Original Article

Expression and Clinical Significance of CD82/KAI1 and E-cadherin in Non-Small Cell Lung Cancer

WU Shiwu MD[1], Yu Lan MD[1], Song Wenqing MD[1], Zhou Lei MD[1], Tao Yisheng MD•[1]

Abstract

Background: This study investigates the expression of CD82/KAI1 and epithelial-cadherin (E-cad) in non-small cell lung cancer (NSCLC).

Methods: Tissues of resected primary NSCLC and normal lung tissue were investigated. Protein expression was detected with immunohistochemical staining. mRNA expression levels of CD82/KAI1 and E-cad were determined by semiquantitative reverse transcriptase polymerase chain reaction (RT-PCR) after mRNA extraction.

Results: The expression of CD82/KAI1 and E-cad was significantly lower in NSCLC compared to normal lung tissue ($P < 0.01$). CD82/KAI1 and E-cad mRNA and protein expression were found to be in close relationship with the grade of differentiation, lymph node metastasis and pathologic tumor-node-metastasis (pTNM) stages, and survival in NSCLC ($P < 0.01$), but no relationship was observed with gender, diameter, type, histological type and age ($P > 0.05$). Expression of mRNA CD82/KAI1 and E-cad were consistent with their proteins ($P < 0.01$), and there was a significant relationship between expression of CD82/KAI1 and E-cad. The survival rate of the CD82/KAI1-positive and CD82/KAI1-negative groups was significantly different ($P < 0.01$). In addition, the survival rate was significantly different between the E-cad-positive and E-cad-negative groups. pTNM stages and positive expression of CD82/KAI1 and E-cad were independent prognostic factors of NSCLC ($P < 0.05$).

Conclusion: Lower expression of CD82/KAI1 and E-cad was found in NSCLC compared to normal lung tissue. Decreased expression of CD82/KAI1 and E-cad was closely related to cellular differentiation, pTNM stages, invasion and metastasis.

Keywords: CD82/KAI1, E-cadherin, NSCLC, prognosis

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with nearly 1.4 million deaths annually,[1] and non-small cell lung cancer (NSCLC) accounts for nearly 85% of all lung cancer cases.[2] The CD82/KAI1 gene was originally identified as a putative metastasis suppressor gene for prostate cancer.[3] Recently, studies have shown that decreased CD82/KAI1 expression is a useful marker for metastasis and invasive potential in various human cancers, such as lung, bladder, pancreatic, colon and breast.[4–10] CD82/KAI1 is a gene located on human chromosome 11p11.2. It is a member of the structurally distinct family of cell surface glycoproteins, the transmembrane 4 protein superfamily (TM4SF).[11] Expression of epithelial cadherin (E-cad) is a transmembrane glycoprotein that functions to maintain stable cell-cell contact in epithelial cell types, thereby inhibiting aberrant cell proliferation and migration. It's down-regulation or loss of regulation is a sign of poor prognosis, and shows invasion and metastasis for multiple types of epithelial carcinomas.[12,13]

To date, the correlation between CD82/KAI1 and E-cad expression is unknown in NSCLC. Therefore, this study intends to investigate the expression of CD82/KAI1 and E-cad in postoperative NSCLC patients following primary lung resection in order to determine the correlation between CD82/KAI1 and E-cad expression.

Materials and Methods

Specimens of 50 patients with primary resected NSCLC tissues were collected from the First Hospital affiliated with Bengbu Medical College between 2003 and 2005. We excluded patients who received preoperative chemotherapy or radiotherapy. Tumor tissue specimens and 20 patient-matched non-tumor tissue specimens were collected and immediately snap frozen in liquid nitrogen. Clinical data were obtained from the medical records. The patients consisted of 38 males and 12 females, of ages 32 to 77 years (average: 58.6 years). There were 38 tumors that were centrally located and 12 that were peripheral. Histologically, specimens consisted of 36 squamous carcinomas and 14 adenocarcinomas. A total of 26 specimens had no lymph node metastasis, whereas 24 specimens showed evidence of lymph node metastasis. There were 5 cases whose tumors were ≤ 3.0 cm in diameter and 45 cases that were > 3.0 cm. According to the grading system of the World Health Organization (WHO), 8 specimens were classified as grade I, 28 specimens were grade II and 14 specimens were grade III. The specimens were also staged as follows according to the tumor-node-metastasis (TNM) staging system of the International Union against Cancer (UICC): stage I (14 cases), stage II (20 cases), and stage III (16 cases). The mean clinical follow-up time was 41.6 ± 29.5 months (n = 50) with a range of 4

Authors' Affiliations: [1]Department of Pathology, First Affiliated Hospital of Bengbu Medical College, Bengbu Medical College, Bengbu City, 233000, Anhui Province, P.R. China.

•Corresponding author and reprints: Tao Yisheng MD, Department of Pathology, First Affiliated Hospital of Bengbu Medical College Bengbu Medical College, Anhui Key Laboratory of Infection and Immunology, Bengbu City, 233000, Anhui Province, P.R. China. Tel: +86-552-3070209,
E-mail: tys101041@126.com.
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– 88 months. Controls comprised 20 cases of normal lung tissues taken at a distance of > 10.0 cm from the tumor site.

Immunohistochemistry

An Elivision™ Plus Kit (Labvision Co., Ltd) was used for immunohistochemical analysis. We cut 4 micrometer (μm) thick tissue sections of tumor for analysis. All sections were deparaffinized and dehydrated in a graded alcohol. The sections were washed for 10 min in phosphate buffered saline (PBS; pH 7.2). The endogenous peroxidase activity was quenched by incubation in methanol that contained 3% H_2O_2 for 10 min at room temperature, then heated for 30 min at 95ºC to repair the antigens, with a final rinse in PBS. After several washes in PBS, sections were blocked with goat serum for 20 min at room temperature, and then incubated with mouse monoclonal CD82/KAI1 (Santa Cruz) and E-cad (Labvision Co., Ltd.) primary antibodies overnight at 4°C in a humidified chamber. Replacing the primary antibodies by PBS, we performed staining for the negative control. The slides were treated with polymer enhancer (reagent A) for 20 min at room temperature. Washing in PBS, the slides were treated with goat anti-mouse antibody (reagent B) for 30 min at room temperature. After another wash in PBS, the slides were developed in freshly prepared diaminobenzedine solution (DAB) for 8 min, and then counterstained with hematoxylin, air-dried, and mounted.

Slides were independently reviewed by two observers to evaluate the staining pattern of the protein under the light microscope. Ten visual fields were randomly selected from each slide. For scoring expression of CD82/KAI1 and E-cad protein, we considered both the extent and intensity of immunopositivity. The intensity of the positive result was scored as follows: negative (0); weak (1); moderate (2); and strong (3). The extent of positivity was scored according to the percentage of cells that stained positive: < 10% (1); 11% – 50% (2); 51% – 75% (3); and > 75% (4). The final score was determined by multiplying the intensity of the positive reaction and the extent of positivity scores, which yielded a range from 0 to 12. Expression for CD82/KAI1 and E-cad were considered positive when the scores were > 1.

Staining for CD82/KAI1 was mainly confined to the membrane and cytoplasm. The staining for E-cad was mostly located in the cytoplasm and membrane, and visualized as brown granular material.

Total RNA was isolated from the specimens using Trizol (Invitrogen, USA), and 1 mg of total RNA was converted to cDNA using the Takara RNA PCR Kit (TaKaRa, Japan) according to the manufacturer's instructions. PCR reactions were performed in a 20 ml volume. A 1 ml aliquot of the cDNA was used for PCR amplification with the following primers. The CD82/KAI1 primers were 5'-AGG ATG CCT GGG ACT ACG TG-3' and 5'-GCT CAG CGT TGT CTG TCC AGT-3', which produced a 735-bp fragment. PCR conditions were 94°C for 30 s, 61°C for 30 s and 72°C for 1 min, for 30 cycles. Under the same PCR conditions, β-actin was amplified as an internal control for semiquantitative reverse transcriptase polymerase (RT-PCR) analysis and the primers were 5'-TCG TGC GTG ACA TTA GGA G-3' and 5'-GTC AGG CAG CTC GTA GCT CT-3' with a product of 247 bp. E-cad primers were 5'-GGG TGA CTA CAA AAT CAA TC-3' and 5'-GGG GGC AGT AAG GGC TCT TT-3' which produced a 252-bp fragment. PCR conditions were 94°C for 45 s, 60°C for 45 s, 72°C for 1 min, for 30 cycles. Under the same PCR conditions as E-cad, β-actin was amplified as an internal control for RT-PCR analysis and the primers were 5'- CCT TCC TGG GCA TGG AGT CCT -3' and 5'- GGA GCA ATG ATC TTG ATC TT -3', which amplified a 201-bp fragment. Semi-quantitative data regarding the PCR products were obtained by comparing the intensity of the PCR band of CD82/KAI1 and E-cad with that of β-actin (internal control) using gene tools software (Tanon GeI Image Software).

The clinical and pathologic characteristics of the patients in relation to CD82/KAI1 and E-cad were compared by Student's-test for continuous variables and the chi-square test for categorical variables. The correlation between CD82/KAI1 and E-cad were assessed by Spearman correlate analysis. Overall, cumulative survival rates were obtained using the Kaplan-Meier method. The difference in free survival between groups was compared using the log-rank test. All analyses were performed with SPSS version 17.0 software. A value of $P < 0.05$ was considered statistically significant.

Results

Expression of CD82/KAI1 and E-cad proteins

CD82/KAI1 and E-cad were localized in the membrane or cytoplasm of the tumor cell. In normal lung tissue, CD82/KAI1 was localized in the cytoplasm, whereas E-cad was localized in either the cytoplasm or membrane. CD82/KAI1 was expressed in 38% and E-cad was expressed in 48% of NSCLC cases. In controls, CD82/KAI1 was expressed in 95% and E-cad had 100% expression. A significant difference was found between the NSCLC and control groups (chi-square test, $P < 0.01$). Staining results are given in Table 1 and Figure 1. There was a significance difference between expression of CD82/KAI1 and E-cad and pathologic TNM (pTNM) stages, differentiation grades, and lymph node involvement in NSCLC. However, the expression of CD82/KAI1 and E-cad was not associated with gender, age, tumor localization, histological type and tumor diameter ($P > 0.05$; Table 1).

Expression of CD82/KAI1 and E-cad mRNA

CD82/KAI1 and E-cad mRNA were detected by the RT-PCR method in both cancer and normal tissues. The expression level of CD82/KAI1 and E-cad mRNA was significantly less in NSCLC than in control tissues ($P < 0.05$). There was a negative association between the expression of CD82/KAI1 and E-cad mRNA and pTNM stages, grades of differentiation and lymph node metastasis ($P < 0.05$; Table 2).

Combined expression of CD82/KAI1 and E-cad

The results of Spearman correlate analysis showed a positive correlation between the expression of mRNA and protein ($P < 0.01$; Table 3) and a positive correlation between the expression of CD82/KAI1 and E-cad ($P < 0.01$).

Correlation between expression of CD82/KAI1, E-cad and prognostic implications in NSCLC patients

All 50 patients were followed for 4 – 88 months after surgery. Data were analyzed by the log-rank test. The expression of CD82/KAI1 and E-cad were closely related to the prognosis of NSCLC patients without consideration of the pTNM stage. Positive expression of CD82/KAI1 and E-cad were related to a better prognosis. Multivariate analysis showed that pTNM stages and positive expression of CD82/KAI1 and E-cad were independent prognostic factors of NSCLC ($P < 0.05$; Table 4).

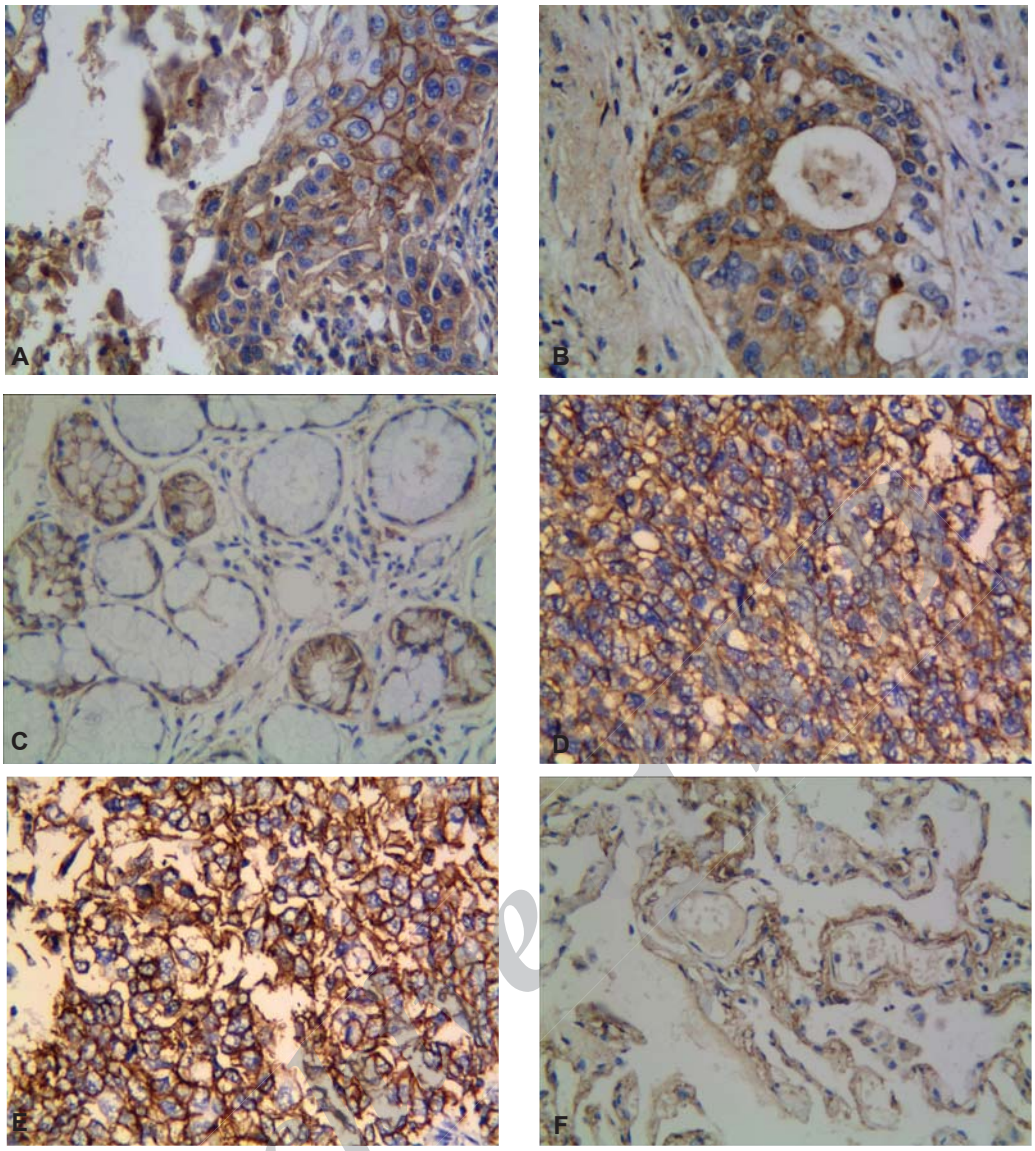

Figure 1. A and B: positive staining of CD82/KAI1 in the membrane and cytoplasm (A: Poor grading of differentiation, B: Moderate grading of differentiation; Elivision™ × 400); C: Positive staining of CD82/KAI1 in the cytoplasm and membrane of the control group (Elivision™ × 400); D and E: Positive staining of E-cad in the cytoplasm and membrane (D and E: Poor grading of differentiation; Elivision™ × 400); F: Positive staining of E-cad in the cytoplasm and membrane of the control group (Elivision™ × 100).

Discussion

The CD82/KAI1 gene as a metastasis suppressor gene may be a useful marker for the metastatic and invasive potential in a series of human tumor types. The deletion of wild-type p53 and of JunB or AP2 protein is closely related to the decreased expression of CD82/KAI1.[14] CD82/KAI1 is in contact with other members of the TM4SF, such as E-cad and integrins. This contact indicates that it may play an important role in cellular adhesion activity, and invasion or metastasis suppressor by signal transduction. Some studies show a significant correlation between CD82/KAI1 and E-cad expression and invasion or metastasis of malignant tumors.[15,16]

In this study we examined CD82/KAI1 and E-cad expression in primary resected cancer and normal tissues of the lung on levels of mRNA and protein by RT-PCR and immunohistochemistry. Both RT-PCR and immunohistochemistry revealed decreased CD82/KAI1 and E-cad expression from normal tissue to cancer tissue, and a positive relationship was detected between the mRNA levels and the protein levels of CD82/KAI1 and E-cad. CD82/KAI1 and E-cad mRNA and protein expression were found to be in close correlation with the grades of differentiation, lymph node metastasis and clinical stages of NSCLC. Low CD82/KAI1 and E-cad expression were detected in poorly differentiated cancers and late clinical stage NSCLC with lymph node metastasis, which has indicated that down-regulation of CD82/KAI1 and E-cad might impact the invasion, metastasis, and progression of NSCLC. Determination of CD82/KAI1 and E-cad mRNA and protein levels might be valuable in evaluating the invasion and metastasis of human NSCLC. Our data are consistent with previous studies.[17–22]

We have found a positive relationship between the expression

Table 1. Expression of CD82/KAI1 and E-cad protein.

Variable	CD82/KAI1		*P*-value	E-cad		*P*-value
	Negative	Positive		Negative	Positive	
Tissue			0.000			0.001
Non-tumor lung tissue	1	19		0	20	
NSCLC	31	19		26	24	
Gender			0.081			0.243
Male	21	17		18	20	
Female	10	2		8	4	
Age (years)			0.369			0.924
< 60	12	5		9	8	
≥ 60	19	14		17	16	
Tumor localization			0.081			0.243
Central	21	17		18	20	
Peripheral	10	2		8	4	
Histological type			0.392			0.278
Squamous carcinoma	21	15		17	19	
Adenocarcinoma	10	4		9	5	
Diameter of tumor			0.285			0.706
< 3.0cm	2	3		3	2	
≥ 3.0cm	29	16		23	22	
Grade of tumor			0.003			0.036
Well	1	7		2	6	
Moderately	18	10		13	15	
Poorly	12	2		11	3	
Lymph node metastasis			0.003			0.002
Yes	11	15		8	18	
No	20	4		18	6	
pTNM stage			0.000			0.000
I	1	13		1	13	
II	16	4		11	9	
III	14	2		14	2	

Table 2. Expression of CD82/KAI1 and E-cad mRNA.

Variable	CD82/KAI1 mRNA	F	*P*-value	E-cad mRNA	F	*P*-value
Grade of tumor		6.831	0.002		8.060	0.001
Well	0.50±0.06			0.82±0.04		
Moderately	0.43±0.09			0.70±0.14		
Poorly	0.37±0.05			0.62±0.09		
Lymph node metastasis		8.649	0.005		6.017	0.018
No	0.46±0.09			0.74±0.14		
Yes	0.39±0.07			0.65±0.11		
pTNM stage		52.323	0.000		24.361	0.000
I	0.52±0.06			0.83±0.07		
II	0.43±0.04			0.69±0.11		
III	0.34±0.05			0.59±0.09		
Gender		1.086	0.303		1.578	0.215
Male	0.43±0.09			0.71±0.13		
Female	0.40±0.07			0.65±0.13		
Tumor localization		2.424	0.126		2.406	0.127
Central	0.44±0.09			0.71±0.13		
Peripheral	0.39±0.08			0.64±0.13		
Diameter of tumor		0.147	0.703		0.001	0.971
<3.0cm	0.44±0.09			0.70±0.16		
≥3.0cm	0.42±0.09			0.69±0.13		
Age (years)		0.377	0.542		0.217	0.643
<60	0.41±0.09			0.68±0.14		
≥60	0.43±0.09			0.70±0.13		
Histological type		0.114	0.737		0.104	0.748
Squamous carcinoma	0.43±0.09			0.70±0.13		
Adenocarcinoma	0.42±0.08			0.68±0.13		

levels of CD82/KAI1 mRNA or protein and E-cad mRNA or protein in NSCLC. CD82 may stabilize or strengthen E-cad-dependent intercellular adhesion by regulating β-catenin-mediated signal transduction on cancer cells, and consequently, prevent cancer cells from seceding from the primary tumor site.[23] It has been confirmed in previous studies that CD82/KAI1 and E-cad play an important role in tumor occurrence and progression. CD82/KAI1 and E-cad expression was highly down-regulated in varieties of cancers, including hepatocellular cancer, retinoblastoma, endometrial carcinoma and gastric cancer,[16,24–27] which correlated with malignancy, metastasis and clinical stages. But in human lung cancer, until now, no study has examined CD82/KAI1 and

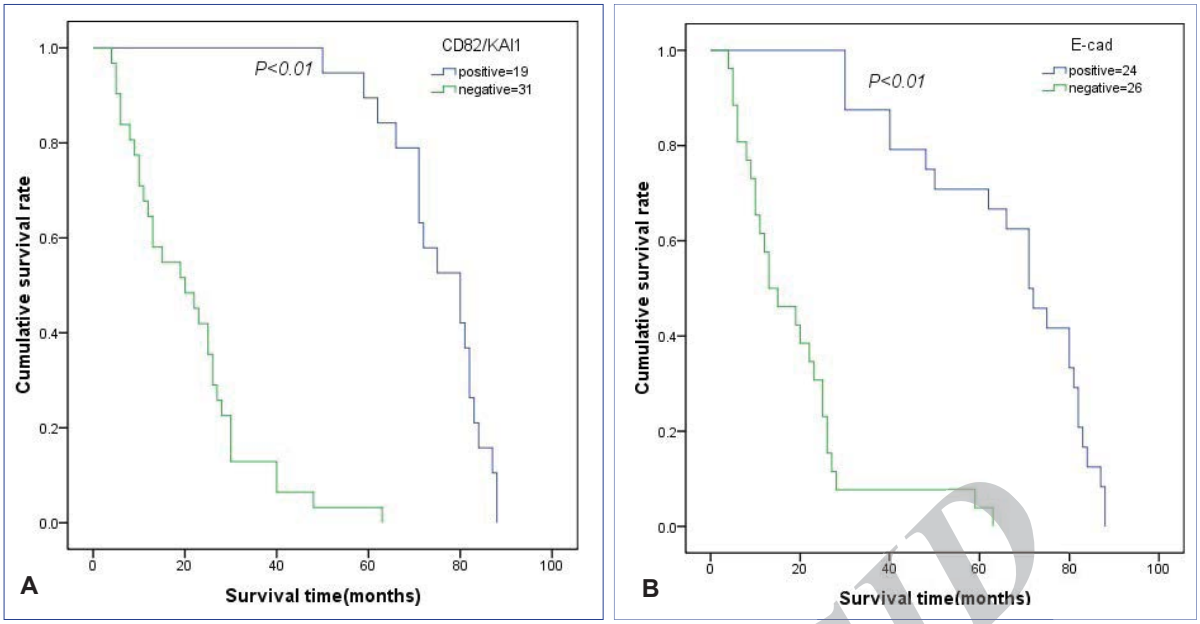

Figure 2. AB Kaplan-Meier survival analysis by CD82/KAI1 and E-cad status (A: CD82/KAI1; B: E-cad; n=50). The y-axis represents the percentage of patients. The x-axis represents their survival in months. A: The blue line represents CD82/KAI1-positive patients with a trend for better survival than the green line, which represents CD82/KAI1-negative non-small cell lung cancer (NSCLC) patients (P<0.01). Mean survival times were 75.3 ± 2.4 months for the CD82/KAI1-positive group and 20.9 ± 2.5 months for the CD82/KAI1-negative group. B: The blue line represents E-cad-positive patients with a trend for better survival than the green line, which represents E-cad-negative NSCLC patients (P<0.01). Mean survival times were 66.3 ± 4.0 months for the E-cad-positive group and 18.8 ± 2.9 months for the E-cad-negative group.

Table 3. Correlation between CD82/KAI1 and E-cad mRNA and protein expression.

	n	Protein	mRNA — (Ex **X** ±s)	*P*-value
CD82/KAI1	31	Negative	0.37±0.05	0.000
	19	Positive	0.52±0.05	
E-cad	26	Negative	0.59±0.07	0.000
	24	Positive	0.81±0.08	

Table 4. Multivariate survival analysis of 50 patients with NSCLC.

Covariate	B	SE	Sig	Exp (B)	95%CI
pTNM	2.102	0.424	0.000	8.179	3.566–18.759
CD82/KAI1	3.232	0.912	0.000	25.321	4.240–151.222
E-cad	1.833	0.714	0.010	6.254	1.542–25.364
B: Partial regression; SE: Standard error; Exp: Relative risk; CI: Confidence interval					

E-cad expression.

Immortalization and invasiveness are important characteristics for cancer tissues. Postoperative recurrence and metastasis are the principal causes for treatment failure and death in patients with NSCLC. Based on our current experiments, multivariate analysis showed that pTNM stages and positive expression of CD82/KAI1 and E-cad were independent prognostic factors of NSCLC (P < 0.05). It has been well accepted that pTNM stage is the standard of therapy, thus it is more important to seek a new molecular marker which can reflect tumor cell biological behavior and play a complementary role for pTNM staging. Survival analysis showed that the survival rate of the CD82/KAI1-positive or CD82/KAI1-negative group significantly differed (P < 0.01). Also, the survival rate was significantly different between the E-cad-positive and E-cad-negative groups. The survival-rate of the CD82/KAI1 and E-cad positive expression group was significantly higher than the negative expression group. Furthermore, we analyzed the relation of CD82/KAI1 and E-cad expression of protein and mRNA in NSCLC, and determined that a positive correlation between the expression of mRNA and protein existed, which has revealed that the expression of CD82/KAI1 and E-cad were down-regulated at both the transcriptional and protein levels. Loss of CD82/KAI1 expression may affect the proliferation, invasion and metastasis of tumor, suppress E-cad production and inhibit adhesion of NSCLC cells.[24]

In conclusion, by detecting the expression of CD82/KAI1 and E-cad in resected primary NSCLC, we have found that the low expression of CD82/KAI1 and E-cad was closely related to the invasion, progression and metastasis of NSCLC. There was a positive correlation between the expression of CD82/KAI and E-cad in NSCLC. However the number of subjects in our study was relatively small. Further studies with a larger specimen size are needed to verify the present observation.

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References

1. Jemal A, Center MM, Desantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev*. 2010; **19:** 1893 – 1907.
2. Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: new biological insights and recent therapeutic advances. *CA Cancer J Clin*. 2011; **61:** 91 – 112.
3. Dong JT, Lamb PW, Rinker-Schaeffer CW, Vukanovic J, Ichikawa T, Isaacs JT, et al. KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11P11.2. *Science*. 1995, **268:** 884 – 886.
4. Adachi M, Taki, T, Ieki Y, Huang CI, Higashiyama M, Miyake M. Correlation of KAI1/CD82 gene expression with good prognosis in patients with non-small cell lung cancer. *Cancer Res*. 1996; **56:** 1751 – 1755.
5. Adachi M, Taki T, Konishi T, Huang CI, Higashiyama M, Miyake M. Novel staging protocol for non-small cell lung cancers according to MRP-1/CD9 and KAI1/CD82 gene expression. *J Clin Oncol*. 1998; **16:** 1397 – 1406.
6. Yu Y, Yang JL, Markovic B, Jackson P, Yardley G, Barrett J, et al. Loss of KAI1 messenger RNA expression in both high-grade and invasive human bladder cancers. *Clin Cancer Res*. 1997; **3:** 1045 – 1049.
7. Guo X, Friess H, Graber HU, Kashiwagi M, Zimmermann A, Korc M, et al. KAI1 expression is up-regulated in early pancreatic cancer and decreased in the presence of metastasis. *Cancer Res*. 1996; **56:** 4876 – 4880.
8. Friess H, Guo XZ, Berberat P, Graber HU, Zimmermann A, Korc M, et al. Reduced KAI1 expression in pancreatic cancer is associated with lymph node and distant metastases. *Int J Cancer*. 1998; **79:** 349 – 355.
9. Maurer CA, Graber HU, Friess H, Beyermann B, Willi D, Netzer P, et al. Reduced expression of the metastasis suppressor gene KAI1 in advanced colon cancer and its metastasis. *Surgery*. 1999; **126:** 869 – 880.
10. Yang X, Welch DR, Phillips KK, Weissman BE, Wei LL. KAI1, a putative marker for metastatic potential in human breast cancer. *Cancer Lett*. 1997; **119:** 149 – 155.
11. Jean M. New clue to prostate cancer spread. *Science*. 1995; **268:** 799 – 800.
12. Nass SJ, Herman JG, Gabrielson E, Iversen PW, Parl FF, Davidson NE, et al. Aberrant methylation of the estrogen receptor and E-cadherin 5' CpG islands increase with malignant progression in human breast cancer. *Cancer Res*. 2000; **60:** 4346 – 4348.
13. Dunsmuir WD, Gillett CE, Meyer LC, Young MP, Corbishley C, Eeles RA, et al. Molecular markers for predicting prostate cancer stage and survival. *BJU Int*. 2000; **86:** 869 – 878.
14. Marreiros A, Dudgeon K, Dao V, Grimm MO, Czolij R, Crossley M, et al. KAI1 promoter activity is dependent on p53, JunB and Ap2: evidence for a possible mechanism underlying loss of KAI1 expression in cancer cells. *Oncogene*. 2005; **24:** 637 – 649.
15. Jackson P, Kingsley EA, Russell PJ. Inverse correlation between KAI1 mRNA levels invasive behavior in bladder cancer cell lines. *Cancer Lett*. 2000; **156:** 9 – 17.
16. Liu J, Yang GF, Gong LL, Liu H, Xiong YY. Expression of KAI1/CD82, E-cadherin and integrin beta-1 and their relationship with tumor invasion and metastasis in gastric cancer. *Chinese Journal of Pathology*. 2007; **36:** 558 – 559.
17. Takeda T, Hattori N, Tokuhara T, Nishimura Y, Yikoyama M, Miyake M. Adenoviral transduction of MRP - 1/CD9 and KAI1 /CD82 inhibits lymph node metastasis in orthotopic lung cancer model. *Cancer Res*. 2007; **67:** 1744 – 1749.
18. Zheng HC, Tsuneyama K, Cheng C, Takahashi H, Cui Z, Nomot K, et al. Expression of KAI1 and tenascin, and microvessel density are closely correlated with liver metastasis of gastrointestinal adenocarcinoma. *J Clin Pathol*. 2007; **60: 50 –** 56.
19. Falkenback D, Nilbert M, Oberg S, Johansson J. Prognostic value of cell adhesion in esophageal adenocarcinomas. *Dis Esophagus*. 2008; **21:** 97 – 102.
20. Mcphee TR, McDonald PC, Oloumi A, Dedhar S. Integrin-linked kinase regulates E-cadherin expression through PARP-1. *Dev Dyn*. 2008; **237:** 2737 – 2747.
21. Nelson WJ, Nusse R. Convergence of Wnt, beta-catenin, and cadherin pathways. *Science*. 2004; **303:** 1483 – 1487.
22. Guo C, Liu QG, Zhang L, Song T, Yang X. Expression and clinical significance of p53, JunB and KAI1/CD82 in human hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int*. 2009; **8:** 389 – 396.
23. Abe M, Sugiura T, Takahashi M, Ishii K, Shimoda M, Shirasuna K. A novel function of CD82/KAI-1 on E-cadherin –mediated homophilic cellular adhesion of cancer cell. Cancer Lett. 2008; 266:163-170.
24. Yu Y, Han DE, Liu W. Effect of metastasis suppressor gen KAI1 on adhesion of hepatocellular carcinoma cell line MHCC97-H. *Ai Zheng*. 2007; **26:** 498 – 503.
25. Fadare O, Zheng W. Insights into endometrial serous carcinogenesis and progression. *Int J Clin Exp Pathol*. 2009; **2:** 411 – 432.
26. Mohan A, Nalini V, Mallikarjuna K, Jyotirmay B, Krishnakumar S. Expression of motility-related protein MRP1/CD9, N-cadherin, E-cadherin, alpha-catenin beta-cantenin in retinoblastoma. *Exp Eye Res*. 2007; **84:** 781 – 789.
27. Kim JH, Kim MA, Lee HS, Kim WH. Comparative analysis of protein expression in primary and metastatic gastric carcinomas. *Hum Pathol*. 2009; **40:** 314 – 322.