |
| Gender (male vs. female) | 0.736 (0.234–2.320) | 0.601 | 0.592 (0.141–2.484) | 0.474 | | | | |
| Smoking (non-smoker vs. smoker) | 0.918 (0.269–3.139) | 0.892 | 1.690 (0.422–6.764) | 0.459 | | | | |
| TNM stage (I–II vs. III–IV) | 2.011 0.588–6.878) | 0.266 | 1.621 (0.327–8.047) | 0.554 | 2.456 (0.569–10.594) | 0.228 | 2.519 (0.480–13.228) | 0.275 |
| Rab27B expression (low vs. high) | 0.743 (0.186–2.972) | 0.675 | 0.947 (0.226–3.971) | 0.941 | 0.631 (0.152–2.627) | 0.527 | 0.804 (0.183–3.532) | 0.773 |

ADC, adenocarcinoma; CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; NSCLC, non-small cell lung cancer; SQCC, squamous cell carcinoma; TNM, tumor node metastasis.

  

**Table 4** Clinicopathological data of SQCC patients with high Rab27B expression ($n$ = 7)

| Patient number | Gender/age | TNM stage | Tumor differentiation | Smoking history | Surgical method | DSS (months) | Mean DSS by TNM stage (months) |
|---|---|---|---|---|---|---|---|
| 1 | M/68 | IA3 | PD | Smoker | Lobectomy | 95 | 43.88 |
| 2 | M/66 | IB | MD | Smoker | Lobectomy | 27 | 47.61 |
| 3 | M/66 | IIA | MD | Smoker | Lobectomy | 29 | 45.29 |
| 4 | M/68 | IIA | PD | Smoker | Lobectomy | 14 | 45.29 |
| 5 | M/61 | IIB | MD | Non-smoker | Pneumonectomy | 9 | 44.30 |
| 6 | M/72 | IIB | MD | Smoker | Lobectomy | 7 | 44.30 |
| 7 | M/71 | IIIA | MD | Smoker | Pneumonectomy | 9 | 25.71 |

DSS, disease-specific survival; MD, moderately-differentiated; PD, poorly-differentiated; SQCC, squamous cell carcinoma; TNM, tumor node metastasis.

Rab27B expression should receive early treatment. To our knowledge, this is the first study to show that high Rab27B expression is closely related to prognosis in patients with SQCC of the lung.

We also revealed that Rab27A and Rab27B expression was more frequent in women than in men and in patients with ADC than in those with SQCC. However, these results may have been a result of selection bias because the enrolled cases in this study are mainly composed of male SQCC patients. Therefore, an organized study is required for further evaluation.

Interestingly, in this study, tumors with distant metastasis showed a higher percentage of Rab27A and Rab27B expression. This result is difficult to explain because the number of cases with distant metastasis in our sample was too small, but it may reveal a relationship between Rab27A and Rab27B expression, exosomes, and tumor metastasis. We hope that future studies could elucidate the exact mechanisms.

Previous studies have found that high Rab27B expression is related to prognosis in patients with hepatocellular carcinoma, pancreatic ductal ADC, ovarian cancer, and gastrointestinal tumors; our findings are consistent with these results.[6,7,9,18] In addition, other studies have shown that Rab27A has a prognostic effect in several cancers, including hepatocellular carcinoma, colorectal cancer, glioma, and pancreatic ductal ADC.[7,13,14,16,19] However, we did not observe any relationship between Rab27A expression and prognosis in patients with NSCLC. Therefore, we recommend a larger study with a larger sample of ADC cases to better assess this relationship.

In summary, we verified that high Rab27B expression serves as an independent factor for unfavorable DSS in patients with SQCC. The current study is the first to show a relationship between Rab27B expression and SQCC of the lung.

## Disclosure

No authors report any conflict of interest.

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