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Original Article

The expression of metastasis-associated in colon cancer-1, Snail, and KAI1 in esophageal carcinoma and their clinical significance

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Abstract: Objective: Metastasis-associated in colon cancer-1 (MACC1) is a key transcriptional regulator of mesenchymal-epithelial transition (MET) gene and so involved in the hepatocyte growth factor/MET signaling pathway. Snail has been reported to be associated with tumor epithelial-mesenchymal transition (EMT) and involved in the process of invasion and metastasis. KAI1 is a suppressor gene of tumor metastasis. The aim of this study is to explore the associations of MACC1, Snail, and KAI1 expression in esophageal squamous cell carcinoma (ESCC) and clinicopathologic characteristics of ESCC patients and their associations with each other. Methods: Immunohistochemistry was conducted to detect the expression of MACC1, Snail, and KAI1 in 214 whole-ESCC-tissue samples and corresponding normal esophageal mucosa tissues. All clinicopathologic, demographic, and follow-up data were collected. Results: MACC1 and Snail were significantly up-regulated in ESCC samples when compared with control samples; KAI1 was significantly down-regulated in ESCC group when compared with control group. Furthermore, positive expression of MACC1 and Snail was positively associated with tumor stages, lymph-node-metastasis (LNM) stages, and tumor-node-metastasis (TNM) stages. Positive expression of KAI1 was negatively associated with tumor grade, tumor stage, and LNM stages as well as TNM stage. The MACC1- or Snail-positive expression group had more unfavorable overall survival (OS) time than did the MACC1- or Snail-negative group; the positive expression of KAI1 group had significantly longer OS time than did the KiSS-1 negative group. Multivariate analysis of OS showed that overexpression of MACC1 and Snail, and down expression of KAI1 and tumor stages as well as TNM stages were independent prognostic factors for patients with ESCC. Conclusions: Levels of expression of MACC1, Snail, and KAI1 are associated with the duration of OS in patients with ESCC. MACC1, Snail, and KAI1 should be considered as useful biomarkers and therapeutic targets in ESCC.

Keywords: ESCC, MACC1, Snail, KAI1, EMT

Introduction

Esophageal carcinoma is one of the most common cancers in China, with an estimated 478 thousand new cases and 375 thousand deaths in 2015 [1], which also makes it one of the most common cancer-related deaths. Relapse and metastasis are the main reasons of cancer treatment failure. This may be related to the activation of gene of tumor metastasis or inactivation of suppressor of tumor metastasis. Metastasis-associated in colon cancer 1 (MACC1) which is originally found in colon cancer cell lines is considered as an oncogene [2]. MACC1 is a key transcriptional regulator of hepatocyte growth factor/mesenchymal-epithelial transition (HGF/MET) signaling pathway by bounding to MET gene promoter [2, 3]. It has demonstrated that MACC1 not only is involved in cells proliferation, migration, and dissemination through promoting epithelial-mesenchymal transition (EMT) in vitro but also promotes cells proliferation, invasiveness, and metastasis in vivo [2-6]. Studies have indicated that MACC1 should be considered as a useful metastatic and prognostic factor for various cancers.

EMT which has been characterized by losing epithelial features and gaining mesenchymal features, can promote tumor cells invasiveness

Table 1. Patients characteristics

Patients characteristics	Frequency (n)	Percentage (%)
Age (years)		
< 60	98	45.8
≥ 60	116	54.2
Gender		
Male	143	66.8
Female	71	33.2
Location		
Up	1	0.5
Middle	135	63.1
Down	78	36.4
Size (cm)		
< 2.0	102	47.7
≥ 2.0	112	52.3
Smoking		
No	81	37.9
Yes	133	62.1
Alcohol		
No	82	38.3
Yes	132	61.7
Gross type		
Ulcerative	95	44.4
Myeloid	63	29.4
Infiltrating	49	22.9
Constricted	7	3.3
Grade		
Well	75	35.0
Moderate	120	56.1
Poor	19	8.9
Tumor stages		
T1	77	36.0
T2	108	50.5
T3	21	9.8
T4a	8	3.7
Lymph node metastasis stages		
N0	137	64.0
N1	62	29.0
N2	15	7.0
TNM stages		
I	73	34.1
II	60	28.0
III	69	32.2
IVA	12	5.6

and metastasis [7, 8]. The molecular hallmark of EMT is down- or lost-regulation of the cell to cell adhesion molecule E-cadherin (CDH1) and up-regulation of the mesenchymal molecular, such as N-cadherin (CDH2), vimentin, and Snail [9, 10]. Snail is a key transcriptional regulator which promotes EMT. Overexpression of Snail directly activates EMT and promotes tumor metastasis through suppressing the transcription of E-cadherin. Overexpression of Snail also promotes tumor cell proliferation [11]. Recent studies have demonstrated that Snail plays important roles in serials of fundamental biologic behaviors, such as EMT, cells growth, and metastasis [11-13].

KAI1, also named CD82, was originally considered as a suppressor of tumor metastasis in prostate cancer cell lines in 1999. KAI1 gene belongs to tetraspanin superfamily which consists of four transmembrane domains [14]. Normal expression of KAI1 can suppress cell growth, motility, migration, and strengthen cell to cell adhesion by strengthening stabilization of E-cadherin-β-catenin complex [15-17]. It has been also confirmed that overexpression of KAI1 could suppress secondary metastases without interfering primary tumor growth [18]. KAI1 also plays important roles in the process of tumor initiation, invasion, and metastasis in various cancers.

The aim of this study is to evaluate the expression of MACC1, Snail, and KAI1 in the esophageal squamous cell carcinoma (ESCC) tissues of patients and their relationships between clinicopathologic characteristics and prognosis of patients with ESCC. Immunohistochemical staining was used to assess the expression of MACC1, Snail, and KAI1 in ESCC specimens and the corresponding adjacent normal esophageal mucosa specimens of patients with ESCC.

Methods

Patients and specimens

The records of 214 patients (median age: 60.3 years; ranges 43-78 years) with ESCC in our hospital from January 2011 to December 2012 were collected. This study is retrospective. Pa-

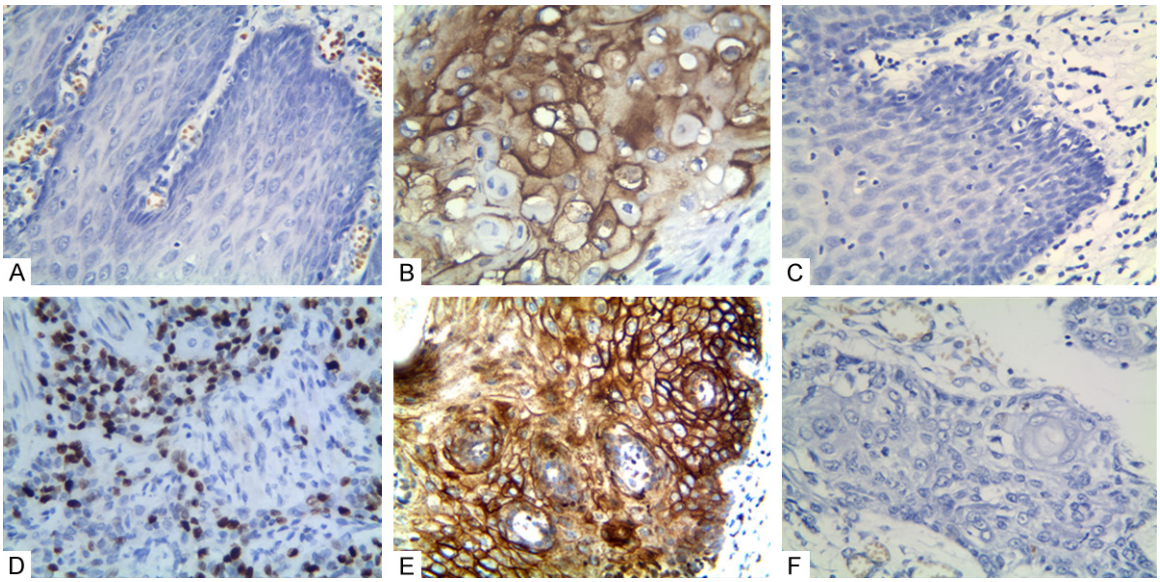

Figure 1. Immunostaining for MACC1, Snail, and KAI1 in esophageal squamous cell carcinoma and control tissue. A: Negative MACC1 in the control tissue (400 magnification); B: Positive MACC1 in the cytoplasm of HCC tissue (400 magnification); C: Negative Snail in the control tissues (400 magnification); D: Positive Snail in the nuclei of cancer cells (400 magnification); E: Positive KAI1 in the membrane and cytoplasm of control cells (400 magnification); F: Negative KAI1 in the cancer tissue (400 magnification).

tients who had any history of chemo-therapy or radio-therapy were excluded. All ESCC patients provided written consent for their samples to be used. The study was approved by the Bengbu Medical University ethics committee before it started and performed in accordance with the Declaration of Helsinki guidelines. Patients' clinicopathologic, demographic, and follow-up data (at 4-month intervals by telephone, mobile phone or social applications) were collected. Overall survival (OS) time was calculated from surgery date to death day or December 2017 (mean OS time: 45.3 months; range: 10-71 months). TNM stages, tumor stages, and LNM stages were assessed in accordance with the 8th edition of the guidelines issued by the American Joint Committee on Cancer (AJCC). Tumor grades were assessed in accordance with the standards issued by the World Health Organization (WHO). Specific clinicopathologic characteristics are shown in **Table 1**.

Immunohistochemistry

All ESCC tissues and the correspondence normal esophageal mucosa tissues were fixed in 10% buffered formalin, embedded in paraffin, and then cut into 4 μm thick slices. Subsequently, all slices were deparaffinized with xylene and dehydrated with graded ethanol. Immunohistochemical staining was carried out in accordance with Elivision^{TM} Plus detection kit instructions (Lab Vision, USA). Endogenous peroxidase activity was quenched by methanol containing 3% H_2O_2 solution. Then, citrate buffer solution was used to repair antigen and goat serum was used for blocking. MACC1 (rabbit polyclonal antibody, Santa Cruz Biotechnology, USA), Snail (mouse monoclonal antibody, Abcam, USA), and KAI1 (mouse monoclonal antibody, Santa Cruz Biotechnology, USA) primary antibodies were added and then incubated overnight at 4°C. Lastly, reagent A (enhancer) and reagent B were added. All slices were to develop in diaminobenzidine substrate and counterstained with hematoxylin.

Evaluation of immunostaining

To avoid any intratumoral heterogeneity of biomarker expression, we selected ten randomly high-power-field (HPF) of each ESCC slice. Immunostaining results were evaluated by multiplying percentage scores and intensity scores. Percentage scores were graded as follows: positive cells ≤ 10% is 1; 10% < positive cells ≤ 50% is 2; 50% < positive cells ≤ 75% is 3; positive cells > 75% is 4. Intensity scores were grades as follows: no staining is 1; weak

Table 2. The associations between expression of MACC1, Snail, and KAI1 and clinicopathological characteristics of esophageal squamous cell carcinoma (ESCC)

Variables	MACC1		P	Snail		P	KAI1		P
	-	+		-	+		-	+	
Age			0.386			0.185			0.450
< 60 years	39	59		36	62		49	49	
≥ 60 years	53	63		53	63		64	52	
Gender			0.185			0.456			0.466
Male	66	77		62	81		73	70	
Female	26	45		27	44		40	31	
Location			0.436			0.549			0.441
Up	0	1		0	1		1	0	
Middle	55	80		54	81		74	61	
Down	37	411		35	43		38	40	
Size (cm)			0.048			0.003			< 0.001
< 2.0	51	51		53	49		41	61	
≥ 2.0	41	71		36	76		72	40	
Smoking			0.234			0.630			0.006
No	39	42		32	49		33	48	
Yes	53	80		57	76		80	53	
Alcohol			0.722			0.002			0.447
No	34	48		23	59		46	36	
Yes	58	74		66	66		67	65	
Gross type			0.073			0.067			0.013
Ulcerative	40	55		34	61		52	43	
Myeloid	32	31		28	35		30	33	
Infiltrating	15	34		21	28		31	18	
Constricted	5	2		6	1		0	7	
Grade			0.025			0.072			< 0.001
Well	41	34		37	38		29	46	
Moderate	46	74		48	72		67	53	
Poor	5	14		4	15		17	2	
Tumor stages			0.004			< 0.001			< 0.001
T1	43	34		55	22		18	59	
T2	43	65		30	78		70	38	
T3	6	15		4	17		17	4	
T4a	0	8		0	8		8	0	
LNM stages			< 0.001			< 0.001			< 0.001
N0	72	65		76	61		49	88	
N1	20	42		11	51		50	12	
N2	0	15		2	13		14	1	
TNM stages			< 0.001			< 0.001			< 0.001
I	42	31		59	14		13	60	
II	27	33		20	40		35	25	
III	23	46		8	61		53	16	
IVA	0	12		2	10		12	0	

staining is 2; moderate staining is 3; strong staining is 4. The final scores ranged 0-12. Here ≥ 3 is considered positive expression. The average score of all slices was taken.

Table 3. Correlation among expression of MACC1, Snail, and KAI1 in ESCC

Variable	MACC1		r	P	Snail		r	P
	-	+			-	+		
MACC1							0.244	< 0.001*
-					51	41		
+					38	84		
KAI1			-0.503	< 0.001@			-0.608	< 0.001@
-	22	91			15	98		
+	70	31			74	27		

*: positive association; @: negative association.

Statistical analysis

All data were analyzed using SPSS 19.0 software (Chicago, IL, US) for Windows. Countable data was conducted using the Chi-square test or Fisher's exact test for comparisons between two groups. Univariate OS analysis was conducted using the Kaplan-Meier method with log-rank test. Multivariate OS analysis was conducted using Cox regression model test. $P < 0.05$ was considered a significant difference.

Results

Associations between MACC1, Snail, and KAI1 in the specimens of ESCC for patients and clinicopathologic characteristics

As shown in **Figure 1A** and **1B**, positive expression of MACC1 protein was mainly located at the cytoplasm. The positive rate of MACC1 expression in the ESCC group (57.0%, 122/214) was significantly higher than that in the control group (7.9%, 17/214; P < 0.001). Moreover, the positive rate of MACC1 in ESCC was positively associated with tumor size, grade of differentiation, tumor stage, lymph node metastasis (LNM) stage, and tumor-node-metastasis (TNM) stage (**Table 2**). There was no association between positive rate of MACC1 expression and ESCC patient's age, gender, tumor location, type, smoking, or alcohol.

As shown in **Figure 1C** and **1D**, positive expression of Snail protein was mainly located at the nucleus. The positive rate of Snail expression in the cancer group (58.4%, 125/214) was significantly higher than that in the control group (7.0%, 15/214; P < 0.001). Furthermore, the positive rate of Snail in cancer was positively associated with tumor size, alcohol, tumor stages, LNM stages, and TNM stages. There was no association between positive rate of Snail expression and patient's age, gender, tumor location, type, grades of differentiation, and smoking (**Table 2**).

As shown in **Figure 1E** and **1F**, positive expression of KAI1 was mainly located at the membrane and cytoplasm. The positive rate of KAI1 expression in cancer group (47.2%, 101/214) was significantly lower than that in the control group (93.5%, 200/214; P < 0.001). The positive rate of KAI1 in cancer was inversely associated with tumor type, size, smoking, grades of differentiation, LNM stages, tumor stages, and TNM stages. And there was no association between KAI1 expression and patient's age, gender, alcohol, and tumor location (**Table 2**).

Associations among MACC1, Snail, and KAI1 in ESCC

There was a negative association between KAI1 expression and MACC1 expression (r = -0.503, P < 0.001) or Snail expression (r = -0.608, P < 0.001). There was a positive association between MACC1 expression and Snail expression (r = 0.244, P < 0.001) (**Table 3**).

Univariate and multivariate analyze

As shown in **Figure 2A**, Kaplan-Meier analysis demonstrated that OS time of MACC1 positive expression (39.0 ± 15.1 months) for patients with ESCC was significantly lower than that of MACC1 negative for patients (53.7 ± 11.3 months; log-rank = 36.601, P < 0.001). As shown in **Figure 2B**, the univariate OS time of Snail positive expression (39.0 ± 14.5 months) was significantly shorter than that in Snail negative patients (54.1 ± 12.1 months; log-rank = 56.305, P < 0.001). As shown in **Figure 2C**, the univariate OS time of KAI1 positive expression (53.4 ± 11.7 months) was significantly longer than that in KAI1 negative patients (38.1 ± 14.8 months; log-rank = 54.476, P < 0.001). As shown in **Figure 2D**, the univariate OS time of the combination of KAI1- and MACC1+Snail+ was significantly lower than that in KAI1+ and MACC1-Snail- patients (log-rank = 85.730, P < 0.001) (**Table 4**).

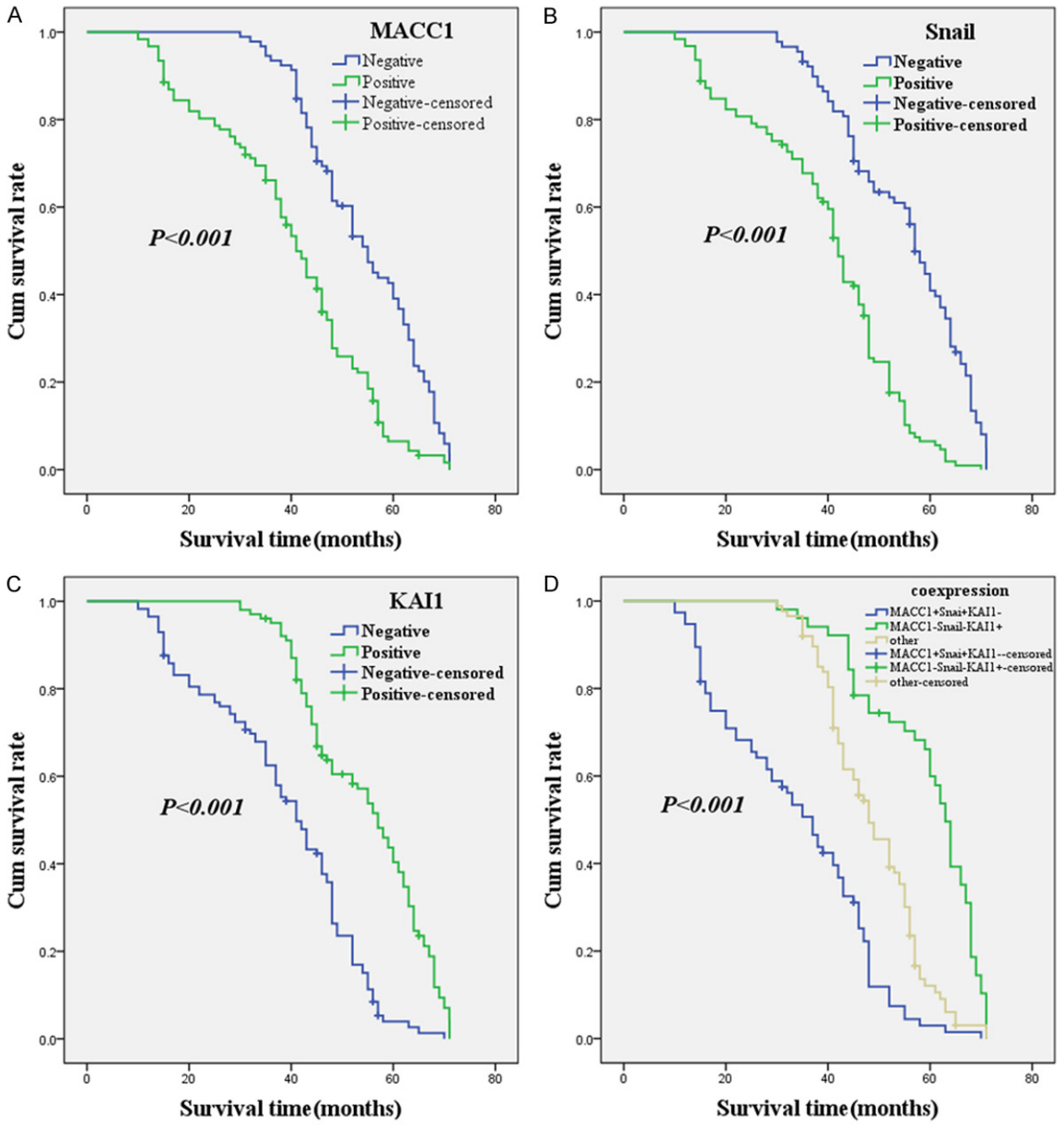

Figure 2. Kaplan-Meier analysis curve of the survival rate of patients with ESCC. The y-axis means the percentage of patients; the x-axis means their survival in months. A: OS analysis of all patients in relation to MACC1 (log-rank = 36.601, P < 0.001); B: OS analysis of all patients in relation to Snail expression (log-rank = 56.305, P < 0.001); C: OS analysis of all patients in relation to KAI1 expression (log-rank = 54.476, P < 0.001); A-C analyses, the green line represents patients with positive MACC1, or Snail, or KAI1; the blue line representing the negative MACC1, or Snail, or KAI1 group. D: OS survival of all patients in relation to the combination of KAI1, MACC1, and Snail expression (log-rank = 85.730, P < 0.001). The green line represents negative KAI1 and positive MACC1 and Snail. The blue line represents positive KAI1 and negative MACC1 and Snail. The brown line represents other positive or negative proteins.

Multivariate analysis demonstrated that MACC1, Snail, and KAI1 expression, tumor stages, and TNM stages should be considered independent factors affecting patient survival (**Table 5**).

Discussion

Esophageal cancer is the second most common malignant tumor of the digestive system in China [1]. Esophageal squamous cell carcino-

Table 4. Results of univariate analyses of overall survival (OS) time

Variable	n	Mean OS (months)	Log-rank	*P* value
MACC1			36.601	< 0.001
Negative	92	53.7±11.3		
Positive	122	39.0±15.1		
Snail			56.305	< 0.001
Negative	89	54.1±12.1		
Positive	125	39.0±14.5		
KAI1			54.476	< 0.001
Negative	113	38.1±14.8		
Positive	101	53.4±11.7		
Age			1.645	0.200
< 60 years	98	44.4±14.0		
≥ 60 years	116	46.0±16.6		
Gender			0.741	0.389
Male	143	46.7±14.4		
Female	71	42.4±17.0		
Location			106.656	< 0.001
UP	1	10.0		
Middle	135	43.7±16.3		
Down	78	48.5±12.8		
Size (cm)			2.749	0.097
< 2.0	102	47.8±13.9		
≥ 2.0	112	43.0±16.4		
Smoking			1.987	0.159
No	81	45.6±17.5		
Yes	133	45.1±14.1		
Alcohol			3.776	0.052
No	82	43.0±16.0		
Yes	132	46.7±14.9		
Gross type			7.439	0.059
Ulcerative	95	42.0±16.2		
Myeloid	63	49.5±10.1		
Infiltrating	49	43.9±17.5		
Constricted	7	61.3±11.8		
Grade			6.914	0.032
Well	75	44.9±18.5		
Moderate	120	46.2±13.4		
Poor	19	41.4±13.6		
Tumor stages			60.459	< 0.001
T1	77	52.4±13.0		
T2	108	43.7±14.8		
T3	21	35.9±13.6		
T4a	8	23.8±10.3		
LNM stages			27.535	< 0.001
N0	137	50.0±13.3		
N1	62	38.8±16.1		
N2	15	32.1±14.2		

ma (ESCC) which accounts for approximately 90% is the most common type of esophageal cancer. ESCC is a high heterogeneity disease which influences its comprehensive evaluation of biomarkers. It has demonstrated that MACC1 should promote cells growth, motility, and migration and be involved in the process of invasiveness and metastasis of cancers [2, 3]. In this study, the results showed that positive rate of MACC1 expression in ESCC was positively associated with tumor size, grade of differentiation, tumor stage, LNM stage, and TNM stage. Moreover, patients with MACC1 positive expression had an unfavorable OS time when compared with patients with MACC1 negative. These indicated that MACC1 should play an important role in invasion and metastasis of ESCC and be considered a useful biomarker for prediction of prognosis [2-6, 19-21].

Epithelial-mesenchymal transition (EMT) is a process by which cells gain the ability to invade through the basement membrane appears as part of normal embryonic development and tumor development [22, 23]. EMT has been characterized by losing epithelial features and gaining mesenchymal features. It can allow tumor cells leave the primary tumor to promote invasion and metastasis. Snail is a critical transcriptional regulator of EMT. In this study, we found that overexpression of Snail was positively associated with tumor size, grade of differentiation, tumor stage, LNM stage, as well as TNM stage. Furthermore, we also found that overexpression of Snail for patients had an unfavorable OS time when compared with negative expression of Snail for patients. The above results suggested that Snail should be considered a useful and effective biomarker for invasion and metastasis as well as in prediction of prognosis [12, 24, 25].

It is well known that KAI1 is a suppressor of tumor metastasis in various cancers [15-18]. Accumulating evidence has demonstrated that KAI1 could inhibit tumor cells proliferation, fusion, motility, and migration. In this study, we found that positive rate of KAI1 expression was inversely associated with tumor size, grade of differ-

TNM stages			59.662	< 0.001
I	73	54.4±12.3		
II	60	46.6±12.1		
III	69	37.1±15.3		
IVA	12	31.0±13.7		

Table 5. Results of multivariate analyses of overall survival (OS) time

Covariate	B	SE	P	HR	95% CI
MACC1	0.597	0.170	< 0.001	1.816	1.302-2.533
Snail	0.461	0.215	0.032	1.586	1.040-2.419
KAI1	-0.455	0.219	0.037	0.634	0.413-0.974
TNM stages	0.399	0.164	0.015	1.491	1.081-2.056
Tumor stages	0.275	0.138	0.047	1.317	1.004-1.727

entiation, tumor stages, LNM stages, and TNM stages. Kaplan-Meier analysis indicated that positive expression of KAI1 for patients had a favorable OS time when compared with negative expression of KAI1 with patients. These results demonstrated that aberrant expression (down or lost) of KAI1 should promote tumor cells invasion and metastasis, therefore, should be considered a potential predictor for invasiveness and metastasis of ESCC, as well as prognosis [16, 18, 26-28].

In this study, Kaplan-Meier analysis showed that positive expression of MACC1, Snail, and KAI1 significantly associated with OS time in patients with ESCC. Multivariate analysis indicated that tumor stages, TNM stages, positive expression of MACC1, Snail, and KAI1 should be involved in the process of invasiveness and metastasis of ESCC, as well as should be considered a useful predictor of prognosis.

Abnormal KAI1 expression should be involved in the initiation and recurrence of ESCC through its involvement in suppressor genes. KAI1 can suppress β-catenin tyrosine phosphorylation and stabilize E-cadherin-β-catenin complexes to inhibit tumor metastasis [17]. Furthermore, KAI1 can also inhibit the EMT process of a tumor [27]. Overexpression of MACC1 should be involved in the tumorigenesis by activation of HGF/MET signaling pathway [2, 3]. MACC1 also promotes EMT of tumor and suppresses apoptosis by activation of HGF/MET pathway [27, 29]. Overexpression of Snail directly activates EMT and promotes tumor metastasis by suppressing the transcription of E-cadherin and activation of N-cadherin. EMT can allow tumor cells leave the primary tumor to promote invasion and metastasis. Aberrant expression of KAI1 should lost or decrease its ability to suppress tumor cells invasiveness and metastasis [27-29].

Conclusions

This study indicated that expression of MACC1, Snail, and KAI1 were associated with duration of OS time among patients with ESCC. So, MACC1, Snail, and KAI1 should considered as valuable biomarkers in ESCC and may be helpful for the prediction of metastasis and prognosis for ESCC.

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Disclosure of conflict of interest

None.

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