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■ ORIGINAL ARTICLE ■

Clinicopathologic Implication of Ezrin Expression in Non-small Cell Lung Cancer

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Background: Ezrin, a member of the ezrin-radixin-moesin family, is implicated in tumor progression, metastatic dissemination, and adverse outcomes, in several cancer types. In this study, we explored the clinicopathological significance of ezrin expression in non-small cell lung carcinomas (NSCLCs). **Methods:** Immunohistochemical analysis of tissue microarray with 112 surgically resected NSCLC specimens, was performed to examine the ezrin expression. We also correlated ezrin expression with other clinicopathological features and prognosis. **Results:** The ezrin-positive group revealed significantly higher correlation with pleural invasion ($p = 0.016$) and pathologic stage ($p = 0.050$). Univariate survival analysis showed that ezrin-positive group had a significantly shorter cancer-specific survival than ezrin-negative group ($p = 0.016$). Meanwhile, female ($p = 0.030$), no pleural invasion ($p = 0.023$), no lymphatic invasion ($p = 0.026$), and early pathologic stage ($p = 0.008$) significantly correlated with longer survival. Multivariate survival analysis showed that variables such as ezrin positivity ($p = 0.032$), female ($p = 0.035$), and early pathologic stage ($p = 0.001$) were independent prognostic factors for NSCLC. **Conclusions:** Ezrin might be a molecular marker to predict poor prognosis of NSCLC.

Key Words: Carcinoma, non-small cell lung; Ezrin; Prognosis

Lung cancer is the leading cause of cancer-related deaths, worldwide, in both men and women, with over one million cases diagnosed yearly.[1] Despite progress in the multimodality treatment of lung cancer, prognosis is still poor with 10 to 15% 5-year survival rates. Even in patients with resected stage IA tumors, the survival rate still ranges from 66 to 85%.[2] Non-small cell lung cancer (NSCLC) accounts for >80% of all lung cancers. However, only a minority of NSCLC patients would be eligible for radical treatment as a curative care.

Ezrin belongs to the ezrin-radixin-moesin protein family, which acts as membrane organizers and linkers between the plasma membrane and cytoskeleton.[3] Ezrin plays a positive role in maintaining the shape and the polarity of the cells in membrane-trafficking, cell migration, cell signaling, growth regulation, and differentiation.[4] The cell signaling pathways associated with ezrin, include many oncogenic routes, such as protein kinase C, Rho-kinase, epidermal growth factor receptor, Src, mammalian target of rapamycin (mTOR), and PI3 kinase/Akt.[5] Because of its unique functions, ezrin is actively involved in the biology of tumor development, especially in regulating the growth and metastatic capacity of cancer cells.[6]

Recently, many studies have suggested that increased ezrin expression was associated with certain outcome in various types of cancers.[7-18] To date, however only a few studies have reported association between ezrin expression and clinicopathological parameters as well as its prognostic role in lung cancer.[19-21] In this study, we examined ezrin expression in resected NSCLC specimens, explored the possible correlation between ezrin expression and clinicopathological variables, and determined its potential prognostic value.

MATERIALS AND METHODS

Patients and tissues

We retrospectively obtained formalin-fixed and paraffin-embedded tissues from 112 resected primary NSCLC cases, which were obtained from the Soonchunhyang University Cheonan Hospital, between January 1996 and October 2009. Tumors from patients who died from causes other than lung carcinoma and recurrent or metastatic tumors were excluded from this study. The patients with NSCLC consisted of 81 men and 31 women. The mean patient age was 63 years (standard deviation,

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8.0; range, 42 to 82 years), and the mean tumor size was 3.8 cm (standard deviation 1.9; range, 1.0 to 8.6 cm).

Hematoxylin and eosin (H&E) stained slides were reviewed for each case to confirm the original diagnosis. Two pathologists (M.H.Oh and H.W.Lee) independently reviewed these slides based on the World Health Organization criteria,[22] to select the most representative sections. Tumor specimens were histopathologically diagnosed as adenocarcinoma (ADC; n=38), squamous cell carcinoma (SCC; n=59), large cell carcinoma (n=1), large cell neuroendocrine carcinoma (n=6), and sarcomatoid carcinoma (n=8). The pathologic stage of each tumor was assigned, following the guidelines from the 7th edition of tumor-node-metastasis (TNM) classification.[23] The total sample set comprised of 57 stage I, 38 stage II, 13 stage III, and 4 stage IV tumors. The patients' medical records were collected to obtain the following information: age, gender, and smoking status. Further data regarding the patients' survival status and cause of death were obtained from the patients' medical records and/or from an interview with the family. The median follow-up period for all patients was 23.0 months, with a range of 1 to 153 months.

Construction of tissue microarray (TMA)

The most representative tumor area was carefully marked on H&E stained slides of the sample tissue cores (2 mm in diameter) from formalin fixed, paraffin embedded tissue blocks. Representative cores were arranged in a trephine apparatus (Superbiochips Laboratories, Seoul, Korea). Core sample was obtained from each tumor and included in the TMA block. Control or normal parenchymal cores were also included. Some tumor cores contained non-neoplastic portion and they were used as internal control. One section from the block was stained with H&E for tissue confirmation.

Immunohistochemistry (IHC) for ezrin

IHC was performed to analyze ezrin expression. The materials and methods used in this study have been described previously.[11,24,25] Sections (4-μm thick) from the TMA blocks were transferred to poly-L-lysine-coated glass slides and incubated in a dry oven, at 60°C for 1 hour. Therefore, they were then dewaxed in xylene (three changes), rehydrated in a graded series of decreasing ethanol concentrations and rinsed in Tris-buffered saline (pH 7.4). Endogenous peroxidase activity was inactivated with 5% hydrogen peroxide in methanol for 15 minutes at 37°C. For ezrin staining, antigen retrieval was performed using a microwave treatment in the pH 6.0-epitope retrieval solution for 20 minutes. The tissue was incubated with a mouse monoclonal antibody against ezrin (1:100, clone 3C12, Abcam, Cambridge, UK) in a humidified chamber at 4°C for 16 hours. Secondary antibody was applied, using a Bond polymer refine detection kit (Leica, Mount Waverley, Australia). Diaminobenzidine was used, as the chromogen, and the sections were counterstained with Mayer's hematoxylin. Positive controls, consisting of cases with known reactivity for the antibody, and negative controls, obtained by omitting the primary antibody, were also included.

Immunohistochemical assessment

Tumor cells were judged as positive if cytoplasmic and circumferential membranous staining were present. Immunohistochemical staining was separately evaluated by two investigators (M.H.Oh and H.W.Lee), and in the rare instance of a discrepancy between their judgment, they reviewed the slides together using a multi-head microscope. A semiquantitative immunohistochemical score was assigned, which included assessment of both intensity and extent of staining. Intensity of staining was given score of 0 to 3 (corresponding to negative, weak, moderate, and strong positivity). The extent of staining was scored as 0 (0%), 1 (1-10%), 2 (11-50%), and 3 (51-100%), according to the percentage of cells which stained positive for each protein. The product of intensity and extent score was used as the final score (0, 1, 2, 3, 4, 6, 9). Tissues having a final score of 9 were considered positive, while those having a final score of ≤6 were regarded as negative. Similar semiquantitative scoring systems have been successfully used for other TMA evaluations.[25]

Statistical analysis

Statistical anlaysis was conducted using SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA). Associations between the ezrin expression and the clinicopathological characteristics were analyzed, using the Pearson χ^2 or Fisher's exact test. Kaplan-Meier analysis was performed for analysis of the survival curves and statistical significance was assessed using the log-rank test. Cancer-specific survival was defined as the time from the date of the surgery to the last follow-up visit or cancer-related death. Univariate analysis of cancer-specific survival was performed using the Kaplan-Meier method. Multivariate Cox proportional hazard regression analysis was used to assess the prognostic significance between ezrin expression, the other clinicopathological characteristics, and survival. Overall, 95% confidence intervals were used throughout the analyses. Statistical significance was defined as $p<0.05$.

RESULTS

Ezrin immunoreactivity

In the non-neoplastic pulmonary parenchyma, ezrin was expressed in the apical membrane of the bronchial epithelium and in the pneumocytes of the alveolar wall and inflammatory cells, including lymphocytes and plasma cells. Ezrin in NSCLC appeared mainly in the cytoplasm and circumferential membrane (Figs. 1, 2). Regarding intensity of staining, 8 cases (7.1%) were scored as 0, 27 cases (24.1%) as 1, 41 cases (36.6%) as 2, and 36 cases (32.2%) as 3. Regarding extent of staining, 8 cases (7.1%) were rated as 0, 0 case (0%) as 1, 3 cases (2.7%) as 2, and 101 cases (90.2%) as 3. As mentioned above, ezrin expression in NSCLC showed a diffuse staining pattern. After multiplying staining intensity and extent scores of the 112 immunostained NSCLC specimens, 8 cases (7.1%) were rated as 0, 3 cases (2.7%) as 2, 27 cases (24.1%) as 3, 0 case (0%) as 4, 41 cases (36.6%) as 6, and 33 (29.5%) as 9. The cases were subdivided into ezrin-negative groups (scores of 0, 2, 3, and 6; n = 79 [70.5%]) and ezrin-positive group (scores of 9; n = 33 [29.5%]) for statistical analysis.

Correlations between Ezrin expression and clinicopathologic parameters

The expression of ezrin was significantly higher in the tumors with pleural invasion and late pathologic stage. A weak correlation between ezrin expression and T status was also found. Other clinicopathologic variables, including sex, age, tumor size, histological type, smoking, lymphatic invasion, perineural invasion, nodal status, and metastasis, showed no correlation with ezrin expression (Table 1). Although we did not include adenocarcinoma *in situ* (formerly bronchioloalveolar carcinoma) for analysis in case of ADC, portions of adenocarcinoma *in situ* showed negativity (Fig. 1A).

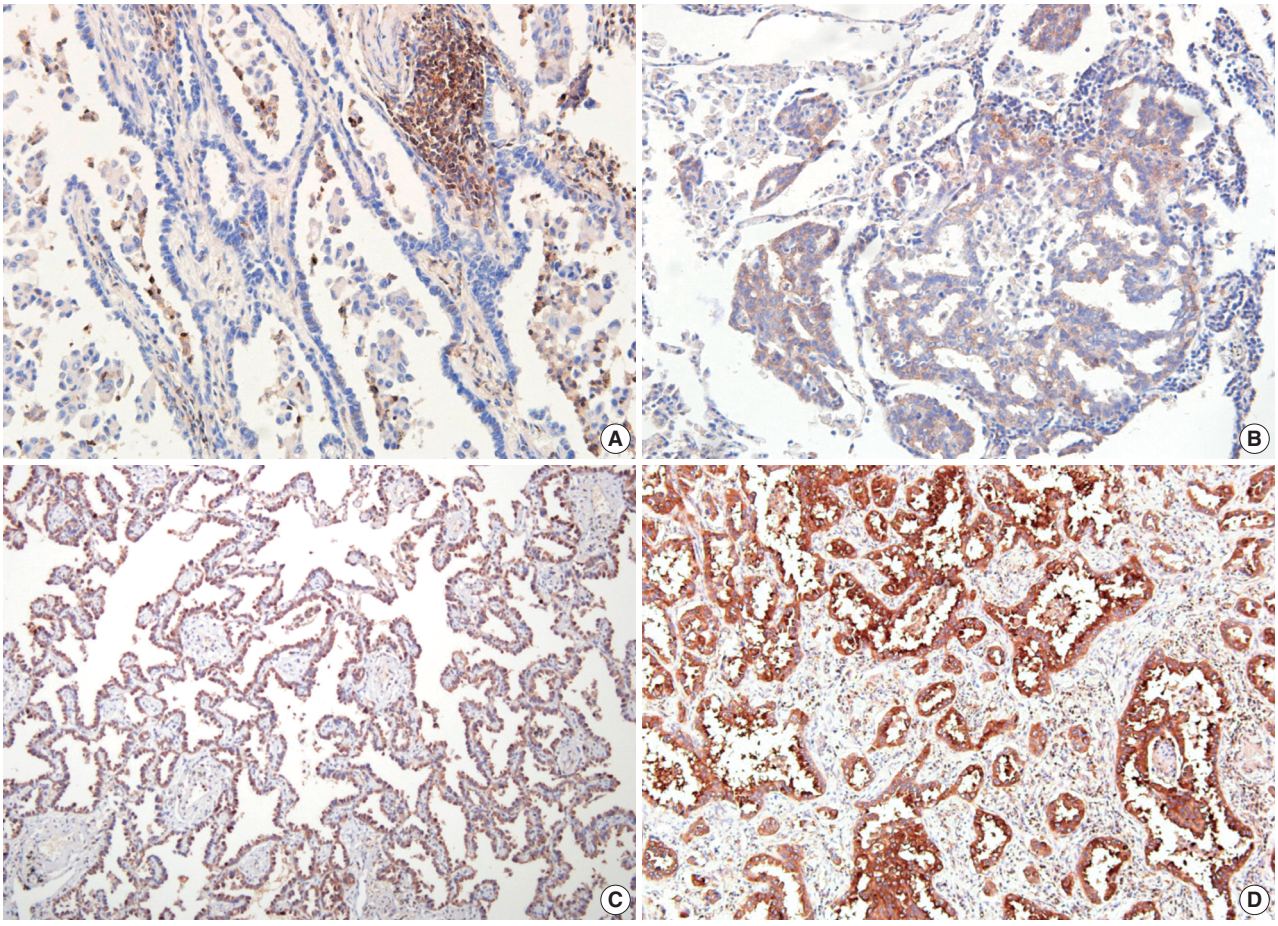

Fig. 1. Immunohistochemical staining of ezrin expression in adenocarcinoma: (A) negative staining in bronchioloalveolar portion of adenocarcinoma and internal positive control in interstitial lymphocytes, (B) weak (1+), (C) moderate (2+), (D) strong (3+) membranous and cytoplasmic staining intensity.

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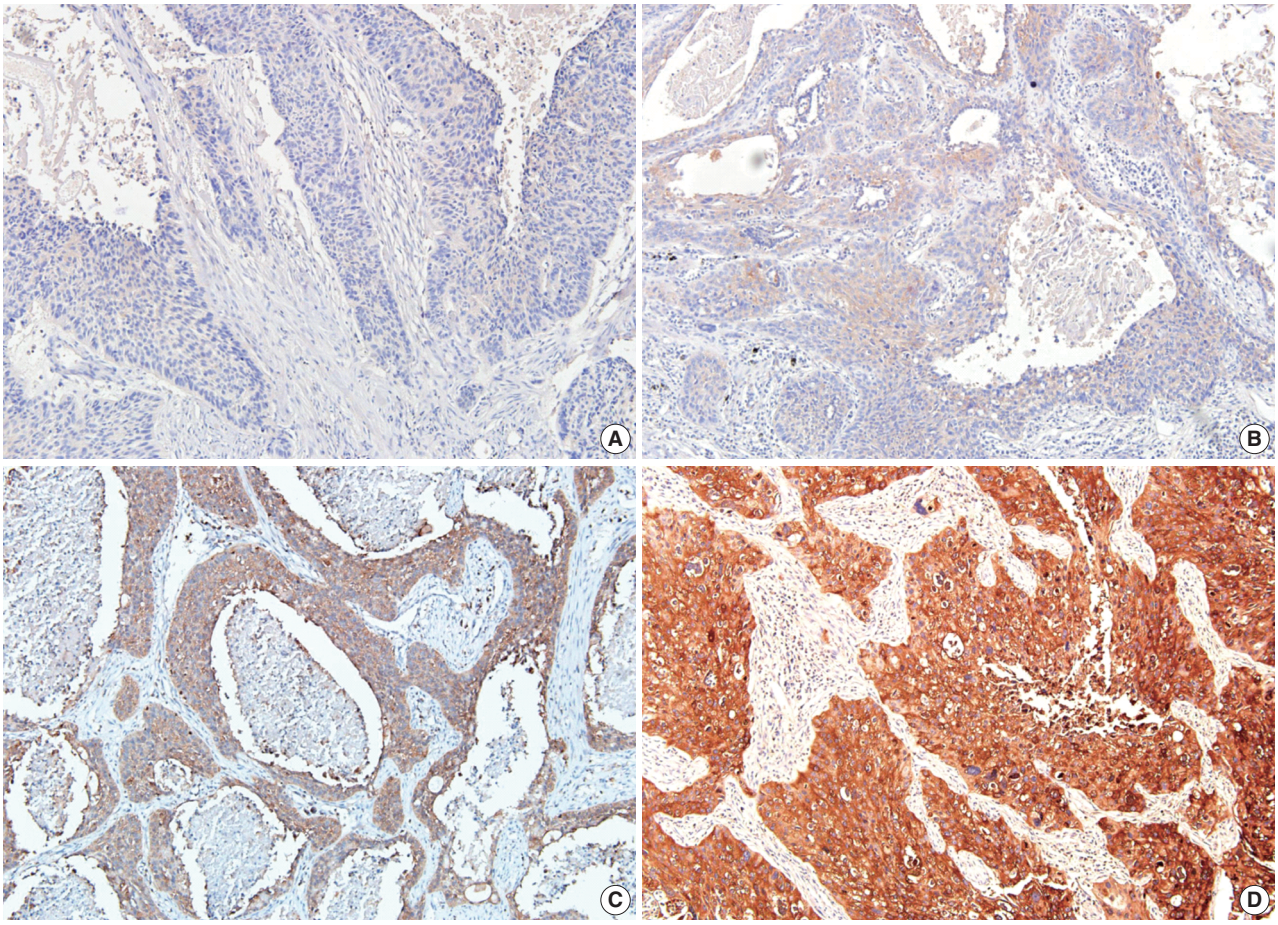

Fig. 2. Immunohistochemical staining of ezrin expression in squamous cell carcinoma: (A) negative, (B) weak (1+), (C) moderate (2+), (D) strong (3+) membranous and cytoplasmic staining intensity.

Survival analysis

At the time of analysis, the number of cancer-specific deaths was 64 (57.1%). Ezrin expression, age, sex, histological type, smoking status, tumor size, pleural invasion, lymphatic invasion, perineural invasion, tumor status and nodal status of TNM, as well as pathologic stage were included in the univariate analysis to evaluate significance of each variable upon cancer-specific survival (Table 2). Ezrin positive groups (see above) displayed a significantly shorter cancer-specific survival than ezrin negative groups ($p = 0.016$) (Fig. 3). Among the above-mentioned variables, female ($p = 0.030$), no pleural invasion ($p = 0.023$), no lymphatic invasion ($p = 0.026$), and early pathologic stage ($p = 0.008$) correlated significantly with longer survival (Table 2). To evaluate whether ezrin positivity in NSCLC is an independent predictor of cancer-specific survival, a multivariate analysis using the Cox proportional hazard model, was performed. This analysis included the variables ezrin expression, sex, pleural invasion, venous lymphatic invasion, and pathologic stage. All variables with a $p < 0.05$ in a univariate analysis were included in a multivariate Cox model. Ezrin positivity ($p = 0.032$), male ($p = 0.035$), and late pathologic stage ($p = 0.001$) were significantly poor prognostic factors for NSCLC. Multivariate analysis demonstrated that ezrin expression was an independent prognostic factor for cancer-specific survival (Table 3).

DISCUSSION

Following the purification of ezrin as a component of the intestinal microvilli that is tyrosine-phosphorylated, by epidermal growth factor,[26] many studies have been focused on the relationship between malignant tumors and tumor invasiveness or related outcomes. Recently, many studies have suggested that increased ezrin expression was associated with poor outcome in various types of cancers, in various organs, including gastric carcinoma,[7] colorectal carcinoma,[8,9] nasopharyngeal carcinoma,[10] esophageal SCC,[11] breast carcinoma,[12] osteosarcoma,[13,14]

Table 1. Relationship of ezrin expression with clinicopathological parameters of 112 patients with NSCLC

Variable		n (%)	Ezrin		
			Negative	Positve	p-value
Total		112 (100)	79 (70.5)	33 (29.5)	
Sex					0.323
	Male	81 (72.3)	55 (67.9)	26 (32.1)	
	Female	31 (27.7)	24 (77.4)	7 (22.6)	
Age (yr)					0.851
	<65	66 (59.9)	47 (72.1)	19 (28.8)	
	≥65	46 (41.1)	32 (69.6)	14 (30.4)	
Tumor size (cm)					0.595
	≤3	45 (40.2)	33 (73.3)	12 (26.7)	
	>3	67 (59.8)	46 (68.7)	21 (31.3)	
Histology					0.706
	SCC	59 (52.7)	44 (74.6)	15 (25.4)	
	ADC	38 (33.9)	26 (68.4)	12 (31.6)	
	LCC	7 (6.3)	4 (57.1)	3 (42.9)	
	SAC	8 (7.1)	5 (62.5)	3 (37.5)	
Smoking					0.692
	Non-smoker	41 (36.6)	28 (68.3)	13 (31.7)	
	Smoker	71 (63.4)	51 (71.8)	20 (28.2)	
Pleural invasion					0.016
	Absent	59 (52.7)	40 (78.0)	19 (22.0)	
	Present[a]	53 (47.3)	36 (56.6)	17 (43.4)	
Lymphatic invasion					0.971
	Absent	88 (78.6)	62 (70.5)	26 (29.5)	
	Present	24 (21.4)	17 (70.8)	7 (29.2)	
Perineural invasion					0.520
	Absent	110 (98.2)	78 (70.9)	32 (29.1)	
	Present	2 (1.8)	1 (50.0)	1 (50.0)	
Tumor status					0.087
	T1	30 (26.8)	24 (80.0)	6 (20.0)	
	T2	67 (59.8)	48 (71.6)	19 (28.4)	
	T3	14 (12.5)	7 (50.0)	7 (50.0)	
	T4	1 (0.9)	0 (0)	1 (100)	
Nodal status					0.168
	N0	74 (66.1)	51 (68.9)	23 (31.1)	
	N1	25 (22.3)	16 (64.0)	9 (36.0)	
	N2	13 (11.6)	12 (92.3)	1 (7.7)	
	N3	0 (0)	0 (0)	0 (0)	
Metastasis					0.207
	M0	108 (96.4)	72 (66.7)	36 (33.3)	
	M1	4 (3.6)	4 (100)	0 (0)	
Pathologic stage					0.050
	I	57 (50.9)	43 (75.4)	14 (24.6)	
	II	38 (33.9)	21 (55.3)	17 (44.7)	
	III	13 (11.6)	11 (84.6)	2 (15.4)	
	IV	4 (3.6)	4 (100)	0 (0)	

NSCLC, non-small cell lung carcinoma; SCC, squamous cell carcinoma; ADC, adenocarcinoma; LCC, large cell carcinoma; SAC, sarcomatoid carcinoma.
[a]Visceral and/or parietal invasion.

various soft tissue sarcomas,[15,16] cutaneous basal cell carcinoma and SCC,[17] and melanoma.[18] Some cohort studies[19,21] suggested the distinct fuction of ezrin in tumor cell invasion or metastasis, however, no report to date has ever identified its favorable prognostic value. In this study, we analyzed the relationship between ezrin expression and clinicopathological parameters as well as survival. We observed that increased ezrin expression correlated with pleural invasion ($p = 0.016$), tumor stage ($p = 0.050$), and shorter survival ($p = 0.016$). However, ezrin expression did not correlate with other clinicopathological parameters, such as sex, age, tumor size, histology, smoking, lymphatic invasion, perineural invasion, tumor status, nodal status, and metastasis.

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Table 2. Univariate analysis of cancer-specific survival in 112 patients with NSCLC

Univariate	Cancer-specific survival (p-value)
Ezrin expression (negative vs positive)	0.016
Sex (female vs male)	0.030
Age (<65 yr vs ≥65 yr)	0.067
Smoking (non-smoker vs smoker)	0.207
Histology (ADC, SCC, LCC, STC)	0.087
Size (≤3 cm vs >3 cm)	0.397
Pleural invasion[a]	0.023
Venous invasion[a]	0.691
Lymphatic invasion[a]	0.026
Perineural invasion[a]	0.211
Tumor status (1, 2, 3, 4)	0.458
Nodal status (0, 1, 2, 3)	0.081
Pathologic stage (I, II, III, IV)	0.008

NSCLC, non-small cell lung carinoma; ADC, adenocarcinoma; SCC, squamous cell carcinoma; LCC, large cell carcinoma; STC, sarcomatoid carcinoma.
[a]Absent vs present.

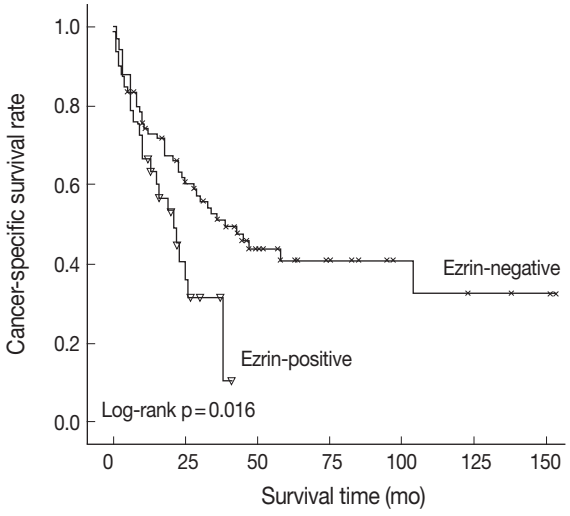

Fig. 3. Kaplan-Meier survival curve for 112 non-small cell lung carcinoma with regard to ezrin expression.

Although the association of ezrin with tumor proliferation and invasiveness was confirmed in several types of cancers, the exact mechanism has not yet been defined. Hiscox and Jiang[27] and McClatchey[28] insisted that the metastatic process begins with a breakdown of the epithelial integrity causing the tumor cells to penetrate into the vascular system, where they finally obtains aggressive proliferation in appropriate target organs. Cell adhesion molecules and actin cytoskeleton play important roles during these processes. Khanna *et al.*[13] and Fiévet *et al.*[29] suggested that ezrin participated in invasiveness and metastasis processes believed to be predominantly late events in tumor progression. Interestingly, our study revealed that ezrin expression correlated to higher tumor stage (p=0.050), and bronchioloalveolar portion of ADC showed a trend of ezrin negativity.

Table 3. Multivariate analysis of cancer-specific survival in 112 patients with NSCLC

Cox regression	Cancer-specific survival		
	p-value	HR	95% CI
Ezrin expression (negative vs positive)	0.032	1.853	1.053-3.623
Sex (female vs male)	0.035	2.000	1.049-3.813
Pleural invasion[a]	0.058	0.854	0.489-1.492
Lymphatic invasion[a]	0.428	1.287	0.690-2.398
Pathologic stage (I, II vs III, IV)	0.001	1.704	1.227-2.368

NSCLC, non-small cell lung carinoma; HR, hazard ratio; CI, confidence interval.
[a]Absent vs present.

Further elucidation of the molecular mechanisms underlying lung cancer progression is essential for the development of new effective therapeutic agents. Recent strategies include personalized treatment selecting those patients that are likely to respond to a particular chemotherapeutic regimen. Such approach may contribute to improved treatment efficacy while avoiding unnecessary side effects. With regard to the potential therapeutic use of ezrin, several possible approaches can be exploited such as the development of an antibody or an inhibitor of ezrin or its downstream molecules. Active researches are ongoing to identify such molecules. Previous studies have elucidated that the metastatic behavior of ezrin is related to the mTOR signaling pathway. Blocking this pathway has been shown to inhibit experimental lung metastasis. Currently, the mTOR inhibitor rapamycin and its analogues are being appraised in preclinical and clinical trials for the treatment of cancer.[9,30] In this study, we used IHC to analyze the levels of ezrin expression in 112 clinicopathologically characterized NSCLC cases. In normal non-neoplastic tissue, ezrin was expressed in the apical portion of bronchial epithelium and pneumocytes. In malignant tumors, however, ezrin showed diffuse cytoplasm and circumferential membranous staining pattern. Wan *et al.*[30] reported that in invasive breast tumors and cancer cell lines, switching the localization of ezrin from the apical membrane to either the complete membrane, or to the cytoplasm was correlated with dedifferentiation and adverse features. In the present study, we found that ezrin expression in NSCLC showed a diffuse staining pattern, such that scores mainly correlated with the staining intensity but not staining extent. Abdou *et al.*[17] have erstwhile suggested that intensity, rather than extent of ezrin expression, had a more probable impact on tumor behavior. At any rate, however, it is necessary to establish detailed and standardized immunohistochemical assessment of ezrin expression. Another

important finding of our study is the consistently significant relationship between survival and ezrin expression in both univariate ($p = 0.016$) and multivariate analyses ($p = 0.032$). It indicates that ezrin might be a new molecular marker to predict the prognosis of NSCLC.

Despite providing new insights into the relationship between ezrin expression and clinical outcome in NSCLC, the present study has some limitations which restrict generalization of our results. For instance, we cannot exclude that selection bias could have influenced our findings because all of the enrolled patients were surgically resectable. Furthermore, our study is retrospective and included only one TMA core per case. It is of note, however, that several recent studies used the same methods we have applied herein such as scoring system and TMA block.[7,11,15,16] Nevetheless, the present findings remain to be confirmed by further studies. Moreover, the value of ezrin as an independent predictor of NSCLC necessitates further multivariate analysis especially in a larger cohort of patients.

In summary, we have demonstrated that ezrin expression is associated with poor prognostic outcome in NSCLC and is higher in late stage tumors and those with pleural invasion. In view of these findings, it is suggested that ezrin might be a new molecular marker to predict the prognosis of NSCLC.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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