Clinical Trial/Experimental Study

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Expressions of KAI1 and E-cadherin in nonsmall cell lung cancer and their correlation with vasculogenic mimicry

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Abstract

Background: Metastasis and recurrence are the most common reasons for treatment failure of nonsmall cell lung cancer (NSCLC). Vasculogenic mimicry (VM, new blood supply formation in malignant tumors), E-Cadherin (a calcium-dependent transmembrane glycoprotein that mediates intercellular adhesion), KAI1 (a suppressor gene of tumor metastasis) are all valuable factors for metastasis and prognosis in diverse common human cancers. However, the correlation of VM, E-Cadherin, and KAI1 in NSCLC is still unclear. In this study, we analyzed the correlations among these factors as well as their respective correlations with clinicopathological parameters and survival in NSCLC.

Methods: The level of VM, E-Cadherin, and KAI1 in 163 tissue samples of NSCLC was examined by immunhistochemistry. Clinical data were also collected.

Results: Levels of VM was significantly higher, and levels of KAI1 and E-Cadherin significantly lower in NSCLC tissues than in normal lung tissues. Levels of VM were positively associated with lymph node metastasis (LNM), size, grade, and tumor node metastasis (TNM) stages, and negatively associated with patients' overall survival (OS). Levels of KAI1 and E-Cadherin were negatively correlated with LNM, size, grade, and TNM stage, and positively associated with patients' OS. In multivariate analysis, high levels of VM, E-Cadherin, and KAI1, as well as TNM stages were independently correlated with lower OS in patients with NSCLC.

Conclusion: VM and the expression of E-Cadherin and KAI1 may represent promising metastatic and prognostic biomarkers, as well as potential therapeutic targets for NSCLC.

Abbreviations: E-cad = E-cadherin, LNM = lymph node metastasis, NSCLC = nonsmall cell lung cancer, OS = overall survival, TNM = tumor node metastasis, VM = vasculogenic mimicry.

Keywords: E-Cadherin, KAI1, nonsmall cell lung cancer, prognosis, VM

1. Introduction

Nonsmall cell lung cancer (NSCLC) is a kind of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. NSCLC accounts for about 80% to 85% of the total lung cancer; it is the first leading cause of cancer-related death in human.[1] Traditional treatment with surgery and radiotherapy and chemotherapy may improve the prognosis of patients.[2] Currently, there are several new therapies in clinical practice, including those targeting actionable mutations and more recently immunotherapeutic agents.[3] However, the survival rate of NSCLC has not been effectively improved.

KAI1 was first identified in prostate cancer cells by Dong et al[4] and has a significant role in the inhibition of tumor metastasis. Many studies have shown that KAI1 may affect the invasion and metastasis of tumor cells.[5] Decreased KAI1 expression is correlated with the development of tumor metastasis and poor prognosis in a variety of human malignancies, such as breast cancer,[6] lung cancer,[7] and gastric cancer.[8]

E-cadherin is an adhesive transmembrane glycoprotein widely existing in epithelial cells, which mediates the adhesion between epithelial cells stromal cells. Deletion or loss of E-cadherin expression results in tumor cell adhesion to each other lost or weakened, making the tumor cells easy to move, and then make the tumor occurred infiltrate, spread, and metastasis.[9]

Vasculogenic mimicry (VM) is a new tumor microcirculation pattern discovered in recent years. Scholars have detected the presence of VMs successively in highly aggressive malignancies such as breast cancer,[10] liver cancer,[11] ovarian cancer,[12] prostate cancer.[13] The study found that the appearance of VM is closely related to the metastasis and poor prognosis of these tumors.[14]

2. Methods

2.1. Patients and clinical samples

Primary tumor tissues diagnosed NSCLC with pathologic stage I to IIIA patients at the Department of Pathology of the First

Editor: Jianxun Ding.

Funding/support: This study was partially supported by the Natural Science Foundation of Anhui Province (No. 1708085MH230). All authors have contributed greatly, and all authors are in agreement with the content of the manuscript.

The authors of this work have nothing to disclose and have no conflicts of interest.

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Medicine (2018) 97:40(e12293)

Received: 22 January 2018 / Accepted: 16 August 2018

http://dx.doi.org/10.1097/MD.0000000000012293

Affiliated Hospital of Bengbu Medical College, from January 2009 to December 2010, along with 163 samples of the corresponding adjacent normal NSCLC tissues (removed the same patient, from surrounding lung tissue at least 5 cm away from the cancer edge), were used in this retrospective study. In total, 163 patients with complete medical records and adequate paraffin-embedded tissue blocks were eligible. All patients were followed-up at 6-month intervals by phone, mail, or email. Survival time was calculated from surgery to death; data from patients who died from disease unrelated to NSCLC, accident, and those who were lost to follow-up at December 2016 were censored (mean survival time: 34.3 months; range 6–79 months). Tumor differentiation grade was defined according to World Health Organization criteria. Clinical stages were defined according to International Union Against Cancer/American Joint Committee on Cancer TNM criteria. The age of the patients ranged from 39 to 81 years (median age, 60.2 years). Other clinicopathogical characteristics are provided in Table 1.

This study was approved by Ethics Committee of Bengbu Medical College and conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

2.2. Immunohistochemistry

Immunohistochemistry was conducted according to the guideline of ElivisionPlus detection kit instructions (Lab Vision). All NSCLC and corresponding normal tissues were fixed in 10% buffered formalin and embedded in paraffin. Then, continuous 4 μm thick tissue sections were cut. All specimens were deparaffinized and dehydrated with xylene and graded alcohol, subsequently washed for 10 minutes with PBS (phosphate buffer solution, pH 7.2). Endogenous peroxidase activity was quenched by incubation of samples in methanol containing 3% H_2O_2 for 10 minutes at room temperature (RT), then placed in citrate buffer (pH 6.0), and heated to 95°C for 30 minutes for antigen repair. After several washes with PBS, all samples were blocked with goat serum for 20 minutes at RT, and then incubated with mouse monoclonal antibody against human CD34 (Abcam) or KAI1 (Abcam) for 1 hour at 37°C. All sections were performed periodic acid-Schiff (PAS)-CD34 dual staining to characterize endothelial cells in glycosylated basement membranes of vessels, as well as vasculogenic-like structures.[15] Furthermore, there was no necrosis or hemorrhage near the VM channels in cancer tissues.

Table 1

Patients characteristics.

Patients characteristics	Frequency (n)	Percentage (%)
Age, y		
< 60	119	73.0
≥ 60	44	27.0
Smoke		
No	72	44.2
Yes	91	55.8
Gender		
Male	115	70.6
Female	48	29.4
Size, cm		
< 3.0	52	31.9
≥3.0, <7.0	99	60.7
≥ 7.0	12	7.4
Type		
Central	83	50.9
Peripheral	80	49.1
Grade		
Well	25	15.3
Moderate	115	70.6
Poor	23	14.1
LNM stage		
N0	78	47.9
N1	66	40.5
N2	19	11.6
TNM stage		
I	56	34.4
II	76	46.6
IIIa	31	19.0

E-cad = E-cadherin, LNM = lymph node metastasis, NSCLC = nonsmall cell lung cancer, OS = overall survival, TNM = tumor node metastasis, VM = vasculogenic mimicry.

2.3. Evaluation of staining

By light microscopy, representative tissue sections were scored semiquantitatively for cytoplasmic and membrane staining. All samples were anonymized and independently observed by 2 pathologists. If there is a disagreement, the observers would reexamine and reach a consensus. In scoring expression of antibodies, both the intensity and extent of immunopositivity were considered. The dominant staining intensity in tumors was scored as follows: 0 = negative, 1 = weak, 2 = moderate, and 3 = strong. The extent of positive staining tumor cells was scored as follows: <10% is 1, 11% to 50% is 2, 51% to 75% is 3, and >75% is 4. The final score was determined by multiplying the intensity and the extent positivity scores, which yielded a range from 0 to 12. The scores ≥3 was considered positive. Mean score from each individual was calculated in tumor cells.

2.4. Statistical methods

Correlations between clinicopathological variables and KAI1, or E-cadherin, or VM were compared using Fisher exact test or Chi-square test. The correlations among KAI1, or E-cadherin, or VM were compared using Spearman coefficient test. The effects of KAI1, or E-cadherin, or VM on survival were determined using univariate and multivariate analyses. Independent prognostic factors were determined by the Cox regression model for multivariate analysis. The Kaplan–Meier method with log-rank test for univariate overall survival analysis was used to assess the correlation between KAI1+, or E-cadherin+, or VM+ and clinicopathological variables using the statistical software SPSS (SPSS Inc., IBM, IL), version 21.0. A value of $P < .05$ was considered statistically significant.

3. Results

3.1. Correlations between KAI1, E-cadherin, VM, and clinicopathological variables

The positive expression of KAI1 and E-cadherin was found mainly on the membrane and cytoplasm of NSCLC cells and normal lung tissues. They were presented as a brown granular material.

The positive rate of KAI1 expression in the NSCLC samples (36.20%,59/163) was significantly lower than that in the control normal tissues (88.34%, 144/163; $P < .001$; Fig. 1A, B). The positive expression of E-cadherin (38.65%, 63/163) was significantly lower than that in the control normal tissues (85.28%, 139/163; $P < .001$; Fig. 1C, D). The positive expression

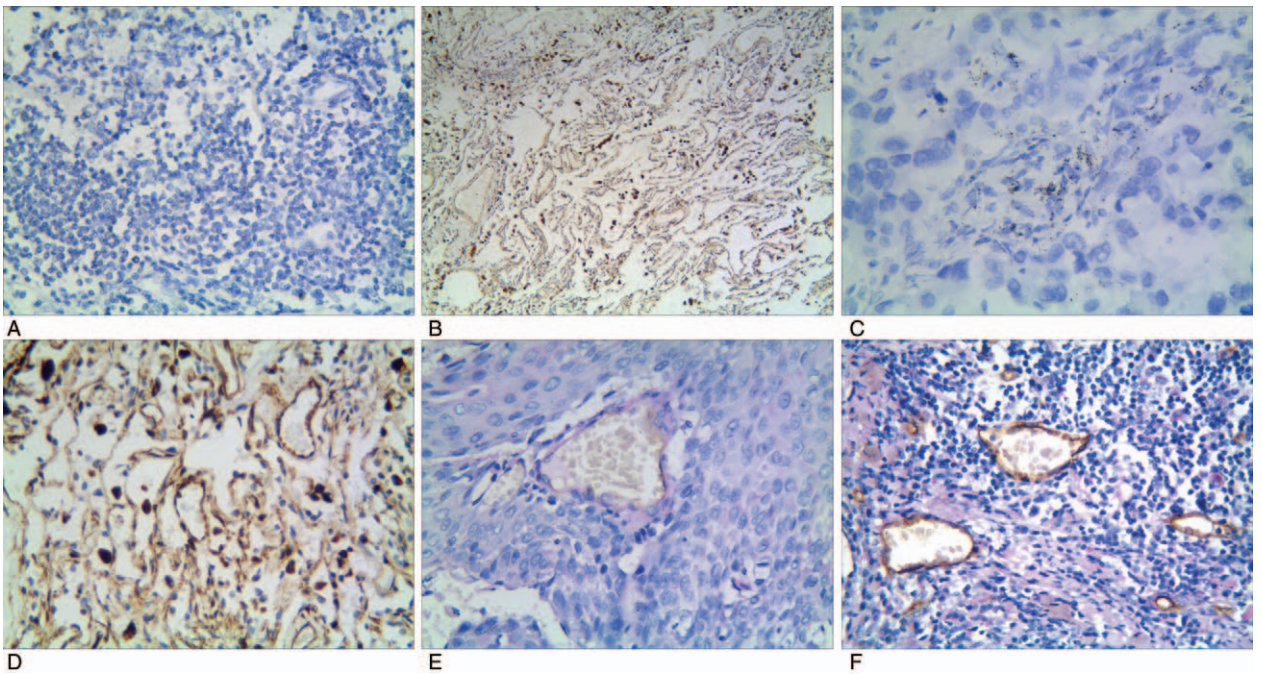

Figure 1. Immunostaining of KAI1, or E-cad or VM in NSCLC or the control tissue. (A) Negative staining of KAI1 in NSCLC (200× magnification); (B) Positive staining of KAI1 in the control tissue (100× magnification); (C) Negative staining of E-cad in NSCLC (400× magnification); (D) Positive staining of E-cad in the control tissues (200× magnification); € Positive staining of VM in the NSCLC (400× magnification); (F) Negative staining of VM in the control tissues (200× magnification).

of VM (42.33%, 69/163) was significantly higher than that in the control tissues (0%, 0/163; $P<.001$, Fig. 1E, F). The positive expression rate of KAI1 in NSCLC was positively correlated with size and grades of tumors ($P<.001$) and LNM and TNM stage ($P<.001$), but not with patients age, gender, or location (Table 2). The positive expression rate of E-Cadherin in NSCLC was positively correlated with size and grades of tumors ($P<.001$) and LNM and TNM stage ($P<.001$), but not with patients age, gender, or location (Table 2).

Contrast to KAI1, the positive rate of VM (small vessel like lumen in NSCLC that were PAS-positive but CD34-negative were to be VM. The VM channels pattern included linear, tubular, and network, and so on.) in NSCLC was positively correlated with size and grades of tumors ($P<.001$) and LNM and TNM stage ($P<.001$), but not with patients age, gender, or location (Table 2).

3.2. Univariate and multivariate analysis

Follow-up data showed that OS time was significantly shorter in NSCLC patients with negative expression of KAI1 (24.41 ± 10.52 months) than those with KAI1-positive (51.69 ± 15.86 months; log-rank = 90.493, $P<.001$; Fig. 2A). Similarly, the OS time of VM-positive patients (21.86 ± 11.05 months) was significantly lower than those of VM-negative patients (43.41 ± 17.10 months; log-rank = 71.338, $P<.001$; Fig. 2B). The OS time of E-cadherin positive patients (51.65 ± 15.09 months) was significantly longer than those who were E-Cad-negative (23.35 ± 9.49 months; log-rank = 115.946, $P<.001$; Fig. 2C). The combination of KAI1 and E-cadherin negative expression and positive expression of VM had a poorer prognosis than did the reverse combination (log-rank = 90.493, $P<.001$; Fig. 2D). In the univariate analysis, OS time was significantly correlated with clinicopathological variables, including grade ($P<.001$, log-rank = 131.148), size ($P<.001$, log-rank = 117.885), TNM ($P<.001$, log-rank = 171.958), and LNM stage ($P<.001$, log-rank = 161.680) (Table 3).

Multivariate analysis suggested that KAI1 and E-cadherin positive expression, VM, size, as well as TNM and LNM stage, were independent prognostic indicators for NSCLC (Table 4).

3.3. Association among KAI1, and E-cadherin VM in NSCLC

Spearman correlation coefficient analysis indicated a negative association between the positive expression of VM and that of KAI1 ($r=-0.490$, $P<.001$), or E-cadherin ($r=-0.476$, $P<.001$). Expression of KAI1 and that of E-cadherin have a positive association ($r=0.608$, $P<.001$) (Table 5).

4. Discussion

Some highly aggressive tumors have a tube-like structure that is not dependent on vascular endothelial cells but directly formed by the tumor cells through their own deformation and extracellular matrix remodeling, and can communicate with the host blood vessels to obtain blood supply, that is, VM.[16,17] VM should be involved in the process of progression and metastasis of various cancers,[10–13,18–22] suggesting that VM should be considered as a potential candidate therapeutic target. The purpose of this concept not only poses a challenge to the classical theory of angiogenesis but also an important complement to the theory of tumor angiogenesis.

In this study, 69 patients with NSCLC found the VM standard structure, confirming the presence of VM in NSCLC. The structural features of VM are surrounded by tumor cells. There is only 1 layer of PAS-positive substance between tumor cells and blood flow, and there is no vascular endothelial cell barrier,

Table 2

The correlation between VM, or KAI1, or E-Cad and clinicopathological characteristics in NSCLC.

	VM			KAI1			E-Cad		
Variable	**Negative**	**Positive**	***P***	**Negative**	**Positive**	***P***	**Negative**	**Positive**	***P***
Age, y			.348			.479			.278
<60	66	53		74	45		76	43	
≥60	28	16		30	14		24	20	
Smoke			.267			.728			.788
No	45	27		47	25		45	27	
Yes	49	42		57	34		55	36	
Gender			.420			.561			.874
Male	64	51		75	40		71	44	
Female	30	18		29	19		29	19	
Size, cm			<.001			<.001			<.001
<3.0	42	10		16	36		16	36	
≥3.0, <7.0	49	50		78	21		73	26	
≥7.0	3	9		10	2		11	1	
Type			.364			.187			.322
Central	45	38		57	26		54	29	
Peripheral	49	31		47	33		46	44	
Grade			<.001			<.001			<.001
Well	22	3		5	20		6	19	
Moderate	67	48		78	37		74	41	
Poor	5	18		21	2		20	3	
LNM stage			<.001			<.001			<.001
N0	61	17		36	42		33	45	
N1	31	35		51	15		49	17	
N2	2	17		17	2		18	1	
TNM stage			<.001			<.001			<.001
I	51	5		16	40		13	43	
II	38	38		60	16		58	18	
IIIa	5	26		28	3		29	2	

E-cad = E-cadherin, LNM = lymph node metastasis, NSCLC = nonsmall cell lung cancer, OS = overall survival, TNM = tumor node metastasis, VM = vasculogenic mimicry.

which leads to the tumor with easy recurrence and metastasis, poor prognosis, and high mortality rate.[14,23–25] This study also showed that VM was closely related to whether the tumor had lymph node metastasis and the degree of tumor differentiation and size of tumor. Survival analysis also showed that the survival time of NSCLC patients with VM negative expression group was significantly longer than that of the positive expression group. We can conclude that tumors with VM have poorer differentiation, lower clinical staging, and lymph node metastasis, which is more likely to occur.[15,26–28]

KAI1 gene has been considered as a prostate cancer specific metastasis suppressor gene. Its expression level is closely related to tumor invasion and metastasis, belonging to a member of TM4SF family.[4,5,29] The study found that the expression of KAI1 in 163 cases of tumor tissue was 36.20%, and with the lower tumor differentiation, larger size of the tumor, the more advanced clinical stage, its expression levels were also reduced, and the difference was statistically significant; Survival analysis also showed that the survival time of NSCLC patients with negative expression of KAI1 was significantly shorter than that of patients with positive expression of KAI1, which was consistent with the related literature.[30,31] The abnormal expression of *KAI1* gene is closely related to the occurrence, development, and metastasis of NSCLC.[32–37] We can conclude that the tumors expressing KAI1 protein have better differentiation, earlier clinical stage, and less lymph node metastasis.

The loss or decrease of E-cadherin expression leads to the loss or weakening of adhesion of tumor cells to each other. It is easy to make the tumor cells to infiltrate, spread, and metastasize.[9,38–41] This study found that in NSCLC tissues, with the worse differentiation of tumor, larger size of the tumor, the lower expression rate of E-cadherin protein. This study found that in NSCLC tissues, with the worse differentiation of tumor, and also with the larger size of the tumor, the lower expression rate of E-cadherin protein, and the difference were statistically significant. Survival analysis also showed that the survival time of NSCLC patients with negative expression of E-cadherin was significantly shorter than that of patients with positive expression of E-cadherin, which was consistent with the related literature.[7,42]

In this study, we analyzed the correlation between the expression of KAI1 protein and E-cadherin and VM, and found that with the decrease of KAI1-positive rate in tumor tissue, the positive rate of E-cadherin also decreased. At the same time, the positive rate of VM increased. It is suggested that the expression of KAI1 may be related to the positive rate of E-cadherin and VM. With tumor progression, tumor tissue prone to ischemia and hypoxia, and this process will easy to induce the formation of VM.[43,44] KAI1 expression decrease at this time will result in cell adhesion weakened and poor cell differentiation. The VM structure with tumor cells and channel is only separated by a layer of PAS-positive substances; low adhesion of tumor cells under the impact of blood flow will be easily detached from the primary tumor lymph and result in node metastasis and distant metastasis. However, the number of specimens in our study was relatively small. Further studies with larger sized specimens, related cytology experiment, and molecular experiments are needed to verify the present observations.

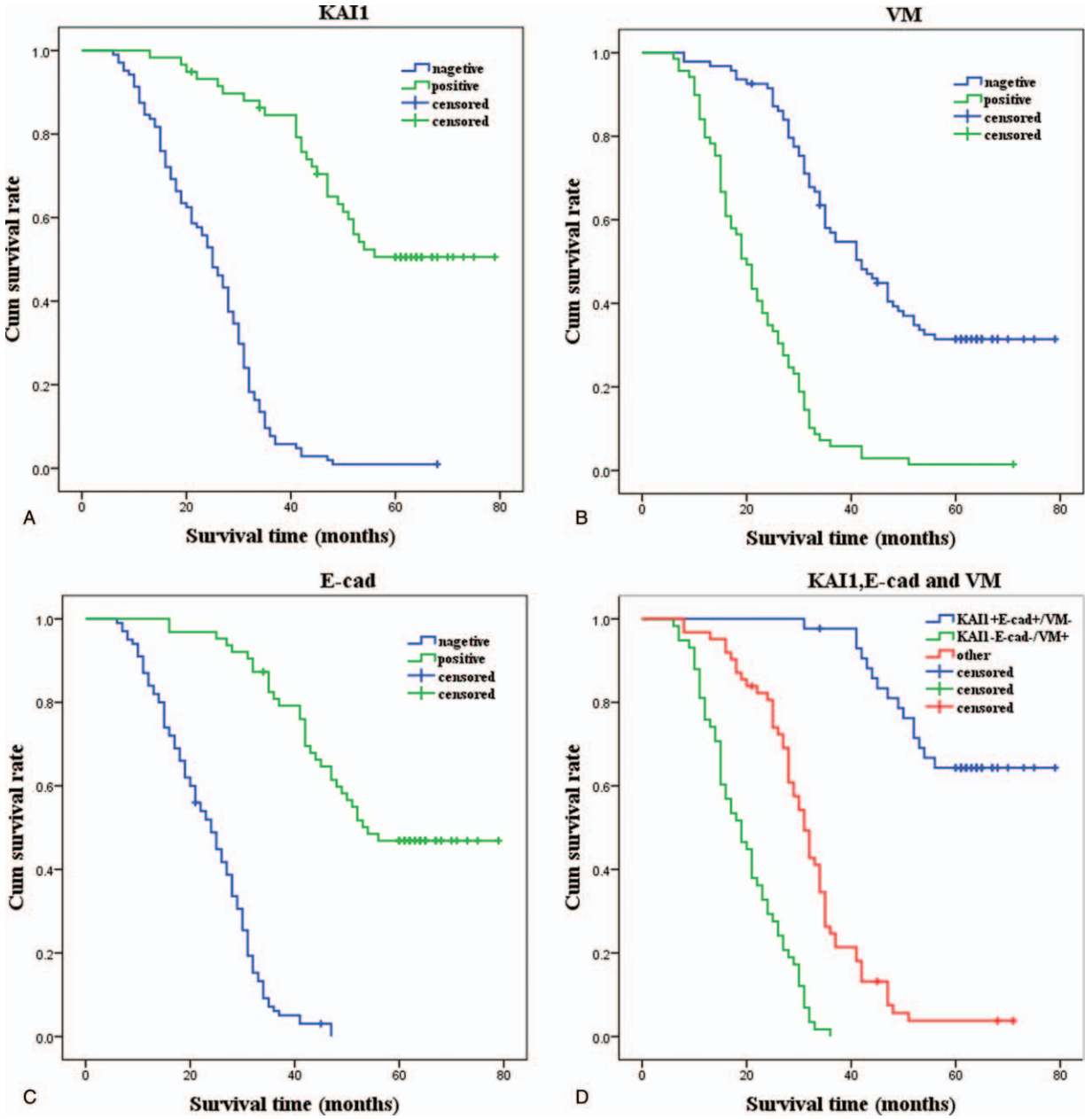

Figure 2. Kaplan–Meier analysis of the survival rate of patients with NSCLC. (A) Overall survival of all patients in relation to KAI1 expression (log-rank = 90.493, $P < .001$); (B) Overall survival of all patients in relation to VM (log-rank = 71.338, $P < .001$); (C) Overall survival of all patients in relation to E-cad (log-rank = 115.946, $P < .001$); (D) Overall survival of all patients in relation to the combination of KAI1, E-cad, and VM (log-rank = 90.493, $P < .001$). The green line represents positive expression of KAI1, E-cad, and VM and the blue line represents negative expression of KAI1 E-cad and VM. The red line represents other positive or negative expression of the proteins.

5. Conclusion

The expression of KAI1 decrease may be the molecular basis of NSCLC recurrence and metastasis, and VM may be the key event in its invasion and metastasis. Therefore, KAI1, E-cadherin, and VM can be used as indicators to assess the metastasis and prognosis of NSCLC.

Acknowledgments

We thank all colleagues in Department of Pathology, the First Hospital Affiliated to Bengbu Medical College for their help and support in this study.

Author contributions

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Software: Jing Xu.
Supervision: Shiwu Wu.
Validation: Shiwu Wu.

Table 3

Results of univariate analyses of overall survival (OS) time.

Variable	n	Mean OS, mo	Log-rank	*P*
KAI1			90.493	<.001
Negative	104	24.4±10.5		
Positive	59	51.7±15.9		
E-cad			115.946	<.001
Negative	100	23.4±9.5		
Positive	63	51.7±15.1		
VM			71.328	<.001
Negative	94	43.4±17.1		
Positive	69	21.9±11.1		
Age, y			0.754	.385
<60	119	34.5±19.0		
≥ 60	44	33.7±16.2		
Smoke			0.127	.721
No	72	33.7±18.0		
Yes	91	34.8±18.5		
Gender			0.210	.646
Male	115	33.9±17.9		
Female	48	35.2±19.0		
Size, cm			117.885	<.001
<3.0	52	47.9±18.4		
≥3.0, <7.0	99	29.8±14.0		
≥7.0	12	12.4±3.9		
Type			2.707	.100
Central	83	32.6±17.9		
Peripheral	80	36.1±18.5		
Grade			111.148	<.001
Well	25	50.1±18.2		
Moderate	115	35.0±15.7		
Poor	23	13.1±6.0		
LNM stage			161.680	<.001
N0	78	44.2±16.4		
N1	66	28.9±14.2		
N2	19	12.2±3.9		
TNM stage			171.958	<.001
I	56	49.2±15.5		
II	76	31.4±13.9		
IIIa	31	14.3±5.2		

E-cad = E-cadherin, LNM = lymph node metastasis, NSCLC = nonsmall cell lung cancer, OS = overall survival, TNM = tumor node metastasis, VM = vasculogenic mimicry.

Table 4

Results of multivariate analyses of overall survival (OS) time.

Variable	B	SE	*P*	RR	95% CI	
E-cad	−1.445	0.300	<.001	0.236	0.131	0.424
KAI1	−1.362	0.303	<.001	0.256	0.141	0.464
TNM	0.572	0.243	.018	1.772	1.102	2.850
LNM	0.764	0.216	<.001	2.147	1.407	3.277
Size	0.660	0.233	.005	1.935	1.225	3.056
VM	0.483	0.231	.036	1.621	1.032	2.547

E-cad = E-cadherin, LNM = lymph node metastasis, NSCLC = nonsmall cell lung cancer, OS = overall survival, TNM = tumor node metastasis, VM = vasculogenic mimicry.

Table 5

Correlation among KAI1, E-cad, and VM in NSCLC.

	VM				KAI1		*r*	*P*
Variable	Negative	Positive	*r*	*P*	Negative	Positive	−0.490	<.001
VM					41	53		
Negative					63	6		
Positive								
E-cad			−0.476	<.001			0.608	<.001
Negative	39	61			87	13		
Positive	55	8			17	46		

E-cad = E-cadherin, LNM = lymph node metastasis, NSCLC = nonsmall cell lung cancer, OS = overall survival, TNM = tumor node metastasis, VM = vasculogenic mimicry.

Writing – original draft: Hongfei Ci.
Writing – review & editing: Hongfei Ci.

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