

The expression of ubiquitin-conjugating enzyme E2C and KAI1 in ovarian carcinoma and their clinical significance

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Abstract

Ubiquitin-conjugating enzyme E2C (UBE2C) is considered to play an important role in the tumorigenesis of many cancers and promote cell cycle progression. Kangai 1 (KAI1) is considered as a suppressor gene of tumor metastasis. However, the clinicopathological significance and their each relationship of UBE2C and KAI1 in epithelial ovarian carcinoma (EOC) are not widely reported. The purpose of this study is to detect the expression of UBE2C and KAI1 in EOC and their clinical significance.

The expression of UBE2C and KAI1 in 180 cases of EOC tissues, 60 cases of normal ovarian epithelial tissues, and 60 cases of ovarian benign tumor tissues were detected by immunohistochemistry. Patients data were also collected.

Positive expression of UBE2C in EOC (38.9%) was significantly higher than that both in the normal group (0%) and benign tumors group (10.0%). Furthermore, the expression of UBE2C was positively associated with grades of differentiation, implants, lymph node metastasis (LNM), as well as the International Federation of Gynecology and Obstetrics (FIGO) stages. Positive expression of KAI1 in EOC (25.0%) was significantly lower than that both in the normal group (100%) and benign tumors group (75.0%). And the expression of KAI1 was inversely associated with grades of differentiation, implants, LNM, and FIGO stages. Kaplan–Meier survival analyses demonstrated that UBE2C positive expression for patients with EOC had unfavorably overall survival (OS) time when compared with negative UBE2C for patients. And KAI1 positive expression for patients had favorably OS time when compared with negative KAI1 for patients. Multivariate analysis showed that positive expression of UBE2C and KAI1, implants, and FIGO stages were considered as independently prognostic factors for OS in patients with EOC. Moreover, UBE2C expression was significantly higher in high grade serous adenocarcinoma (SA) when compared with low grade SA; and KAI1 expression was significantly lower in high grade SA when compared with low grade SA. High grade SA patients had higher rates of implants, LNM, and high FIGO stages when compared with low grade SA. High grade SA patients had unfavorably OS time when compared with low grade SA.

UBE2C and KAI1 should be considered as potential biomarkers of EOC prognosis.

Abbreviations: DAB = diaminobenzidine, ECM = extracellular matrix, EOC = epithelial ovarian carcinoma, FIGO = International Federation of Gynecology and Obstetrics, LNM = lymph node metastasis, OS = overall survival, SA = serous adenocarcinoma, UBE2C = ubiquitin-conjugating enzyme E2C.

Keywords: EOC, immunohistochemistry, KAI1, prognosis, UBE2C

1. Introduction

An estimated 239 thousand new ovarian cancer cases and 152 thousand deaths worldwide occurred in 2012.^[1] And there were an estimated 52 thousand new ovarian cancer cases and 22 thousand deaths China in 2015.^[2] Epithelial ovarian carcinoma (EOC)

which accounts for 85% approximately is the most common type.^[3] Because of insidious onset, more than 70% of EOC patients were at advanced stage when diagnosed. EOC is a group of highly heterogeneous cancers which makes it urgent to find some biomarkers for early evaluation of progression and prognosis.

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Ubiquitin-conjugating enzyme E2C (UBE2C), a key part of the ubiquitin-conjugating enzyme complex, is an important member of the E2 family. *UBE2C* gene, which is located on human chromosome 20q13, encodes 19.6 kDa protein and is involved in the destruction of mitotic system. UBE2C can promote cell cycle progression and strengthen genetic stability.^[4] UBE2C expression is extremely low in normal tissue. Aberrant expression of UBE2C may suppress the autoregulatory feedback loop for the regulation of antigen-presenting cells and cause the dysregulation of cell growth.^[5,6] Accumulating evidence showed that overexpression of UBE2C may be involved in various biological processes, including tumorigenesis, proliferation, cycle, and apoptosis.^[6–10]

Tumor invasiveness and metastasis are closely associated with the inactivation of tumor metastasis suppressor gene. *KAI1*, also named as CD82, is originally found in prostate cancer cell lines.^[11] *KAI1* gene, which is located on human chromosome 11p11.2, is widely reported as a suppressor gene of tumor metastasis.^[11] *KAI1* gene that contains 10 exons and 9 introns is an important member of the transmembrane 4 protein superfamily.^[12] *KAI1* plays an important role not only in extensive physiological processes, but also in pathological processes such as tumor invasion and metastasis.^[13,14] *KAI1* can strengthen cell to cell adhesion and cell to extracellular matrix (ECM) by enhancing the stabilization of E-cadherin/ β -catenin complex to inhibit metastasis.^[15] Increasing evidence has indicated that down- or lost-expression of *KAI1* should be involved in cancer cell proliferation, progression, fusion, motility, migration, invasion, and metastasis.^[16]

Overall, the studies of UBE2C and *KAI1* have demonstrated that they should be associated with cancer invasion and metastasis. However, the clinicopathological significance of UBE2C and *KAI1* in EOC are not widely reported. The purpose of this study is to analyze the association between UBE2C and *KAI1* as well as with metastasis and prognosis of EOC's patients.

2. Methods

2.1. Patients and samples

All samples were collected from 180 patients who were diagnosed EOC at the Department of Pathology of the First Affiliated Hospital of Bengbu Medical University. The median age of patients was 55.8 years and time was from January 2010 to December 2012. Sixty cases of normal ovarian epithelial tissues and 60 cases of benign ovarian tumors (such as serous or mucinous cystadenoma) were also collected in the same period. Patients who had underwent any history anticancer therapy were excluded. The data of patients consisted of clinicopathological characteristics, demography, and follow-up time. Follow-up time was calculated from removal date to December 2017 or her death date (median age was 49.1 months, range 6–93 months). Grades of differentiation were assessed in accordance with the guidelines issued by the World Health Organization. Tumor-node-metastasis stages were assessed in accordance with the guideline issued by the 2015th version of the International Federation of Gynecology and Obstetrics (FIGO). The type of implants as follows: serous type had 56 cases of implant; mucinous type had 9 cases of implants; endometrial type had 7 cases of implant; clear cell type had 3 cases of implants. Tissue samples were obtained with each patients' consents and the research was approved by the ethical committee of Bengbu Medical University and conducted in accordance with the guidelines issued of the Declaration of Helsinki. Specific clinicopathological characteristics see Table 1.

Table 1

Patients characteristics.

Patients characteristics	Frequency (n)	Percentage (%)
Ages, yr		
≤56	117	65.0
>56	63	35.0
Location		
Left	76	42.2
Right	70	38.9
Bilateral	34	18.9
Histological type		
Serous	137	76.1
Mucinous	25	13.9
Endometrial	13	7.2
Clear cell	5	2.8
Size, cm		
≤8.0	108	60.0
>8.0	72	40.0
Ascites		
No	107	59.4
Yes	73	40.6
Implantation		
No	105	58.3
Yes	75	41.7
Grades of differentiation		
Low	103	57.2
High	77	41.7
Lymph node metastasis		
No	110	61.1
Yes	70	38.9
FIGO stages		
I + II	88	48.9
III + IV	92	51.1

FIGO = International Federation of Gynecology and Obstetrics.

2.2. Immunohistochemistry

All EOC and control samples were fixed in 10% buffered formalin, then embedded in paraffin. 4 μ m thickening sections were cut. Deparaffinized and dehydrated were used in the xylene solution and gradient alcohol solution. Immunohistochemistry was performed according to Elivision™ Plus method (Lab Vision, Fremont, CA) and the procedure was carried out in accordance with the kit instructions. Rabbit anti-human monoclonal antibody against UBE2C and mouse anti-human monoclonal antibody against *KAI1* were both purchased from Abcam, Co, Ltd. (San Francisco, CA) Other reagents (such as diaminobenzidine [DAB], reagent A, and reagent B) were purchased from Fuzhou Maixin Biotechnology Development Co, Ltd (China). Antigen repair was in the citrate buffer solution (pH 6.0) and endogenous peroxidase activity of all samples was quenched by 3% H₂O₂ solution. All sections were incubated by goat serum for 30 minutes. Then, UBE2C and *KAI1* primary antibodies were added and incubated overnight at 4°C. Subsequently, reagent A (polymer enhancer) and reagent B (goat anti-mouse antibody) were added. Finally, all sections were developed in DAB substrate solution and re-dyed with hematoxylin.

2.3. Assessment of immunohistochemical staining

Ten high-power-field fields of each EOC section was chosen to prevent possible intratumoral heterogeneity of biomarker expression. Final immunostaining results were reached by multiplying the score of staining intensity (0 means no staining;

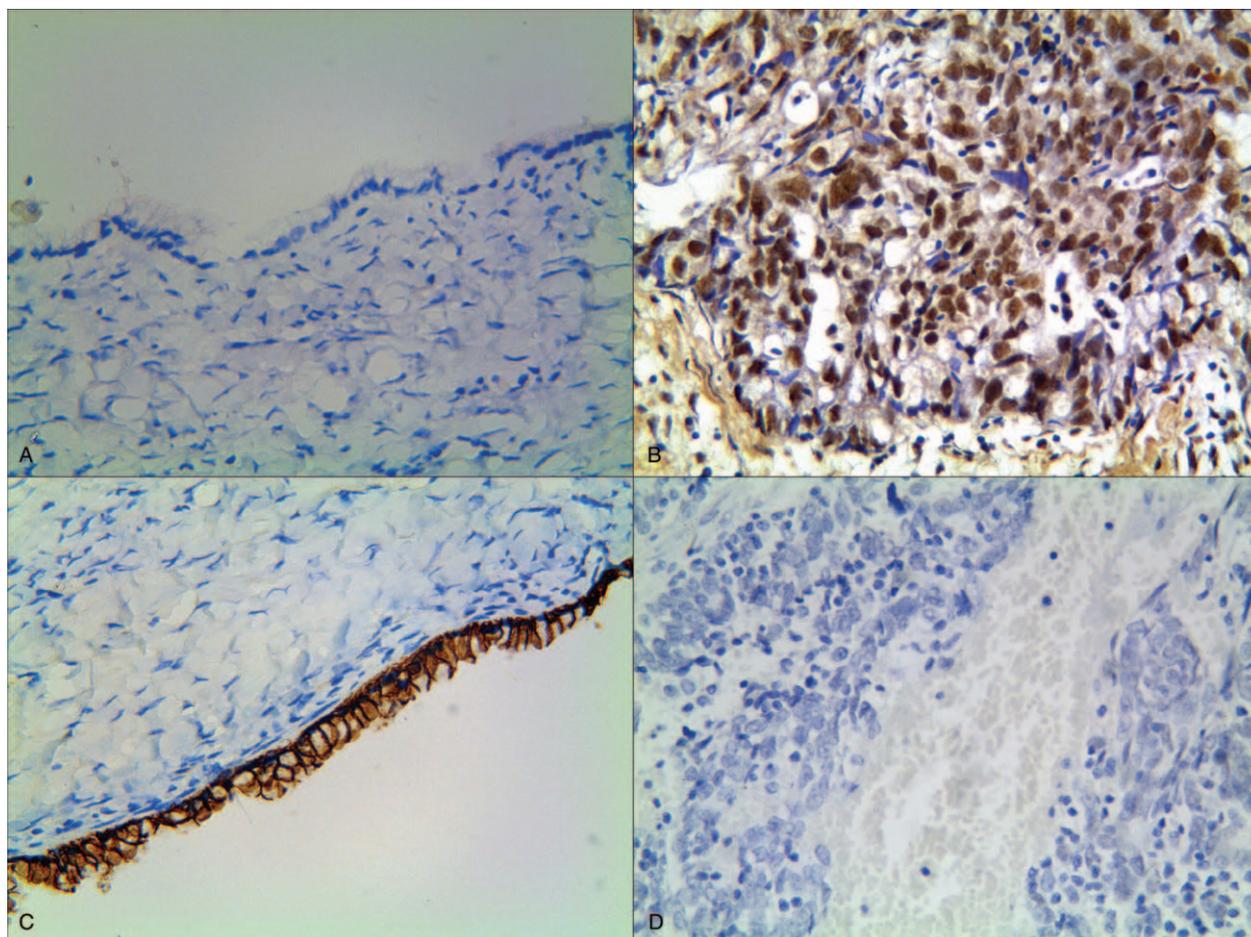


Figure 1. Immunostaining of UBE2C or KAI1 in EOC or the control tissues (400 magnification). (A) Negative staining of UBE2C in the control tissues; (B) positive staining of UBE2C in nuclei and cytoplasm of the EOC cells; (C) positive staining of KAI1 in the membrane and cytoplasm of the EOC cells; (D) negative staining of KAI1 in the EOC cells. EOC = epithelial ovarian carcinoma, UBE2C = ubiquitin-conjugating enzyme E2C.

1 means weak staining; 2 means moderate staining; 3 means strong staining.) and the score of staining extent (1 means <11% positive cells; 2 means 11%–50% positive cells; 3 means 51%–75% positive cells; 4 means >75% positive cells). The final immunostaining scores were from 0 to 12. The determination of the immunostaining results was considered as positive (score >2). The average score of all sections was taken.

2.4. Statistical analysis

Chi-square test was used to evaluate the positive expression of UBE2C and KAI1 in EOC and the control samples, as well as the associations between both 2 biomarkers expression and clinicopathological characteristics of EOC. Overall survival (OS) analysis was conducted used log-rank test with the Kaplan–Meier method. Multivariate OS analysis was conducted using Cox regression model test. Correlation coefficient analysis was performed using the Spearman correlation test. $P < .05$ was defined as statistically significant differences.

3. Results

3.1. Associations between UBE2C and KAI1 expression in EOC and clinicopathological characteristics

The positive expression of UBE2C was mainly located in both the nuclei and cytoplasm. The positive expression of

UBE2C in EOC samples (38.9%, 70/180) was significantly higher than that in the control samples (10.0%, 6/60) (Fig. 1A and B). Furthermore, the positive expression of UBE2C in EOC was significantly associated with grades of differentiation, implants, lymph node metastasis (LNM), as well as FIGO stages. Furthermore, UBE2C expression was significantly higher in high grade serous adenocarcinoma (SA) when compared with low grade SA. And there was no association between positive expression of UBE2C and EOC patients age, tumor size, location, histological type, and ascites (Table 2).

The positive expression of KAI1 was mainly located in both the membrane and cytoplasm. The positive expression of KAI1 in EOC samples (25.0%, 45/180) was significantly lower than that in the control samples (75.0%, 45/60) (Fig. 1C and D). In addition, the positive expression of KAI1 in EOC was inversely associated with grades of differentiation, implants, LNM, and FIGO stages. And there was no association between KAI1 expression and patients age, tumor size, location, histological type, as well as ascites (Table 2). Moreover, KAI1 expression was significantly lower in high grade SA when compared with low grade SA. High grade SA patients had higher rates of implants, LNM and high FIGO stages when compared with low grade SA patients (all $P < .05$).

Table 2
Correlation between the expression of UBE2C and KAI1 and clinicopathological characteristics in EOC.

Variable	UBE2C		P-value	KAI1		P-value
	Negative	Positive		Negative	Positive	
Ages, yr			.873			.086
≤56	71	46		83	34	
>56	39	24		52	11	
Location			.705			.054
Left	46	30		54	22	
Right	45	25		50	20	
Bilateral	19	15		31	3	
Histological type			.164			.508
Serous	79	58		106	31	
Mucinous	18	7		16	9	
Endometrial	8	5		9	4	
Clear cell	5	0		4	1	
Size, cm			.755			.482
≤8.0	67	41		79	29	
>8.0	43	29		56	16	
Ascites			.904			.430
No	65	42		78	29	
Yes	45	28		57	16	
Implantation			.034			.018
No	71	34		72	33	
Yes	39	36		63	12	
Grades of differentiation			.001			.001
Low	74	29		68	35	
High	36	41		67	10	
Lymph node metastasis			.034			.022
No	74	36		76	34	
Yes	36	34		59	11	
FIGO stages			.001			<.001
I + II	65	23		52	36	
III + IV	45	47		83	9	

EOC=epithelial ovarian carcinoma, FIGO=International Federation of Gynecology and Obstetrics, UBE2C=ubiquitin-conjugating enzyme E2C.

3.2. Association between UBE2C expression and KAI1 expression in EOC

There was a negative association between UBE2C expression and KAI1 expression ($r = -0.329$, $P < .05$) (Table 3).

3.3. Univariate and multivariate analyze

As shown in Figure 2A, OS analysis indicated that the OS of patients with UBE2C-positive ovarian tumors was significantly lower than that of patients with UBE2C-negative tumors (log-rank=22.185, $P < .001$). As shown in Figure 2B, OS analysis indicated that the OS of patients with KAI1-positive ovarian tumors was significantly higher than that of patients with KAI1-negative tumors (log-rank=20.960, $P < .001$). In univariate

analysis, OS time was significantly associated with the following clinicopathological characteristics, grades of differentiation (log-rank=8.426, $P = .004$; Fig. 2C), implants (log-rank=47.021, $P < .001$; Fig. 2D), LNM (log-rank=14.971, $P < .001$; Fig. 2E), as well as FIGO stages (log-rank=39.558, $P < .001$; Fig. 2F) (Table 4). High grade SA tumors had unfavorably OS time when compared with low grade SA tumors (log-rank=12.012, $P = .001$; Fig. 2G). Patients with UBE2C-negative/KAI1-positive expression had favorable OS time when compared with UBE2C-positive/KAI1-negative expression group or UBE2C-negative/KAI1-negative expression group (log-rank=36.214, $P < .001$; Fig. 2H). In metastasis-free patients, KAI1-positive expression had a favorable OS time when compared with KAI1-negative expression (log-rank=16.135, $P < .001$; Fig. 2I).

Multivariate analysis of OS demonstrated that positive expression of UBE2C and KAI1, implants, and FIGO stages were independently prognostic factors affecting patients' OS time (Table 5).

4. Discussion

Ovarian cancer is the fifth most common malignant tumor in women. Due to the heterogeneity of EOC, it seriously threatens the health and lives of women. It is an urgent need to study pathogenesis of EOC and comprehensively and thoroughly assesses effectiveness of EOC biomarkers. UBE2C is an important regulator of degradation of mitotic cyclins, regulation

Table 3
The association between UBE2C and KAI1 expression and clinicopathological characteristics in EOC.

Variable	UBE2C		r	P-value
	Negative	Positive		
KAI1			-0.329	<.001*
Negative	70	65		
Positive	40	5		

EOC=epithelial ovarian carcinoma, UBE2C=ubiquitin-conjugating enzyme E2C.

* Negative association.

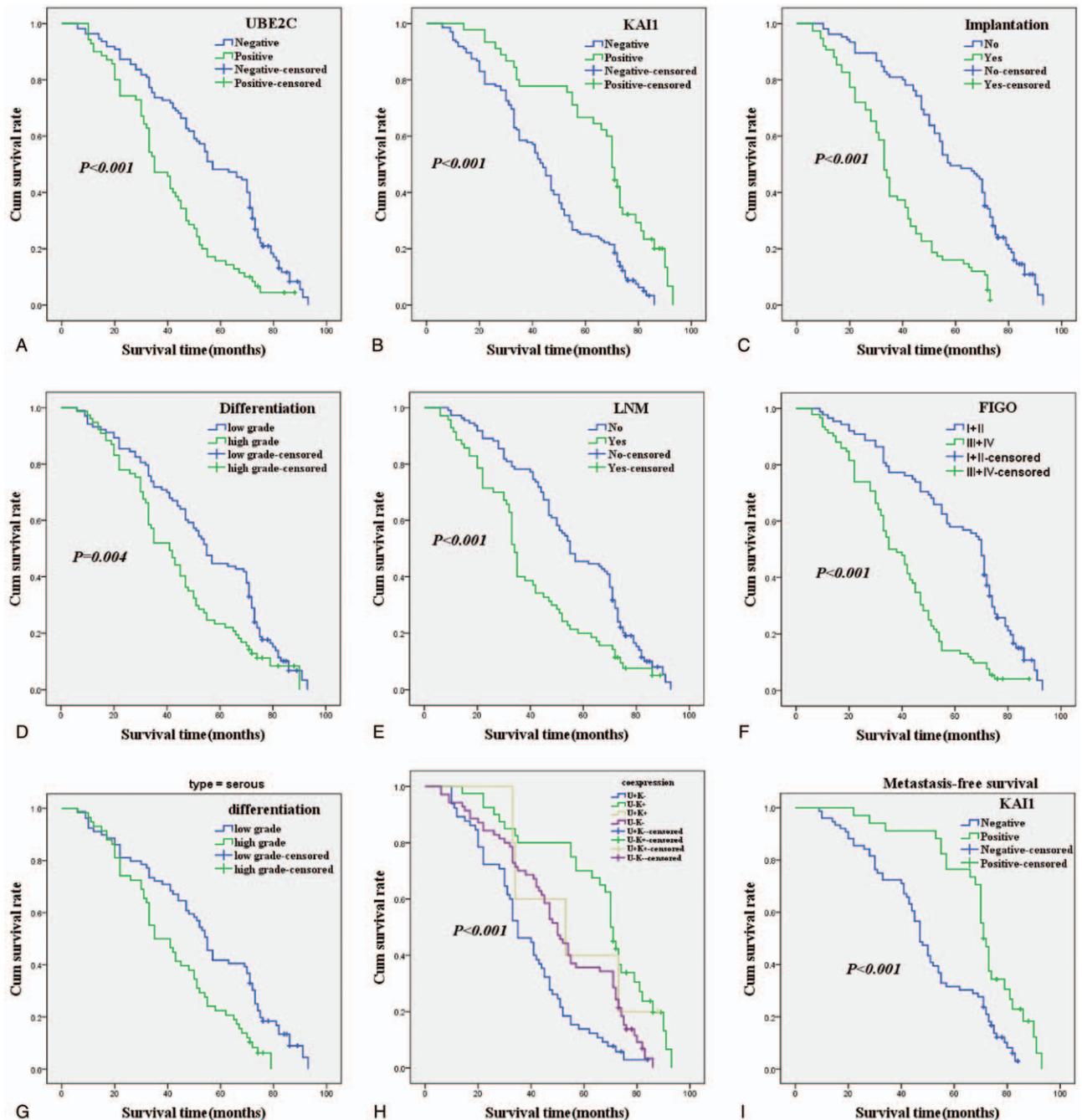


Figure 2. Kaplan–Meier analysis of the survival rate of patients with EOC. The y-axis represents the percentage of patients; the x-axis represents their survival in months. (A) OS of all patients in relation to UBE2C (log-rank=22.185, $P < .001$); (B) OS of all patients in relation to KAI1 expression (log-rank = 20.960, $P < .001$); In A-B analyses, the green line represents patients with positive expression of biomarkers and the blue line representing the negative expression of biomarkers. (C) OS of all patients in relation to grades of differentiation (log-rank = 8.426, $P = .004$; the blue line represents patients with low grades, the green line represents patients with high grades); (D) OS of all patients in relation to implants (log-rank = 47.021, $P < .001$; the blue line represents patients with no implants group, the green line represents patients with implants group); (E) OS of all patients in relation to LNM (log-rank = 14.971, $P < .001$; the blue line represents patients with no LNM group, the green line represents patients with yes LNM group); (F) OS of all patients in relation to FIGO stages (log-rank = 39.558, $P < .001$; the blue line represents patients with I + II stages; the green line represents patients with III + IV stages). (G) OS of all patients in relation to differentiation of serous adenocarcinoma (log-rank = 12.012, $P = .001$; the blue line represents patients with low-grade serous adenocarcinoma; the green line represents patients with high-grade serous adenocarcinoma). (H) OS of all patients in relation to coexpression of UBE2C and KAI1 (log-rank = 36.214, $P < .001$; the blue line represents patients with UBE2C+ KAI1-; the green line represents patients with UBE2C- KAI1+; the brown line represents patients with UBE2C+ KAI1+; the purple line represents patients with UBE2C- KAI1-). (I) OS of metastasis-free patients in relation to KAI1 expression (log-rank = 16.135, $P < .001$; the blue line represents patients with KAI1-negative expression; the green line represents patients with KAI1-positive expression). EOC = epithelial ovarian carcinoma, FIGO = International Federation of Gynecology and Obstetrics, LNM = lymph node metastasis, OS = overall survival, UBE2C = ubiquitin-conjugating enzyme E2C.

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

Variable	n	Mean OS, mo	Log-rank	P-value
UBE2C			22.185	<.001
Negative	110	55.3 ± 23.1		
Positive	70	39.4 ± 19.4		
KAI1			20.960	<.001
Negative	135	44.4 ± 21.5		
Positive	45	63.4 ± 21.7		
Implantation			47.021	<.001
No	105	58.1 ± 21.5		
Yes	75	36.5 ± 18.9		
Grades			8.426	.004
Low	103	53.8 ± 23.5		
High	77	42.8 ± 21.0		
LNM			14.971	<.001
No	110	55.4 ± 21.7		
Yes	70	39.2 ± 21.7		
FIGO stages			39.558	<.001
I and II	88	59.7 ± 22.2		
III and IV	92	39.0 ± 18.9		

FIGO = International Federation of Gynecology and Obstetrics, LNM = lymph node metastasis, OS = overall survival, UBE2C = ubiquitin-conjugating enzyme E2C.

of anaphase-promoting complex, as well as cell cycle progression.^[17,18] Overexpression of UBE2C can promote tumor cell proliferation and malignant transformation.^[6] In this study, positive expression of UBE2C was significantly higher in EOC samples than that in the control samples. Furthermore, overexpression of UBE2C was significantly associated with grades of differentiation, implants, LNM, as well as FIGO stages. OS survival demonstrated that positive expression of UBE2C for EOC's patients had an unfavorable OS time when compared with negative for UBE2C. These findings demonstrated that overexpression of UBE2C should promote EOC invasion and metastasis, should be considered a useful biomarker for prediction of prognosis which is consistent with the previous studies.^[19–22]

Inactivation of tumor metastasis suppressor genes is an important step in tumor invasion and metastasis. KAI1, which belongs to the transmembrane 4 superfamily, is widely considered as a suppressor of tumor metastasis. KAI1 suppresses tumor metastasis through not only inhibiting cell motility, but also suppressing degradation of the ECM.^[23] In this study, positive expression of KAI1 in EOC's samples was significantly lower than that in the control samples. Moreover, positive expression of KAI1 was inversely associated with grades of differentiation, implants, LNM, and FIGO stages. Kaplan–Meier OS analysis demonstrated that EOC's patients with KAI1+ had a favorable OS time when compared with KAI1– for patients. The above results indicated that down- or lost-expression of KAI1 should

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

Variable	B	SE	P	RR	95% CI
UBE2C	0.377	0.186	.043	1.457	1.011–2.100
KAI1	–0.494	0.212	.020	0.610	0.403–0.925
Implantation	0.742	0.190	<.001	2.099	1.445–3.049
FIGO stages	0.707	0.201	<.001	2.028	1.368–3.005

CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, OS = overall survival, RR = Relative risk, SE = Standard error, UBE2C = ubiquitin-conjugating enzyme E2C.

promote tumor cell invasion and metastasis and mean an unfavorable prognosis. Therefore, KAI1 should be considered a useful and valuable biomarker for prediction of metastasis and prognosis of EOC which are similar to the previous studies.^[13,14,16,24,25]

In this study, multivariate analysis demonstrated that positive expression of UBE2C and KAI1, implants, and FIGO stages were independent prognostic factors of OS for EOC's patients. Moreover, UBE2C expression was significantly higher in high grade SA when compared with low grade SA; and KAI1 expression was significantly lower in high grade SA when compared with low grade SA. High grade SA patients had higher rates of implants, LNM, and high FIGO stages when compared with low grade SA. High grade SA patients had unfavorably OS time when compared with low grade SA. Spearman coefficient analysis demonstrated that UBE2C expression was negatively associated with KAI1 expression. It is well known that FIGO stages' system is a crucial guide for determining the clinical therapeutic strategies of EOC. However, FIGO stage's system does not fully show the biological behavior of EOC. So, it is urgent need to find some biomarkers for prediction of tumor invasion, metastasis, and prognosis for EOC. UBE2C is involved in the ubiquitin-proteasome proteolytic pathway which is able to initiate aberrant degradation of proteins encoded by oncogenes and suppressor genes. This may cause aberrant accumulation of these proteins in some organs.^[19] UBE2C may promote cells proliferation, viability, motility, and migration in vitro.^[26,27] Knockdown of UBE2C can lower tumorigenesis.^[28] Down-regulation of UBE2C is able to inhibit N-cadherin expression and enhance E-cadherin expression.^[29,30] Overexpression of UBE2C can promote tumor cell proliferation and malignant transformation and maybe lost promotion of E-cadherin expression which will lead to invade and metastatic. In the same time, down- or lost-expression of KAI1 should lost enhancing stability of E-cadherin/β-catenin complex, this should further promote tumor cell invasion and metastasis. However, the number of specimens in this study is relatively small. Further studies with larger sized specimens, including in vitro, in vivo, and molecular experiment, are needed to support the present observations.

5. Conclusions

Our study indicated that UBE2C and KAI1 are associated with OS time of patients with EOC. Therefore, UBE2C and KAI1 should be considered to show the progression and prognosis of EOC, as well as provide a promising choice of therapeutic target.

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Investigation: Lu Lin, Junjun Dai.

Methodology: Danna Wang.

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Software: Lu Lin, Junjun Dai.

Validation: Lan Yu.

Writing – original draft: Yingying Gong.

Writing – review and editing: Yingying Gong.

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