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ORIGINAL ARTICLE

Expression and significance of ARID1A mRNA in endometriosis-associated ovarian cancer

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Summary

Purpose: *To investigate the expression and relevant clinical and pathological significance of AT-rich interactive domain-containing protein 1A (ARID1A) mRNA in endometriosis-associated ovarian cancer.*

Methods: *The clinical and pathological data of 63 patients with ovarian clear cell carcinoma (OCCC) and of 43 patients with ovarian endometrioid adenocarcinoma (OEAC) were collected. The expression of ARID1A-encoded protein, baf250a, in ovarian cancer tissues was detected using immunohistochemistry. The ARID1A mRNA expression was detected via RNAscope hybridization in situ, and its correlation with the clinical and pathological features of patients was analyzed.*

Results: *The age at the onset of OEAC patients accompanied with endometriosis (CM-EAC) was lower than that of those not accompanied with endometriosis (NCM-EAC) ($p<0.001$). For patients with OCCC, the lymph node metastasis (LNM) rate of CM-CCC patients was significantly lower compared to NCM-CCC ($p=0.02$) and FIGO stage was earlier (stage I and II) ($p=0.013$). The expression of baf250a in OCCC group was significantly lower than that in the EAC group ($p=0.033$). In the OCCC group, baf250a was significantly related to early FIGO staging (stage I and II) ($p=0.026$), while its expression was not significantly associated with FIGO staging of EAC, age, tumor size, occurrence site and LND. The mRNA expression of ARID1A was positively correlated with the expression of baf250a (in OCCC group, $r_p=0.936$, $p<0.01$; in OEAC group, $r_p=0.325$, $p=0.035$). Analysis of prognosis showed that baf250a was an important prognostic factor rather than an independent prognostic factor, affecting the overall survival (OS) of patients with OCCC, while patients with low ARID1A mRNA expression had a longer-term OS.*

Conclusion: *The decreased gene and protein expression levels of ARID1A are related to the occurrence and development of endometriosis-associated ovarian cancer, especially OCCC. The detection of ARID1A mRNA expression may be used to predict the OS of OCCC.*

Key words: *ARID1A, endometrioid adenocarcinoma, endometriosis, ovarian cancer*

Introduction

Ovarian cancer is a malignancy seriously threatening women's life with about 225000 cases newly diagnosed each year worldwide and 52100 new cases in China in 2015. Ovarian cancer is also a gynecologic malignancy with the highest mortality rate. In China 22500 deaths were registered in 2015 [1,2] with a 5-year survival rate about 40% [3]. Early symptoms of ovarian cancer are absent or very wild, and abdominal metastasis often occurs before the symptoms appear. The great majority of the patients (60-70%) are in advanced stage when treated [3].

The pathogenesis of ovarian cancer has not been studied fully, while this malignancy is heterogeneous and its histological types and origin are different. However, the molecular pathogenesis of ovarian cancer is not very clear, because the normal ovarian tissues do not contain epithelial components, so some authors have put forward the idea that most of the ovarian cancers are originated out-

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side the ovary [4]. Studies have found that changes in ectopic endometrium caused by retrograde menstruation or metaplasia may occur in the molecular genetics, which is conducive to the implantation of ectopic lesions. About 1% of endometriosis cases will be malignant [5,6], and the malignancy of ovarian endometriosis cyst is related to the epithelial ovarian carcinoma [4]. The histological types of ovarian cancer derived from endometriosis mainly include endometrioid adenocarcinoma (EAC) and ovarian clear cell carcinoma (OCCC) [7], or mucinous carcinoma and low-grade serous carcinoma occasionally [8]. The occurrence and development of this type of tumor involves many molecules and genetic signaling pathways; the detection at the molecular gene level has found a variety of driver genes of OCCC and EAC, such as KRAS, BRAF, ERBB2, CTNNB1 and PPP2R1A, which are different from other epithelium-originated malignant ovarian tumors [9-14], and ARID1A has been one of the research hotspots in recent years.

ARID1A is one of the members of SWI/SNF chromatin remodeling complex encoding the baf250a protein, and it has been reported in recent years that ARID1A gene mutation exists in various tumors, such as liver cancer, breast cancer, gastric cancer and OCCC, causing deletion of encoded baf250 protein expression, and suggesting that ARID1A, as a tumor suppressor gene, may have multiple functions of anti-proliferation, induction of cell cycle arrest and promotion of cell differentiation, thus playing a role in the neoplastic transformation [9,15-17]. However, genes are mainly activated abnormally through chromosome translocation, point mutation and gene amplification, which are involved in the occurrence and development of tumors. In addition, ARID1A gene mutation can lead to deletion of encoded protein, but will the change in its mRNA level affect the expression of its encoded protein, thus playing a role in promoting tumor progression?

In this study, immunohistochemistry and *in situ* hybridization detection were performed on paraffin samples of endometriosis-associated ovarian cancer, so as to evaluate (1) the correlation between ARID1A mRNA expression and baf250a expression, and (2) the correlation of ARID1A mRNA with clinical and pathological features and prognosis of patients.

Methods

Patients

Pathological data of patients with ovarian cancer diagnosed, treated and followed-up at the General Hospital of PLA from January 2004 to January 2014 were retrospectively reviewed and confirmed by two or more experienced pathologists. Patients receiving radiotherapy or chemotherapy before operation or those with incomplete follow-up data were excluded. A total of 106 formalin-fixed paraffin-embedded (FFPE) tissue samples were studied, coming from 43 cases of OEAC and 63 cases of OCCC; another 30 cases of endometrioid cyst (control group 1) and 25 cases of normal endometrium (control group 2) were used as controls. This retrospective study was approved by the Ethics Committee of General Hospital of PLA. Clinical, pathological and demographic data included age, International Federation of Gynecology and Obstetrics (FIGO) staging, tumor diameter, LNM, occurrence side, menstrual history, carbohydrate antigen 125 (CA125), date of definite diagnosis, record of recurrence or metastasis, and date of death. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and complied with either the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in this study.

Preparation of tissue samples

All the samples were analyzed, the representative area was selected, and the tissue paraffin block of the corresponding area was determined. A total of 10 paraffin blocks made by the tissue chip instrument (QuickRayTM, Unitma, Seoul, Korea) were used in the present study. On each tissue paraffin block 3 different sites were chosen for further chip analysis. Each site was a hole with 1.5mm diameter. Tissue sections (4μm) were cut and placed onto a cation-loaded glass slide.

Immunohistochemistry

All sections were heated at 65°C for 2 hrs, dewaxed and placed into water, treated in 0.01 M sodium citrate buffer (pH=6.0) at 100°C for 2.5 min, and then with 3% H_2O_2 at room temperature for 15 min, washed with distilled water, and then washed with 0.01 M PBS for 5 min for 2-3 times. Then 50 μL goat serum blocking solution was dropped into each section, incubated at room temperature for 30 min, and 50 μL of the primary antibody was added (BAF250a; Sigma, 1:500, USA) for incubation overnight at 4°C. The next day, about 50 μL GTVisionII secondary antibody detection kit (Cell Signalling Technology, Danvers, MA, USA) and mouse/rabbit general sections (Genentech, CA, USA) were incubated at room temperature for 30 min. The sections were then washed with 0.5 M PBS for 3 times (5 min/time), followed by DAB staining for 1-10 min until the optimal staining was observed under the microscope. After washing for 3 min and hematoxylin staining for 5 min, sections were washed, treated with 1% ethanol for 30 s and 0.5M PBS for 2 min, followed by dehydration and sealing. Interpretation of results: All stained sections were independently assessed by two pathologists. The number of cases with uniform staining was evaluated and samples that could not adhere to the slides

were excluded. Baf250a was expressed in the nucleus and the loss of baf250a expression was defined as >90% lack of nuclear staining [16].

RNAscope in situ hybridization

RNA *in situ* hybridization was performed for the experimental and control group 1 using the RNAscope 2.5 high sensitivity brown kit (Advanced Cell Diagnostics, Inc., Hayward, CA). The probe used was the specific Hs-ARID1A. All experimental procedures were based on the manufacturer's instructions. FFPE tissue sections (4μm) were pretreated by protease and then hybridized using ARID1A probes (Advanced Cell Diagnostics, Inc., Hayward, CA). After that, primary amplicons, secondary amplicons and HRP-labeled oligonucleotide probes were added into the stepwise hybridization, followed by color development via DAB. The integrity of RNA in each sample was evaluated using Hs-PPIB as the positive control probe. Non-specific background signals were evaluated using DAPB as the negative control probe. The samples were stained with Gill's hematoxylin to re-stain the nucleus. The specific signal of target RNA was brown, dotted or clustered. Interpretation of results: 1) The number of signal points in each cell was assessed instead of the intensity; each point represented a RNA molecule, and the signal intensity corresponded to the number of probes binding to the RNA molecule; 2) When different results were detected in the three test nuclei, the result with the most average copy number was selected.

Statistics

Statistical Package for Social Sciences (SPSS) 23.0 (SPSS, Chicago, IL) was used for data analysis. Chi-square test or Fisher's exact test were used for classified variables; Pearson chi-square analysis was used for evaluating the correlations among variables, and Kaplan-Meier method and multivariate Cox regression model were used to estimate the progression-free survival (PFS) and OS. All statistical tests were bilateral and $p<0.05$ suggested that the difference was statistically significant.

Results

General clinicopathological data

The age of 106 patient ranged from 23 to 77 years. Among 43 patients with OEAC, there were 12 cases (27.9%) in stage I, 12 cases (27.9%) in stage II, 16 cases (37.2%) in stage III and 3 cases (7.0%) in stage IV. The mean tumor diameter of OEAC was 6.63 cm. Among 63 patients with OCCC, there were 31 cases (49.2%) in stage I, 12 cases (19.0%) in stage II, 18 cases (28.6%) in stage III and 2 cases (3.2%) in stage IV. The mean tumor diameter of OCCC was 6.77 cm.

A total of 50 cases (47.17%) were accompanied with endometriosis. The patients accompanied with endometriosis accounted for 46.03% (29/63) in those with OCCC and 48.84% (21/43) in those with OEAC. According to the results observed under the microscope, patients were divided into 4 groups: CM-OCCC, NCM-OCCC, CM-OEAC and NCM-OEAC. The comparisons of clinical data among the 4 groups are shown Table 1.

In OEAC, CM-OEAC had a statistically significant difference in the onset age compared with NCM-OEAC; 80.95% of patients with CM-OEAC were younger than 50 years, while 81.82% of patients with NCM-OEAC were older than 50 years ($p<0.001$); in terms of FIGO staging, the incidence

Table 1. Correlation analysis of clinicopathologic data of each experimental group

	Group	*CM-OEAC*	*NCM-OEAC*	*p*	*CM-OCCC*	*NCM-OCCC*	*p*
Age, years	≥50	4	18		13	24	
	<50	17	4	<0.001	16	10	0.038
LNM	Yes	4	4		3	12	
	No	17	18	1	26	22	0.02
FIGO stage	I	9	3		16	15	
	II	5	7		9	3	
	III	5	11		3	15	
	IV	2	1	0.117	1	1	0.013
Tumor diameter (cm)	≥6.7	6	13		13	15	
	<6.7	15	9	0.371	16	19	0.955
Occurrence site	Right	12	10		15	14	
Laterality		4	1	0.122	4	8	0.56
Menstrual history	Menopause	8	6		10	26	
	Non-menopause	13	16	0.449 (55)	19	18	0.04
Serum CA125		454.75±650.23	499.14±610.37	0.467	600.04±873.03	430.25±698.60	0.232

For abbreviations see text

rate of CM-OEAC in early FIGO stage (I+II) was 66.67%. Thus, CM-OEAC was more likely to occur in OEAC patients younger than 50 years with earlier FIGO stage.

In OCCC, CM-OCCC patients younger than 50 years accounted for 55.17%, while most NCM-OCCC patients were older than 50 years; 89.66% of the patients with CM-OCCC did not have LNM, while 64.71% of the patients with NCM-OCCC did not have LNM the difference being statistically significant (p=0.02). In terms of FIGO staging, the incidence rate of CM-OCCC in early stages (I+II) was 86.21%, and in the later stages (III+IV) was 13.79%; FIGO stage IV showed significant difference compared with NCM-OCCC (p=0.013). In terms of menstrual history, 65.52% CM-OCCC patients had regular menstruation and 59.09% NCM-OCCC patients were in menopause (p=0.04).

Relationship between protein expression and clinicopathological features

Baf250a was located in the nucleus, and its deletion rate was 44.44% in the OCCC, 32.56% in the OEAC, 33.33% in the ectopic cyst and 20% in the endometrium (Figure 1). The expression of baf250a was significantly different between the OCCC group and the endometrium control group (p=0.033). The different expressions of baf250a in OCCC, OEAC, ectopic cyst and endometrium are shown in Figure 1 and Table 2. In the OCCC group, baf250a was associated with FIGO staging (p=0.026), but not with age, tumor diameter, occurrence site and LNM. The low expression of baf250a was not significantly associated with the clinical and pathological parameters of OEAC.

Relationship between ARID1A mRNA and clinicopathological data

In the *in situ* hybridization detection of ARID1A mRNA, the analysis of clinical data of the OCCC, OEAC and ectopic cyst groups showed that its expression was related to the histological type (p=0.006), and the expressions of ARID1A in different histopathological subgroups were highly correlated. Besides, the proportion of low expression of ARID1A mRNA was 46% (46.03%) in the OCCC subgroup, 34.88% in the OEAC subgroup (p=0.006) and 30% in the ectopic cyst group. In addition, its expressions in EM-OCCC and CM-OEAC were lower (p=0.013) than those in NEM-OCCC and ENM-OEAC. The positive rate of ARID1A mRNA in the OCCC was 53.97%, 65.12% in the OEAC and 70% in the ectopic cyst (Figure 2). The ARID1A mRNA expression was associated with FIGO staging in OCCC (p=0.026). The ARID1A mRNA expression in OCCC was associated with the expression of baf250a (r_p=0.936, p<0.01), as well as the expression of baf250a in OEAC (r_p=0.325, p=0.035).

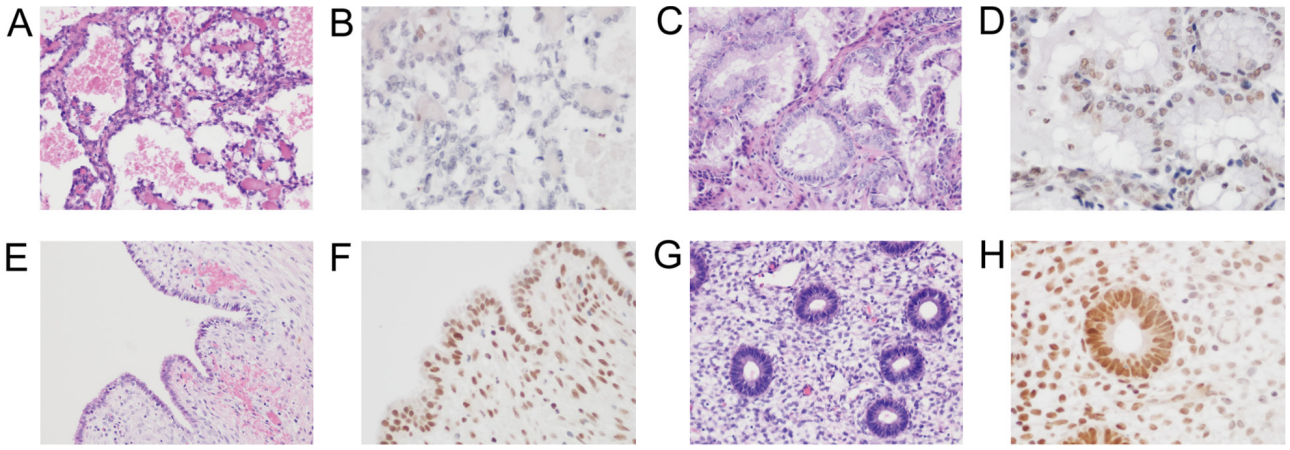

Figure 1. Immunohistochemical expression of ARID1A-encoding protein baf250a in OCCC. **(A)** HE photograph of OCCC, intraglandular eosinophil substrate; hobnail cells (200×); **(B)** In OCCC, baf250a deletion is found (200×); **(C)** HE photograph of OEAC, micropore type, and some eosinophilic tumor cells (200×); **(D)** Inn OEAC, baf250a is expressed in the nucleus of cancer cells (400×); **(E)** HE photograph of ectopic cysts (200×); **(F)** Baf250a is expressed in the nucleus of ectopic cyst epithelial cells, and some interstitial cells are also stained positively (400×); **(G)** HE photograph of normal endometrium (200×); **(H)** Baf250a is expressed in the nucleus of normal endometrial epithelial cells (400×).

Table 2. p-AKT, p-mTOR, p110α and baf250a expressions in test and control groups

		OCCC *n (%)*	*OEAC* *n (%)*	*Ectopic cyst* *n (%)*	*Endometrium* *n (%)*
baf250a	Negative	28 (44.44)	14 (32.56)	10 (33.33)	5 (20)
	Positive	35 (55.56)	29 (67.44)	20 (66.67)	20 (80)

For abbreviations see text

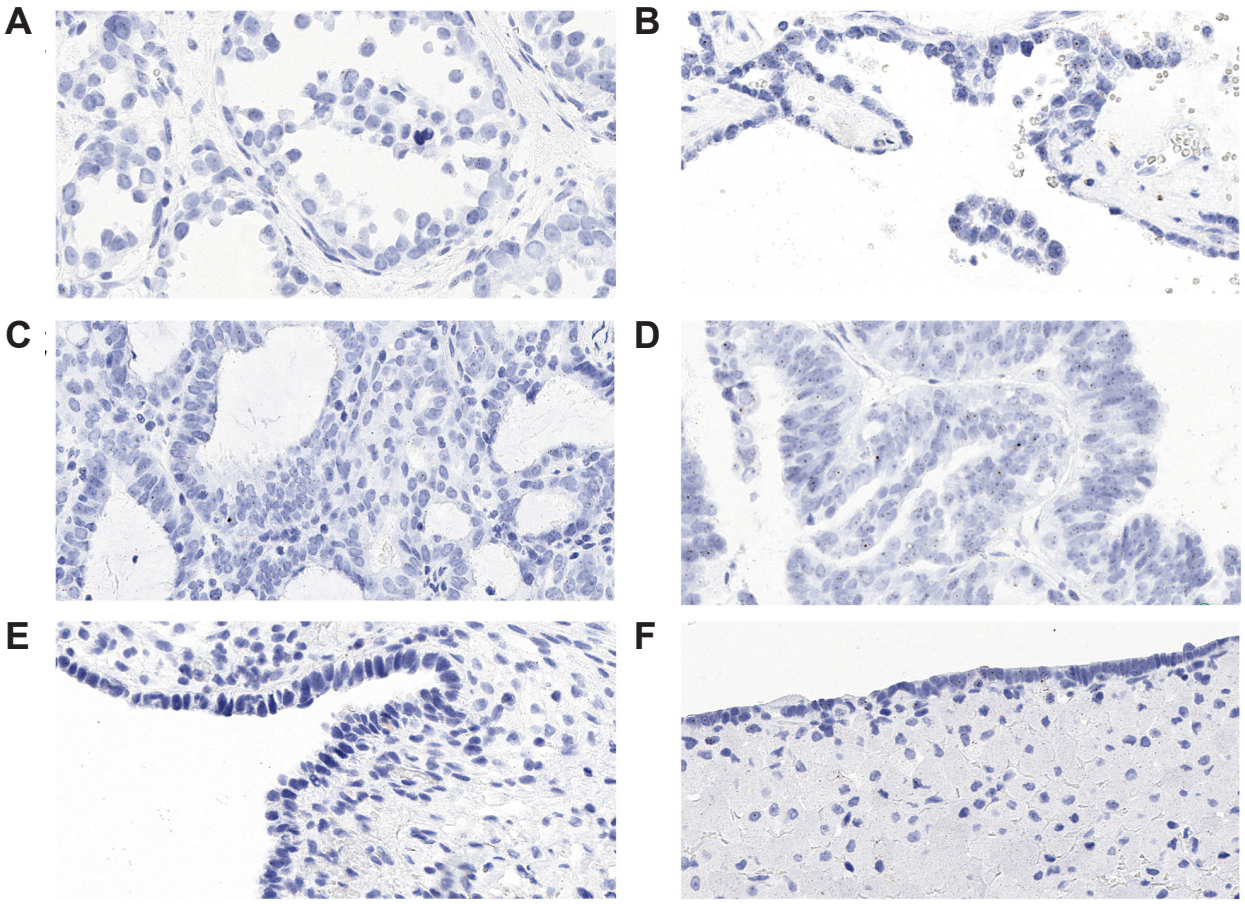

Figure 2. Expression of ARID1A was detected by in situ hybridization. ARID1A is expressed lowly in EM-CCC **(A)**, highly in NEM-CCC **(B)**, lowly in EM-EAC **(C)**, highly in ENM-EAC **(D)** and ectopic cyst **(E, F)**.

Table 3. Univariate analysis of progression-free survival (PFS) and overall survival (OS) in OCCC

	PFS			OS		
	Chi-square	*Df*	*Sig.*	*Chi-square*	*Df*	*Sig.*
LNM	6.029	1	0.014	0.048	1	0.827
FIGO staging	18.240	1	<0.001	0.004	1	0.947
Tumor diameter	0.698	1	0.404	7.127	1	0.008
Occurrence side	19.909	2	<0.001	0.521	2	0.771
baf250a	2.425	1	0.119	7.397	1	0.007
ARID1A mRNA	0.895	1	0.344	4.204	1	0.040

Effects of ARID1A expression and clinical data on prognosis

All patients of this study (n=106) were followed up and 1 case was lost. The total 5-year OS rate in all groups was 88.68%. In the OCCC group, there were 4 deaths accompanied with endometriosis, and 6 deaths not accompanied with endometriosis, but without statistically significant difference between the groups (p=0.741). In the OEAC group, no death accompanied with endometriosis and 2 deaths not accompanied with endometriosis were noticed (p=0.485). The relationship between prognostic indicators in OCCC and OEAC subgroups is discussed below.

Univariate analysis showed that LNM, FIGO staging (I+II and III+IV) and occurrence site of OCCC were important prognostic factors of DFS. Univariate analysis also showed that the tumor diameter and baf250a were important prognostic factors affecting the OS of OCCC patients (Table 3). Cox multivariate analysis showed that FIGO staging was an independent prognostic factor for OS in OCCC patients. In OCCC, patients with low ARID1A mRNA expression had good OS with a statistically significant difference (p=0.023). Univariate and multivariate analyses showed that age in OEAC patients was an important prognostic factor for OS for OEAC (Table 4, Figure 3).

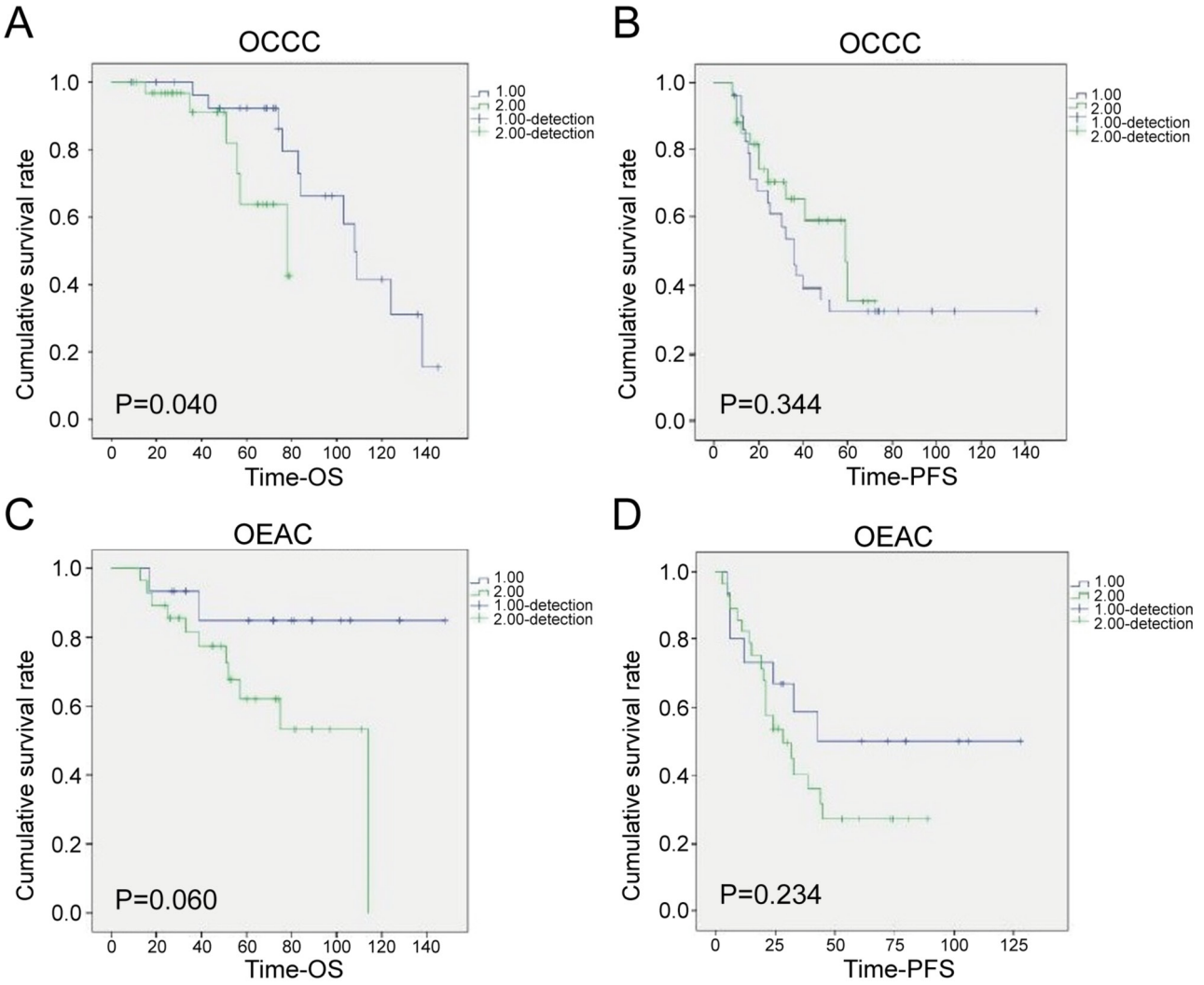

Figure 3. Kaplan-Meier overall survival analysis of ARID1A mRNA. **(A)** Survival curves of overall survival of ARID1A in OSCC (p=0.344); **(B)** survival curves of progression-free survival of ARID1A in OSCC (p=0.060); **(C)** Survival curves of overall survival of ARID1A in OEAC (p=0.040); **(D)** survival curves of progression-free survival of ARID1A in OEAC (p=0.234).

Table 4. Univariate analysis of progression-free survival (PFS) and overall survival (OS) in OEAC

	PFS			OS		
	Chi-square	*Df*	*Sig.*	*Chi-square*	*Df*	*Sig.*
Age	0.464	1	0.496	4.225	1	0.040
baf250a	1.688	1	0.194	1.626	1	0.202
ARID1A mRNA	1.414	1	0.234	3.540	1	0.060

Discussion

ARID1A is the most common inactivated subunit in SWI/SNF complexes. ARID1A gene is currently considered as a tumor suppressor, and its inactivation can be observed in a variety of malignant tumors [18]. ARID1A-encoded baf250a protein inhibits cell proliferation mainly through regulating cell cycle, binds to the cell cycle protein CDK2/CDK4 complex and inhibits its activity by inducing the expression of P21 factor and arrests cell cycle at G1 phase. Except G0 phase, ARID1A is downregulated in other phases, and is almost completely deleted in cells with vivid division [19]. Deletion of baf250a expression is often associated with ARID1A mutations, and its mutation exists widely in OCCC and OEAC, transitional zone and atypical endometriosis [20,21]. The results of this study showed that the deletion rates of baf250a expression in the OEAC and OCCC group were increased compared with those in the ectopic cyst group and endometrium group, suggesting that

baf250a may be a sign of endometriosis malignancy. In the OCCC group, baf250a was associated with FIGO staging, indicating that the deletion of baf250a expression may be an early event in tumorigenesis.

The deletion of baf250a (corresponding to ARID1A gene) is considered as a key event in EM-derived OCCC, because it is specific for this subtype of ovarian cancer; the deletion of nuclear baf250a expression was observed in 36% of OCCC and OEAC groups [22]. The clinical and prognostic effects of baf250a expression in OCCC and OEAC were different in different studies. A study has shown that deletion of baf250a expression did not affect the OS [23], which was consistent with our present study. However, another study has shown that deletion of baf250a expression is significantly associated with the late stage and shorter-term PFS and OS [24], which is consistent with our results in OCCC.

Several authors have reported that the ARID1A gene mutation is a major molecular marker of OCCC and OEAC, and most mutations are intraframe shift or nonsense mutations, indicating its role as a tumor suppressor gene [25-27]. At present, the study on ARID1A gene mainly focuses on the detection of mutations, but there is little research on the ARID1A gene amplification. We tried to use the RNAscope technique in the *in situ* study on ARID1A mRNA. The results obtained showed that the positive rate of ARID1A mRNA in OCCC was 53.97%, 65.12% in OEAC and 70% in ectopic cyst, showing a gradually decreasing trend in the progression of EM, which indicated that the low mRNA expression of ARID1A is related to the progression of disease. In addition, the ARID1A mRNA expression was associated with FIGO staging in OCCC, suggesting that gene changes occur in the early stage of disease. In experimental groups, the ARID1A mRNA expression was related to the expression of its encoded protein baf250a and the ARID1A mRNA expression was also an important prognostic factor in the OCCC subgroup, suggesting that ARID1A mRNA can effectively predict the progression of tumor. No doubt, larger sample sizes are needed in future studies to further determine the role of ARID1A mRNA in prognosis.

We conclude that the decrease in ARID1A mRNA expression level is associated with the histological types of endometriosis-associated ovarian cancer, especially the OCCC subtype, which may occur at the early stage of disease. In OCCC, ARID1A mRNA level is related to the expression of baf250a. Detection of mRNA expression of ARID1A can be used to predict the OS of OCCC.

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Conflict of interests

The authors declare no confict of interests.

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