Int J Clin Exp Pathol 2017;10(5):5655-5664
www.ijcep.com /ISSN:1936-2625/IJCEP0046604

Original Article

Expression of ALDH1, MACC1, and KAI1 in the triple-negative breast cancer and their clinical significance

Zhengquan Han[1*], Xiaomeng Gong[2,3*], Bo Zhu[2,3*], Shiwu Wu[2,3], Lan Yu[2,3], Wenqing Song[2,3], Danna Wang[2,3]

Departments of [1]Medical Oncology, [2]Pathology, The First Affiliated Hospital of Bengbu Medical College, Anhui Province, China; [3]Department of Pathology, Bengbu Medical College, Anhui Province, China. [*]Equal contributors.

Received December 14, 2016; Accepted March 8, 2017; Epub May 1, 2017; Published May 15, 2017

Abstract: Background and purpose: Triple-negative breast cancer (TNBC) is a more aggressive disease and easier to recur and metastasize as compared to non-TNBC. Aldehyde dehydrogenase 1 (ALDH1, cancer stem cell biomarker), metastasis-associated in colon cancer-1 (MACC1), KAI1 (suppressor of cancer metastasis) are all useful predictive factors for metastasis and prognosis in many cancers. In this study, we analyzed associations among ALDH1, MACC1, and KAI1 in TNBC, and their respective correlations with clinicopathological characteristics and survival in TNBC. Methods: Positive rates of ALDH1, MACC1, and KAI1 in 102 whole TNBC tissues specimens were detected by Immunohistochemistry (IHC). Patients' clinical data were also collected. Results: Levels of ALDH1 and MACC1 were significantly higher, and levels of KAI1 significantly lower, in TNBC tissues than in control tissues. Levels of ALDH1, MACC1, and KAI1 were significantly associated with lymph node metastasis and tumor-node-metastasis (TNM) stage, and with patients' overall survival (OS) or progression-free survival (PFS). In multivariate analysis showed that the expression of ALDH1, MACC1, and KAI1 and TNM stage were independent prognostic factors of OS and PFS in TNBC. Conclusion: The expression of ALDH1, MACC1, and KAI1 Represent promising markers for metastasis and prognosis, and potential therapeutic targets for TNBC.

Keywords: TNBC, ALDH1, MACC1, KAI1, prognosis

Introduction

In recent years, along with changes in lifestyle, the incidence of breast cancer has increased rapidly to become the second most commonly diagnosed cancer in the worldwide [1] and the first most commonly diagnosed cancer in China [2]. Triple-negative breast cancer (TNBC) is a subtype of breast cancer and characterized by a lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [3]. TNBC accounts for approximately 15% of all breast cancer [4]. Along with the contribution of adjuvant targeting therapies, the outcome of the major subtypes of breast cancer has been improved greatly. However, the outcome of TNBC remains poor in all breast cancer subtypes [5, 6]. TNBC was related with a higher grade, stem cell-like characteristics, higher invasive and metastatic potential [7].

Tumor recurrence and metastasis may be associated with cancer stem cells (CSCs), also termed as tumor initiating cells (TICs), which have the ability to self-renew and are closely linked to therapy resistance, recurrence, and metastasis [8, 9]. Aldehyde dehydrogenase 1 (ALDH1), which is an important member of ALDH superfamily of conserved enzymes localized in the cytoplasm, mitochondria, and nucleus, is a common marker of CSCs [10]. ALDH1 is not only able to metabolize and detoxify many endogenous and exogenous aldehydes, but able to oxidize retinol to synthesize retinoic acid, which can modulate cell differentiation [11]. ALDH1 is a candidate biomarker for CSCs, metastasis, and prognosis of breast cancer [12], lung cancer [11], ovarian cancer [13], pancreatic cancer [10].

Metastasis-associated in colon cancer-1 (MACC1), the first identified in colon cancer,

Table 1. Patients characteristics

Patients characteristics	Frequency (n)	Percentage (%)
Age		
<50 years	63	61.8
≥50 years	39	39.2
Size		
<2.0 cm	40	39.2
≥2.0 cm, <5.0 cm	53	52.0
≥5.0 cm	9	8.8
Location		
Left	47	46.1
Right	55	53.9
Type		
IDC	59	57.8
ILC	32	31.4
Other type	11	10.8
Differentiation		
Well	0	0
Moderate	29	28.4
Poor	73	71.6
LNM		
No	43	42.2
Yes	59	57.8
TNM stages		
I+II	47	46.1
III+IV	55	53.9

which was bound to the promoter of the MET gene to control MET transcriptional activity [14, 15]. MACC1 was considered as a key modulator of the HGF/MET signal pathway. MACC1 was not only able to promote tumor cells migration and invasion in vitro, but also promote tumor growth and metastasis in vivo [14, 16]. MACC1 was found to affect metastasis, recurrence, and prognosis in colon cancer [14, 15], lung cancer [17], ovarian cancer [18], and breast cancer [19].

KAI1 gene, a suppressor of metastasis, was first identified in prostate carcinoma cells. It is located on human chromosome 11p11.2 [20]. KAI1 which is an important member of the TM4SF (transmembrane 4 superfamily) can suppress invasion and metastasis by regulating inhibition of cell motility, adhesion, fusion, and proliferation [21]. However, the mechanism of KAI1 in cancer metastasis is still unclear. KAI1 is also been considered to be a useful biomarker for metastatic and prognostic in various human cancers [22].

Overall, studies of ALDH1, MACC1, and KAI1 in association with tumor metastasis and prognosis show that these biomarkers affect tumor progression; however, the associations among ALDH1, MACC1, and KAI1 in TNBC have not been widely reported. In this study, we explored the hypothesis that these biomarkers are mutual associated and are correlated with metastasis and prognosis in TNBC.

Materials and methods

Specimens

All 102 TNBC tissues and surrounding "normal" breast tissues were collected from the Department of Pathology, the First Affiliated Hospital of Bengbu Medical College (China), from January 2008 to December 2009. All patients underwent modified radical resection and axillary lymph node dissection (All patients who had received preoperative chemotherapy or radiotherapy or other anti-cancer therapy were excluded). The "normal" breast tissues were removed from the same patient, avoiding necrotic tissue, and from surrounding breast tissue at least 5 cm away from the carcinoma edge. All patients who had completely clinical, pathological, and follow-up (at 6-month intervals by phone, mail, or email) data were sporadic cases. Overall survival (OS) time was collected from surgery to death or December 2014 (mean OS time: 47.5 months; range 21-82 months). Progression-free survival (RFS) time was collected from surgery to recurrence or December 2014 (mean RFS time: 45.7 months; range 18-82 months). Grade of tumor differentiation was according to World Health Organization criteria. Clinical Tumor-node-metastasis stages were according UICC/AJCC TNM criteria. The ages of patients were from 25 to 78 years (median age: 49.7 years) and other characteristics are located in **Table 1**.

All tissue specimens were obtained with patients writing consent and the study was approved by the ethical committee of the Bengbu Medical College and performed in accordance with the guidelines of the Declaration of Helsinki.

Immunohistochemical analysis

All TNBC samples and corresponding normal breast tissues were fixed in 10% buffered formalin, embedded in paraffin, and continuous

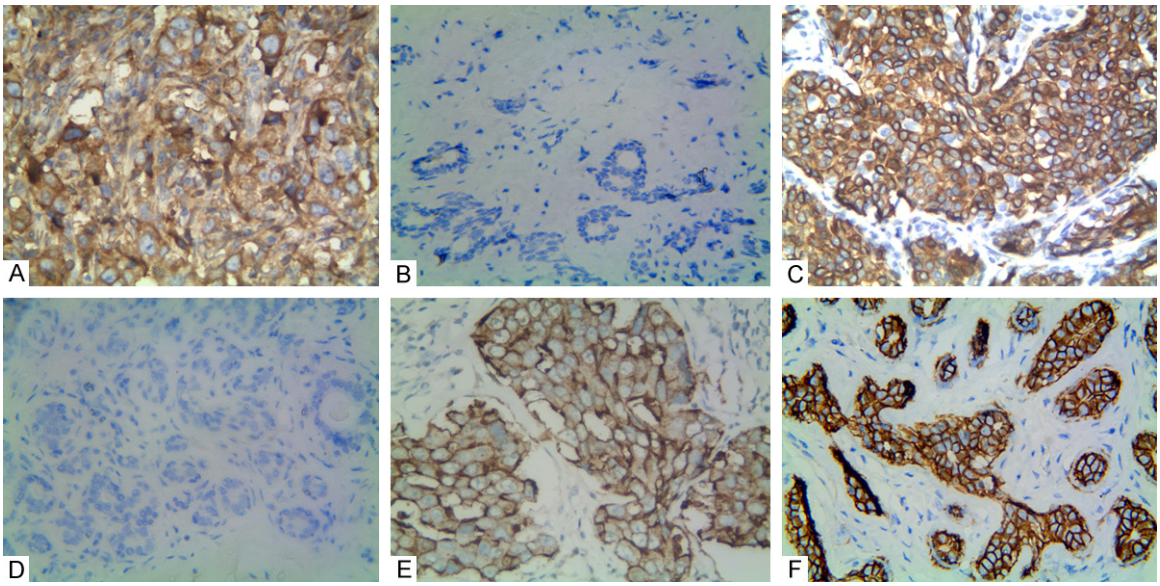

Figure 1. Expression of the patients in triple-negative breast cancer (×400 magnification). A. Positive ALDH1 expression in the cytoplasm and nucleus of cancer cells. B. Negative ALDH1 expression in the "normal" breast epithelial cells. C. Positive MACC1 expression in the cytoplasm of cancer cells. D. Negative MACC1 expression in the "normal" breast epithelial cells. E. Positive KAI1 expression in the membrane and cytoplasm of cancer cells. F. Positive KAI1 expression in the membrane and cytoplasm of "normal" breast epithelial cells.

sectioned (4 μm thickness). Then all sections were deparaffinized and dehydrated with xylene and graded ethanol. Subsequently, all sections were washed for 10 min in phosphate buffered saline (PBS, pH 7.2). The endogenous peroxidase activity was blocked by incubation in 3% hydrogen peroxide for 10 min at room temperature, then were placed in citrate buffer (pH 6.0) and heated to 95°C for 30 min for antigen repair. After three times washes by PBS, all sections were blocked in goat serum at room temperature for 20 min, then incubated with mouse monoclonal antibody against human ALDH1 (Abcam, USA, dilution 1:100) and KAI1 (Abcam, USA, dilution 1:100) and rabbit polyclonal antibody against human MACC1 (Santa Cluz, USA, dilution: 1:50) primary antibodies at 4°C overnight. Immunohistochemistry was performed according to the ElivisionTM Plus detection kit instructions (LabVision, USA). Finally, all sections were counterstained with hematoxylin, dehydrated, air-dried, and mounted.

Evaluation of immunostaining

Immunohistochemical staining was performed by an experienced technician who was blind to the clinical data. Immunostaining results were evaluated semi-quantitatively by two experienced pathologists who were blind to the clinical data and follow-up data. Because of intratumoral heterogeneity of antigen expression, we randomly selected ten visual fields (×400 magnification) from different areas of each slide. Immunostaining results were scored according to intensity and extent [9]. The extent of immunostaining was divided into four grades: 0. <10%; 1. 11%-25%; 2. 26%-50%; 3. 51%-75%; 4. >75%. The intensity of immunostaining was also divided into four grades: none staining, 0. Weak staining, 1. Moderate staining, 2. Strong staining, 3. Finally, the score was determined by multiplying the extent and the intensity scores to yield a range of scores from 0 to 12. The immunostaining score was considered positive when the score was ≥3. For slides that were positive for all three of ALDH1, MACC1, and KAI1, an average of the final score of each slide was taken.

Statistical analysis

Relationships between clinicopathological characteristics and ALDH1, MACC1, or KAI1 were compared using Fisher's exact tests or Pearson Chi-square test. Relationships between ALDH1, or MACC1, or KAI1 was compared using Spearman's coefficient test. Effects of ALDH1, MACC1, or KAI1 on survival were determined by univariate and multivariate analyses. In-

Table 2. The association between expression of ALDH1, MACC1, KAI1 and clinicopathological characteristics of triple-negative breast cancer (TNBC)

Variables	ALDH1		P	MACC1		P	KAI1		P
	Negative	Positive		Negative	Positive		Negative	Positive	
Age			0.581			0.223			0.628
<50 years	32	31		23	40		37	26	
≥50 years	22	17		19	20		21	18	
Size			0.296			0.517			0.275
<2.0 cm	25	15		19	21		19	21	
≥2.0 cm, <5.0 cm	25	28		19	34		34	19	
≥5.0 cm	4	5		4	5		5	4	
Location			0.052			0.176			0.274
Left	20	27		16	31		24	23	
Right	34	21		26	29		34	21	
Type			0.737			0.163			0.938
IDC	30	29		25	34		33	26	
ILC	17	15		10	22		19	13	
Other type	7	4		7	4		6	5	
Differentiation			0.469			0.358			0.004
Well	0	0		0	0		10	19	
Moderate	17	12		14	15		48	25	
Poor	37	46		28	45				
LNM			0.035			<0.001			0.027
No	28	15		30	13		19	24	
Yes	26	33		12	47		39	20	
TNM stages			<0.001			<0.001			<0.001
I+II	35	12		34	13		14	33	
III+IV	19	36		8	47		44	11	

dependent prognostic factors were determined using Cox regression model for multivariate analysis. Kaplan-Meier's method with log-rank test for univariate OS analysis was used to assess the relationship between the positive expression of ALDH1, MACC1, and KAI1 and clinicopathological variate, using SPSS 20.0 software for windows (New York, IBM). A value of $P<0.05$ was considered as statistically significant.

Results

Association between ALDH1, MACC1, and KAI1 expression and clinicopathological parameters

To assess the contributions of ALDH1, MACC1, and KAI1 to TNBC, the results thereof were immunohistochemically assessed for both TNBC and control tissue specimens. These data were then compared to patient's clinicopathological parameters. The positive rate of ALDH1 expression in the TNBC specimens (47.1%; 48/102) was significantly higher than that in the control tissues (14.7%; 15/102; P<0.001) (**Figure 1A** and **1B**). Expression of ALDH1 in TNBC was positively associated with LNM and TNM stages, but not patient age, tumor location, size, type, or grades (**Table 2**).

Similar to ALDH1, MACC1 expression was significantly higher in TNBC tissues (58.8%; 60/102) than that in control tissues (10.8%; 11/102; P<0.001) (**Figure 1C** and **1D**). The positive rate of MACC1 expression in TNBC was associated with LNM and TNM stages, but not patient age, tumor size, location, type, or grades (**Table 2**).

The positive rate of KAI1 expression was significantly lower in TNBC tissues (43.1%; 44/102) than that in control tissues (93.1%; 95/102;

Table 3. Correlation between expression of ALDH1, MACC1, and KAI1 in TNBC

Variable	ALDH1		r	P	KAI		r	P
	Negative	Positive			Negative	Positive		
ALDH1							-0.425	<0.001
Negative					20	34		
Positive					38	10		
MACC1			0.390	<0.001			-0.397	<0.001
Negative	32	10			14	28		
Positive	22	38			44	16		

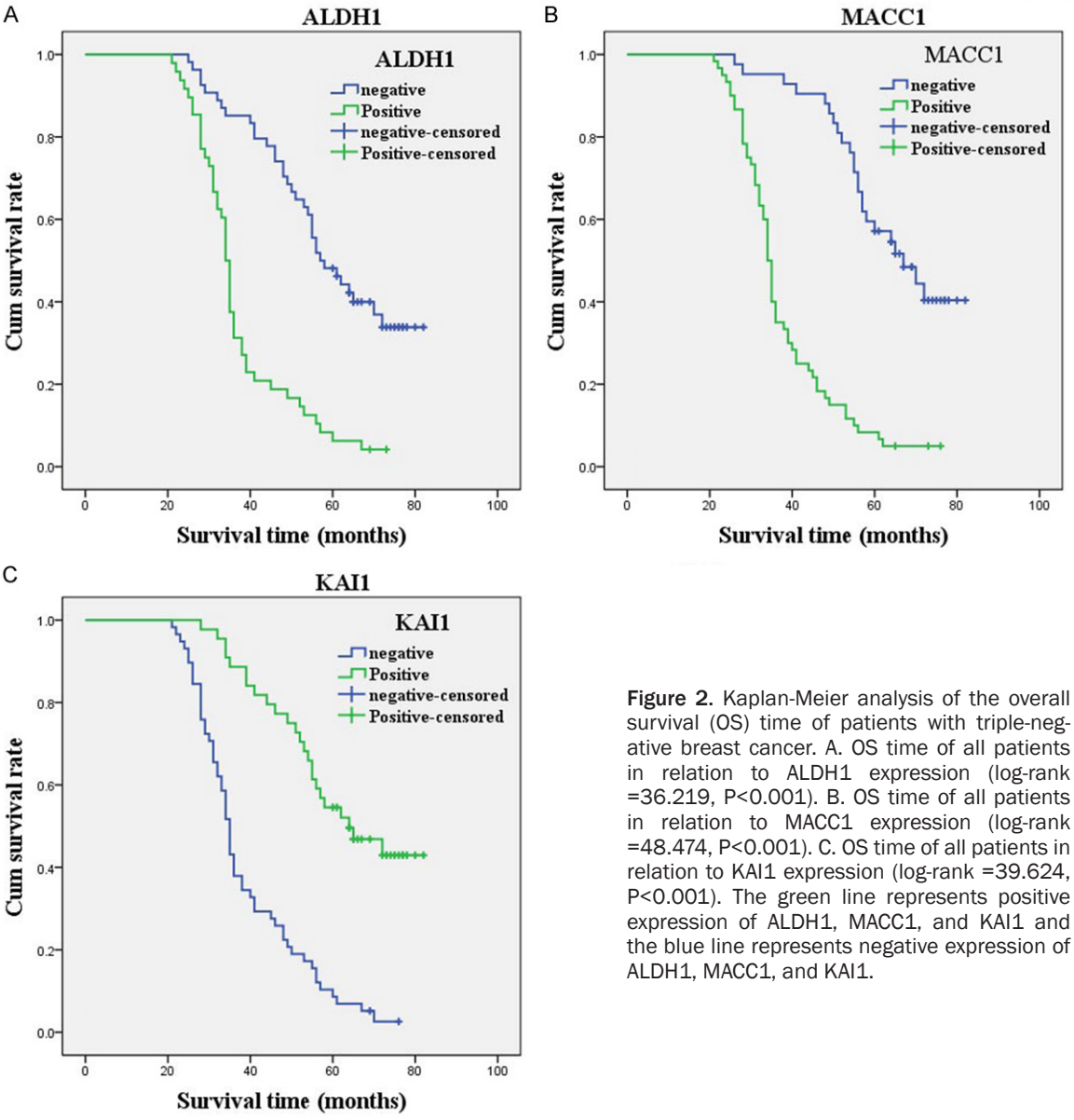

Figure 2. Kaplan-Meier analysis of the overall survival (OS) time of patients with triple-negative breast cancer. A. OS time of all patients in relation to ALDH1 expression (log-rank =36.219, P<0.001). B. OS time of all patients in relation to MACC1 expression (log-rank =48.474, P<0.001). C. OS time of all patients in relation to KAI1 expression (log-rank =39.624, P<0.001). The green line represents positive expression of ALDH1, MACC1, and KAI1 and the blue line represents negative expression of ALDH1, MACC1, and KAI1.

P<0.001) (**Figure 1E** and **1F**). The positive rate of KAI1 expression was negatively associated with tumor grades, LNM, and TNM stages. No association was found between KAI1 expression and patient age, tumor size, location, or type (**Table 2**).

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

Variables	n	Mean OS (months)	Log-rank	*P*-value
ALDH1			36.219	<0.001
Negative	54	56.5±15.7		
Positive	48	37.3±12.3		
MACC1			48.474	<0.001
Negative	42	61.4±13.1		
Positive	60	37.8±12.2		
KAI1			39.624	<0.001
Negative	58	38.8±13.4		
Positive	44	58.9±14.7		
Age			0.092	0.762
<50 years	63	47.2±18.0		
≥50 years	39	48.0±15.7		
Size			6.266	0.044
<2.0 cm	40	52.4±17.3		
≥2.0 cm, <5.0 cm	53	44.3±16.3		
≥5.0 cm	9	44.8±18.0		
Location			0.141	0.708
Left	47	46.8±18.4		
Right	55	48.1±16.0		
Type			1.071	0.585
IDC	59	47.5±17.4		
ILC	32	46.5±17.2		
Other type	11	50.4±16.7		
Differentiation			3.947	0.047
Well	0	0		
Moderate	29	52.4±16.8		
Poor	73	45.6±17.0		
LNM			17.117	<0.001
No	43	57.1±15.1		
Yes	59	40.5±15.0		
TNM stages			61.070	<0.001
I+II	47	60.4±13.6		
III+IV	55	36.5±11.1		

Table 5. Results of multivariate analyses of OS time

Covariate	B	SE	P	HR	95% CI
TNM stages	0.783	0.348	0.024	2.188	1.106-4.326
ALDH1	0.852	0.267	0.001	2.343	1.389-3.954
MACC1	1.021	0.374	0.006	2.775	1.332-5.782
KAI1	-0.612	0.311	0.049	0.542	0.295-0.998

Correlation among ALDH1, MACC1, and KAI1 in TNBC

There was a positive association between ALDH1 expression and MACC1 expression (r=0.390, P<0.001) (**Table 3**). There was a negative association between KAI1 expression and expression of ALDH1 and MACC1 (r=-0.425, r=-0.397, P<0.001) (**Table 3**).

Univariate and multivariate analyzes

Follow-up data indicated that OS was significantly shorter in TNBC patients with ALDH1-positive-expression specimens compared with those with ALDH1-negative patients (log-rank =36.129; P <0.001, **Figure 2A**). Similarly, OS of MACC1-positive-expression patients was significantly shorter than those of MACC1-negative patients (log-rank =48.474; P<0.001; **Figure 2B**). The OS of KAI1-positive-expression patients was significantly longer than those who were KAI1-negative patients (log-rank =36.219; P<0.001; **Figure 2C**). In the univariate analysis, OS time was significantly associated with clinicopathologic characteristics, including diameter of tumor (P=0.044, log-rank =6.266), grade of tumor (P=0.047, log-rank =3.941), lymph node metastasis (P<0.001, log-rank =17.117), TNM stages (P<0.001, log-rank =61.070) (**Table 4**). Multivariate analysis indicated that positive expression of ALDH1, MACC1, KAI1 and TNM stages were independent prognostic factors of OS time for TNBC (P<0.05) (**Table 5**).

PFS time analysis

The PFS of ALDH-positive-expression patients was significantly shorter than those of ALDH1-negative patients (log-rank =37.666; P<0.001; **Figure 3A**). Similarly, the PFS of MACC1-positive-expression patients was significantly shorter than those of MACC1-negative patients (log-rank =46.058; P<0.001; **Figure 3B**). The PFS of KAI1-positive-expression patients was significantly longer than those who were KAI1-negative patients (log-rank =37.672; P<0.001; **Figure 3C**).

In the univariate analysis, PFS time was significantly associated with clinicopathological parameters, including diameter of tumor (log-rank =6.855; P=0.032), grade of tumor (log-rank =4.300; P=0.038), lymph node metastasis (log-rank =16.106; P<0.001), TNM stages (log-rank =59.171; P<0.001) (**Table 6**). Multivariate analysis indicated that positive expression of ALDH1, MACC1, KAI1, and TNM stages were independent prognostic factors of PFS time for TNBC (P<0.05) (**Table 7**).

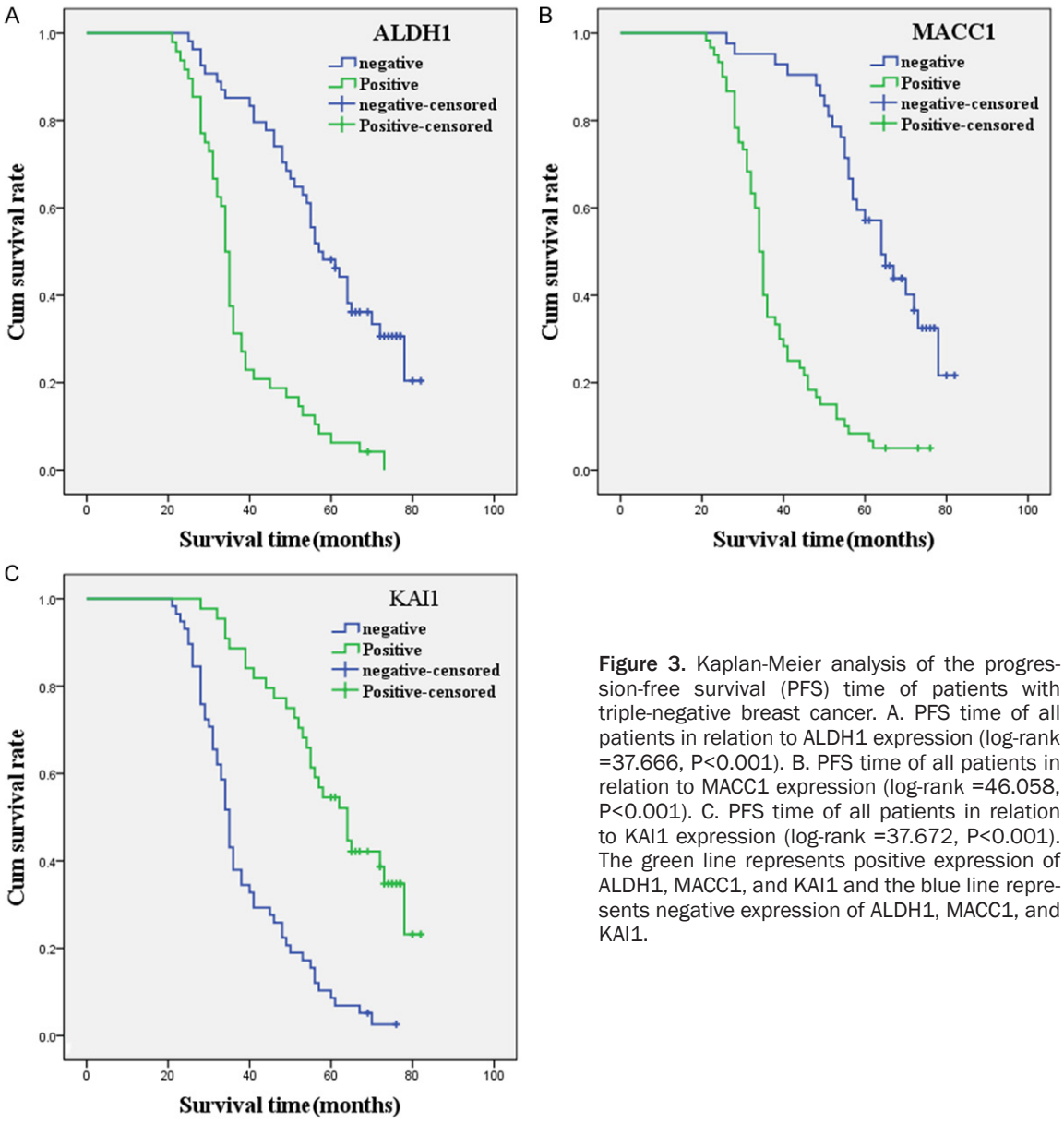

Figure 3. Kaplan-Meier analysis of the progression-free survival (PFS) time of patients with triple-negative breast cancer. A. PFS time of all patients in relation to ALDH1 expression (log-rank =37.666, P<0.001). B. PFS time of all patients in relation to MACC1 expression (log-rank =46.058, P<0.001). C. PFS time of all patients in relation to KAI1 expression (log-rank =37.672, P<0.001). The green line represents positive expression of ALDH1, MACC1, and KAI1 and the blue line represents negative expression of ALDH1, MACC1, and KAI1.

Discussion

TNBC is a highly heterogeneous disease, which can affect the reproducibility of biomarker evaluation. Therefore, prognostic value of candidate biomarker should be thoroughly assessed to ensure their validity. The leading causes of cancer treatment failure are metastasis and recurrence. Recurrence and metastasis are linked to the subpopulation of tumor cells, named cancer stem cells (CSCs) or tumor initiating cells (TICs). The ability of these cells is to be self-renewal and give rise to the different differentiated cells that comprised the bulk of the tumors [9, 23, 24]. ALDH1 is commonly regarded as a marker of CSCs or TICs in many human tumors [10-13]. In this study, we found that ALDH1 expression was positively associated with LNM and TNM stages. Moreover, Kaplan-Meier survival analysis indicated that ALDH1-positive-expression patients had significantly shorter OS or PFS than did ALDH1-negative patients. These results demonstrate that ALDH1 plays a critical role in TNBC progression dan metastasis, and should be a useful biomarker in this disease. Our findings are consistent with others studies, including those of breast cancer and other cancers [12, 13, 25].

Table 6. Results of univariate analyses of recurrence-free survival (RFS) time

Variables	n	Mean OS (months)	Log-rank	*P*-value
ALDH1			37.666	<0.001
Negative	54	54.93±16.3		
Positive	48	35.4±12.5		
MACC1			46.058	<0.001
Negative	42	59.7±13.8		
Positive	60	36.0±12.6		
KAI1			37.672	<0.001
Negative	58	36.6±13.4		
Positive	44	57.7±15.1		
Age			0.205	0.651
<50 years	63	45.5±18.7		
≥50 years	39	46.0±15.7		
Diameter			6.855	0.032
<2.0 cm	40	50.8±17.6		
≥2.0 cm, <5.0 cm	53	42.4±16.8		
≥5.0 cm	9	43.0±18.5		
Location			0.194	0.659
Left	47	45.1±19.0		
Right	55	46.3±16.4		
Type			0.986	0.611
IDC	59	45.8±17.8		
ILC	32	44.6±17.6		
Other type	11	48.6±17.5		
Differentiation			4.300	0.038
Well	0	0		
Moderate	29	51.4±17.4		
Poor	73	43.6±17.3		
LNM			16.106	<0.001
No	43	55.4±15.5		
Yes	59	38.7±15.6		
TNM stages			59.171	<0.001
I+II	47	58.8±14.2		
III+IV	55	34.5±11.3		

Table 7. Results of multivariate analyses of RFS time

Covariate	B	SE	P	HR	95% CI
TNM stages	0.669	0.340	0.049	1.952	1.002-3.802
ALDH1	0.929	0.264	<0.001	2.532	1.509-4.249
MACC1	0.917	0.354	0.010	2.501	1.249-5.006
KAI1	-0.601	0.302	0.047	0.548	0.303-0.991

MACC1 which was the first identified in colon cancer in 2009 is a critical regulator of HGF/c-MET signal pathway which interferes with tumorigenicity, epithelial-mesenchymal transition (EMT), invasion, and metastasis [15]. In this study, we found that MACC1 expression in TNBC tissues was significantly higher than in control tissues. We also found that MACC1-positive expression was positively associated with LNM and TNM stages. Similar to ALDH1, OS or PFS of MACC1-positive-expression TNBC patients was significantly shorter than that for the MACC1-negative subgroup. Our findings are similar to the previous studies which suggest that MACC1 should be considered as a useful biomarker for TNBC [16, 19, 26].

KAI1 is widely considered as a suppressor of cancer metastasis in many human cancers [22, 27-31]. KAI1 can inhibit proliferation, invasion, and metastasis of tumor cells [21]. Results in this study also indicated that KAI1-positive expression was significantly less in TNBC tissues than that in control tissues, and its positive expression was inversely related to tumor grades, LNM, and TNM stages. In addition, Kaplan-Meier OS or PFS indicated that TNBC patients with KAI1-positive-expression specimens had significantly longer than did KAI1-negative patients. These findings indicate that down-regulation of KAI1 promotes TNBC progression and metastasis, which is consistent with the previous studies [22, 27, 28].

TNM stages design therapeutic strategies for TNBC patients, but not offer confirming information about TNBC's biological behavior. Therefore, it is urgently needed to find novel and effective biomarkers to predict TNBC's biological behavior, metastasis, and prognosis. In this study, multivariate analysis of OS or PFS showed that ALDH1, MACC1, and KAI1 expression, as well as TNM stages, are independent prognostic factors for TNBC patients. Our findings thus demonstrate ALDH1, MACC1, and KAI1 as reliable biomarkers for TNBC in predicting metastasis and prognosis. Accumulating evidence indicated that inactivation of suppressor of tumor metastasis and activation of factor of tumor metastasis was critical for tumor metastasis. In particular, KAI1 is a suppressor of tumor metastasis that can inhibit β-catenin tyrosine phosphorylation and stabilize E-cadherin-β-catenin complexes to prevent tumor metastasis [29]. MACC1 promotes tumor cells invasion and metastasis through activation of

the HGF/c-Met signaling pathway [14, 15]. In this study, we demonstrated that KAI1 expression was negatively associated with MACC1 expression. As a tetraspania, KAI1 was bind to c-Met to form complex or blocked the activation of HGF [30, 31], thus might inhibit the activation of MACC1 to slow the migration of cancer cells. On the other hand, KAI1 expression was negative associated with ALDH1 expression. The niche where CSCs reside is mainly composed of vascular and lymphatic vessel. MACC1 may induce tumor angiogenesis and lymphangiogenesis to promote tumor invasion and metastasis [33, 34]. KAI1 may inhibit tumor angiogenesis and lymphangiogenesis through inhibition of β-catenin-mediated epithelial-mesenchymal transition (EMT) [35]. Aberrant expression of KAI1 might lose inhibition of angiogenesis and lymphangiogenesis, thus promote CSCs proliferation, multiple differentiation, invasion, and metastasis. Aberrant expression of MACC1 further promotes tumor cells invasion and metastasis. Although the number of samples was relatively small, our results may still reflect the biological behavior of invasion and metastasis of TNBC.

Conclusion

Our findings imply that ALDH1, MACC1, and KAI1 involves in TNBC evolution; and that combined detection of ALDH1, MACC1, and KAI1 are valuable biomarkers of metastasis and prognosis in TNBC.

Acknowledgements

This work was supported by the Nature Science Foundation of Anhui Province (No. 1708085-MH230) and the Nature Science Key Program of College and University of Anhui Province (No. KJ2015A269 and No. KJ2016A488) and Key projects of support program for outstanding young talents in Colleges and Universities of Anhui Province (No. gxyqZD2016160).

Disclosure of conflict of interest

None.

Address correspondence to: Shiwu Wu, Department of Pathology, Bengbu Medical College, No. 287, Changhuai Road, Anhui Province, China. Tel: +86-13705523357; E-mail: 573448542@qq.com

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Zheng R, Zeng H, Zhang S, Chen T, Chen W. National estimates of cancer prevalence in China, 2011. Cancer Lett 2015; 370: 33-8.

[3] Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, Ollila DW, Sartor CI, Graham ML, Perou CM. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtype. Clin Cancer Res 2007; 13: 2329-34.

[4] Wu K, Yang Q, Liu Y, Wu A, Yang Z. Meta-analysis on the association between pathologic complete response and triple-negative breast cancer after neoadjuvant chemotherapy. World J Surg Oncol 2014; 12: 95.

[5] Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol 2011; 9: 16-32.

[6] Yang L, Perez AA, Fujie S, Warden C, Li J, Wang Y, Yung B, Chen YR, Liu X, Zhang H, Zheng S, Liu Z, Ann D, Yen Y. Wnt modulates MCL1 to control cell survival in triple negative breast cancer. BMC Cancer 2014; 14: 124.

[7] Dey N, Barwick BG, Moreno CS, Ordanic-Kodani M, Chen Z, Oprea-Ilies G, Tang W, Catzavelos C, Kerstann KF, Sledge GW Jr, Abramovitz M, Bouzyk M, De P, Leyland-Jones BR. Wnt signaling in triple negative breast cancer is associated with metastasis. BMC Cancer 2013; 13: 537.

[8] Park IH, Zhao R, West JA, Yabuuchi A, Huo H, Ince TA, Lerou PH, Lensch MW, Daley GQ. Reprogramming of human somatic cells to pluripotency with defined factors. Nature 2008; 451: 141-146.

[9] Wu S, Yu L, Wang D, Zhou L, Cheng Z, Chai D, Ma L, Tao Y. Aberrant expression of CD133 in non-small cell lung cancer and its relationship to vasculogenic mimicry. BMC Cancer 2012; 12: 535.

[10] Kim IG, Lee JH, Kim SY, Kim JY, Cho EW. Fibulin-3 negatively regulates ALDH1 via c-MET suppression and increase γ-radiation-induced sensitivity in some pancreatic cancer cell lines. Biochem Biophs Res Commun 2014; 454: 369-75.

[11] Huo W, Du M, Pan X, Zhu X, Li Z. Prognostic value of ALDH1 expression in lung cancer: a meta-analysis. Int J Clin Exp Med 2015; 8: 2045-51.

[12] Pan H, Wu N, Hang Y, Li Q, Liu C, Liang M, Zhou W, Liu X, Wang S. Aldehyde dehydrogenase 1 expression correlates with the invasion of breast cancer. Diagn Pathol 2015; 10: 66.

[13] Ayub TH, Kewer-Paik MD, Debald M, Rostamzadeh B, Thiesler T, Schröder L, Barchet W, Abramian A, Kaiser C, Kristiansen G, Kuhn W, Kübler K. Accumulation of ALDH1-positive cells after neoadjuvant chemotherapy predicts treatment resistance and prognosticates poor outcome in ovarian cancer. Oncotarget 2015; 6: 16437-48.
[14] Stein U, Walther W, Arlt F, Schwabe H, Smith J, Fichtner I, Birchmeier W, Schlag PM. MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis. Nat Med 2009; 15: 59-67.
[15] Stein U, Smith J, Walther W, Arlt F. MACC1 controls Met: what a difference an Sp1 site makes. Cell Cycle 2009; 8: 2467-9.
[16] Ren B, Zakharov V, Yang Q, McMahon L, Yu J, Cao W. MACC1 is related to colorectal cancer initiation and early-stage invasive growth. Am J Clin Pathol 2013; 140: 701-7.
[17] Chundong G, Uramoto H, Onitsuka T, Shimokawa H, Iwanami T, Nakagawa M, Oyama T, Tanaka F. Molecular diagnosis of MACC1 status in lung adenocarcinoma by immunohistochemical analysis. Anticancer Res 2011; 31: 1141-5.
[18] Zhou HY, Pon YL, Wong AS. HGF/MET signaling in ovarian cancer. Curr Mol Med 2008; 8: 469-80.
[19] Huang Y, Zhang H, Cai J, Fang L, Wu J, Ye C, Zhu X, Li M. Overexpression of MACC1 and its significance in human breast cancer progression. Cell Biosci 2013; 3: 16.
[20] Dong JT, Lamb PW, Rinker-Schaeffer CW, Vukanovic J, Ichikawa T, Isaacs JT and Barrett JC. KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. Science 1995; 268: 884-6.
[21] Smith SC, Theodorescu D. Learning therapeutic lessons from metastasis suppressor proteins. Nat Rev Cancer 2009; 9: 253-64.
[22] Malik FA, Sanders AJ, Jiang WG. KAI-1/CD82, the molecule and clinical implication in cancer and cancer metastasis. Histol Histopathol 2009; 24: 519-30.
[23] O'Brien CA, Pollett A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature 2007; 445: 106-10.
[24] Rosen JM, Jordan CT. The increasing complexity of the cancer stem cell paradigm. Science 2009; 324: 1670-3.
[25] Li X, Xu Q, Fu X, Luo W. ALDH1 overexpression is associated with the progression and prognosis in gastric cancer. BMC Cancer 2014; 14: 705.
[26] Guo T, Yang J, Yao J, Zhang Y, Da M, Duan Y. Expression of MACC1 and c-Met in human gastric cancer and its clinical significance. Cancer Cell Int 2013; 13: 121.
[27] Yu L, Zhou L, Wu S, Gong X, Feng Z, Ma L, Zhu B, Yao N, Wang D, Dong H. Clinicopathological significance of cancer stem cells marked by CD133 and KAI1/CD82 expression in laryngeal squamous cell carcinoma. World J Surg Oncol 2014; 12: 118.
[28] Wu Q, Yang Y, Wu S, Li W, Zhang N, Dong X, Ou Y. Evaluation of the correlation of KAI1/CD82, CD44, MMP7 and β-catenin in the prediction of prognosis and metastasis in colorectal carcinoma. Diagn Pathol 2015; 10: 176.
[29] Abe M, Sugiura T, Takahashi M, Ishii K, Shimoda M and Shirasuna K. A novel function of CD82/KAI-1 on E-cadherin-mediated homophilic cellular adhesion of cancer cells. Cancer Lett 2008; 266: 163-70.
[30] Liu WM, Zhang F, Moshiach S, Zhou B, Huang C, Srinivasan K, Khurana S, Zheng Y, Lahti JM, Zhang XA. Tetraspanin CD82 inhibits protrusion and retraction in cell movement by attenuating the plasma membrane-dependent actin organization. PLoS One 2012; 7: e51797.
[31] Mela A, Goldman JE. The tetraspanin, KAI1/CD82, is expressed by late-lineage oligodendroctye precursors and may function to restrict precursor migration and promote oligodendroctye differentiation and myelination. J Neurosci 2009; 29: 11172-81.
[32] Hilbe W, Dirnhofer S, Oberwasserlechner F, Schmid T, Gunsilius E, Hilbe G, Wöll E, Kähler CM. CD133 positive endothelial progenitor cells contribute to the tumour vasculature in non-small cell lung cancer. J Clin Pathol 2004; 57: 965-969.
[33] Zheng Z, Gao S, Yang Z, Xie H, Zhang C, Lin B, Wu L, Zheng S, Zhou L. Single nucleotide polymorphisms in the metastasis-associated in colon cancer-1 gene predict the recurrence of hepatocellular carcinoma after transplantation. Int J Med Sci 2014; 11: 142-50.
[34] Sun L, Duan J, Jiang Y, Wang L, Huang N, Lin L, Liao Y, Liao W. Metastasis-associated in colon cancer-1 upregulates vascular endothelial growth factor-C/D to promote lymphangiogenesis in human gastric cancer. Cancer Lett 2015; 357: 242-53.
[35] Zhou L, Yu L, Wu S, Feng Z, Song W, Gong X. Clinicopathological significance of KAI1 expression and epithelial-mesenchymal transition in non-small cell lung cancer. World J Surg Oncol 2015; 13: 324.