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Original contribution

GATA6: a new predictor for prognosis in ovarian cancer☆,☆☆

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Summary Ovarian cancer (OC) is the main cause of gynecological cancer–associated mortality. Improving the diagnosis is important for guiding clinical treatment. The present study aimed to investigate the relationship between expression of GATA6, a stem cell factor, and its prognosis in OC. In total, 521 OC cases were included. Immunohistochemistry analysis demonstrated that GATA6 was expressed in both high-grade serous carcinoma as well as non-serous tumors. High grade serous carcinoma showed a higher percentage of GATA6 positive staining. Positive staining of GATA6 showed worse overall survival (OS) in all ovarian cancers or serous and non-serous carcinoma individually. GATA6 was revealed as an independent risk factor for prognosis by multivariate Cox analysis. In all, GATA6 may present as a novel marker for poor prognosis in OC.

1. Introduction

Ovarian cancer (OC) is the most lethal gynecologic malignancy and accounts for the majority of cancer-related deaths among all gynecological malignancies [1]. Due to majority of patients presenting at advanced stage, aggressive nature and nearly ubiquitous emergence of chemo-resistance, OC prognosis is poor, with progression free survival in advanced stage disease around 15 months and 5-year overall survival (OS) around 30% to 40% [2-4]. Although significant changes in the available therapeutic agents and strategies have been made during the past decade, the prognosis of OC remains poor. Therefore, it is important to identify new prognostic indicators to specifically guide therapeutic strategies for these patients.

GATA6 (GATA binding protein 6) is a member of the GATA family, an evolutionarily conserved family of zinc-finger transcription factors. As a transcription factor, GATA6 is involved in cell lineage differentiation and organogenesis of many tissue types and is expressed in early embryonic stem cells, with temporal

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and spatial expression specificity [5-8]. The overexpression of GATA6 helps to maintain heart stem cells during cardiomyogenic differentiation [9], while the targeted inactivation of GATA6 in mice leads to early embryonic lethality due to the inability to achieve endodermal differentiation [5,10,11].

The GATA6 expression in tumor development shows conflicting results; it can function as a tumor promoter or suppressor depending on the tumor type. Its tumor promoting role has been reported in carcinoma from the digestive system including colon cancer [12], pancreatic cancer [13], cholangiocarcinoma [14], and esophageal adenocarcinoma [15]. It has been recently reported that there is GATA6 regulated Wnt niche dependency in human pancreatic ductal adenocarcinoma (PDAC), which confers pancreatic tumors with progressive capacity independently of the stem cell niche [16]. In these studies, overexpression of GATA6 contributes to invasion, metastasis and tumor growth, while also correlating with poor survival. The tumorigenicity of cancer cells has directly been shown to be markedly impaired by knock-down of GATA6 in vitro and in vivo [17,18]. However, other studies demonstrated a suppressor role of GATA6 in cancer. Retinoic Acid induces G0/G1 cell cycle arrest and activates terminal differentiation by activating the expression of GATA6 in TKI resistant lung cancer cells, suggesting a negative role of GATA6 in this process [19]. In gastric cancer, GATA6 methylation was detected in the majority of the patients and was associated with shorter overall survival [20]. Loss of GATA6 was also shown to be involved in malignant transformation in astrocytoma [21].

The role of GATA6 ovarian cancer (OC) progression and prognosis is not clear. In this study, we aim to investigate the expression of GATA6 in a large cohort of ovarian cancer and correlate with clinical pathologic features and prognosis.

Table 1 Clinicopathological features of the ovarian cancer (OC) patients according to GATA binding protein 6 (GATA6) expression grouping

Features	GATA6		$P^{\#}$
	Negative	Positive	
Total cases included	427	94	
Age			1.0
<55	149 (81.9%)	33 (18.1%)	
≥55	277 (82.2%)	60 (17.8%)	
Grade			.367
High grade	375 (81.3%)	86 (18.7%)	
Low grade	31 (88.6%)	4 (11.4%)	
Primary tumor stage			.122
T1/T2	60 (89.6%)	7 (10.4%)	
T3/T4	362 (81.0%)	85 (19.0%)	
Histological type			.019
Serous carcinoma	323 (80.0%)	81 (20.0%)	
Non-serous carcinoma	104 (89.7%)	12 (10.3%)	
Neoadjuvant chemotherapy			.59
Yes	53 (85.5%)	9 (14.5%)	
No	279 (81.3%)	64 (18.7%)	
Ascites			.301
Yes	265 (79.1%)	70 (20.9%)	
No	52 (85.2%)	9 (14.8%)	
Regimen			.172
Platinum	42 (87.5%)	6 (12.5%)	
Platinum and taxol	208 (78.8%)	56 (21.2%)	
Platinum and cytoxan	52 (91.2%)	5 (8.8%)	
No chemotherapy	16 (84.2%)	3 (15.8%)	
Other	81 (83.5%)	16 (16.5%)	
OS			.041
≤5 years	274 (79.7%)	70 (20.3%)	
>5 years	153 (86.9%)	23 (13.1%)	
Clinical response			.725
Complete/partial	332 (82.0%)	73 (18.0%)	
No	49 (80.3%)	12 (19.7%)	

$^{\#}$ P is for χ^2 or Fisher exact test, $P < .05$ regarded as statistically significant.

2. Materials and methods

2.1. OC patients and clinical samples

A total of 521 patients diagnosed with OC between 1987 and 2006, at University of Texas MD Anderson Cancer Center were included. Of the cases, there were 404 serous carcinomas, 41 endometrioid carcinomas, 13 mucinous adenocarcinomas, 12 clear cell carcinomas, 11 undifferentiated adenocarcinomas, 14 Malignant mixed mÜllerian tumors (MMMTs), and 25 other subtypes. The age of the patients ranged from 20 to 92.4 years, with a mean age of 59.2 years. Clinical features of the 521 cases are summarized in Table 1. Overall survival (OS) was defined from the date of diagnosis until the event endpoint or the date of end time of this study, while disease-free survival (DFS) was defined from the date of surgery to tumor recurrence.

2.2. Tissue preparation and ethical considerations

The use of the samples in this study was approved by the institutional review board (IRB) of MD Anderson Cancer Center. After being paraformaldehyde-fixed and paraffin-embedded, tissues were arrayed and were cut into 4-μm sections, coded, and stained with H&E for evaluation; the evaluators were blinded to patient samples. The histological subtypes and grades were defined in surgical pathology reports.

2.3. Immunohistochemistry assay

Expression of GATA6 in the OC tissues and normal ovarian tissue was determined by IHC. The paraffin-embedded TMA slides were deparaffinized with xylene, rehydrated by graded ethanol, and rinsed in deionized water. Antigen retrieval was then performed in a Universal Decloaker (Biocare Medical). After cooling for 20 min, 3% hydrogen peroxide was applied to abolish the endogenous peroxidase reaction. The slides were then subjected to immunohistochemistry, incubated with polyclonal rabbit anti-GATA-6 antibody (Cell Signaling, dilution 1:200) at 4°C overnight. Then a MACH 3

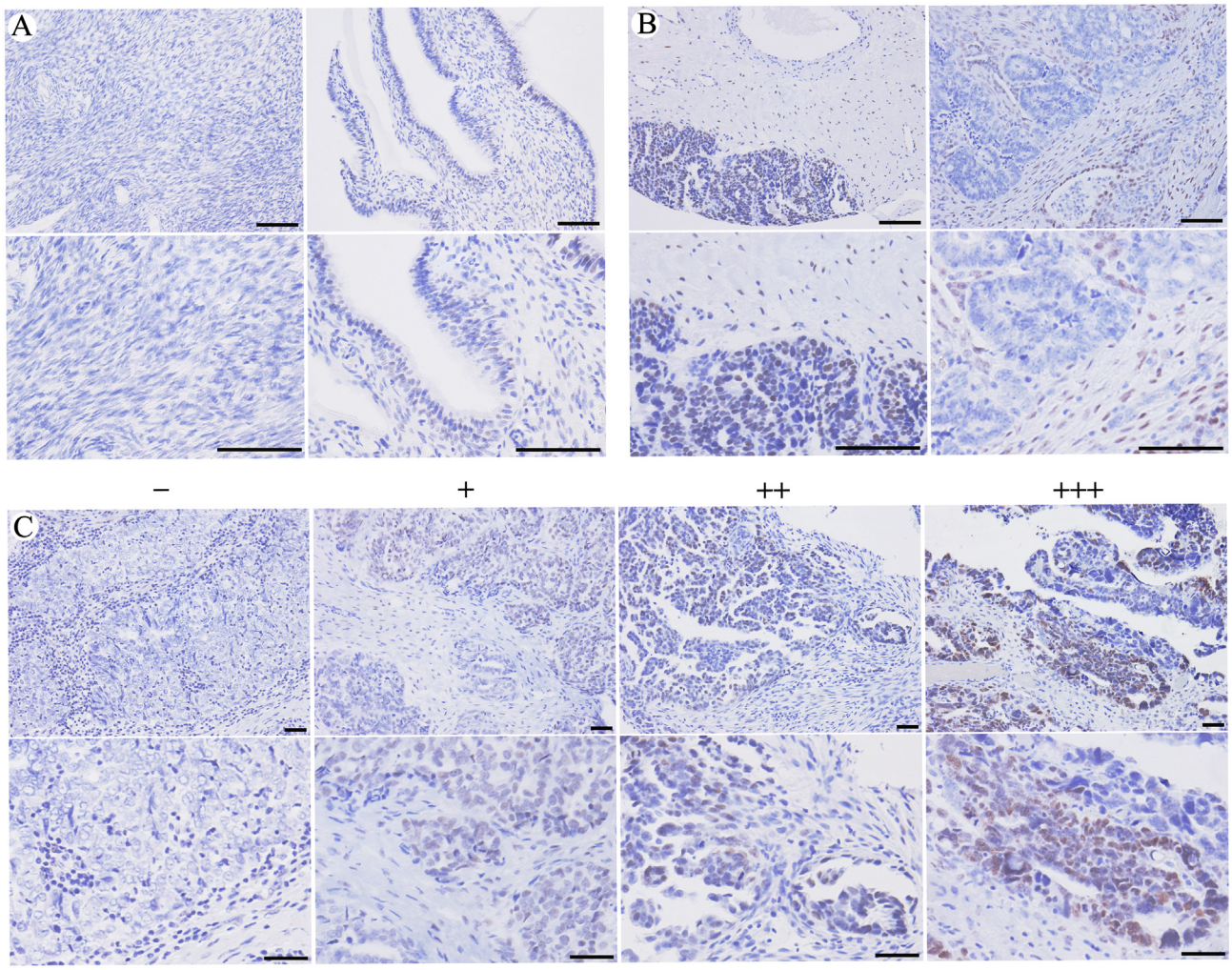

Fig. 1 Expression of GATA6 in normal ovarian tissue and OC clinical samples by IHC. A, Representative images of GATA6 expression in normal ovarian tissues, including the negative staining (left) and the weak positive staining (right). B, Representative images of positive expression of GATA6, including expression of GATA6 in the tumor and stroma cells (left) and expression only in the stroma cells (right). C, Representative images of negative (−), weak positive (+), intermediate positive (++), and strong positive staining (+++) in OC tissues. (Scale equal to 50 um).

Rabbit Probe was applied for 10 min, followed by a MACH 3 Rabbit HRP-Polymer for 10 min. 3,3′-diaminobenzidine (DAB, Sigma) was used to visualize the antibody binding and counterstained with hematoxylin. These incubations were all performed at room temperature, and between incubations sections were washed with TBST buffer. Lastly, these sections were dehydrated, vitrified, and mounted. The specificity of the immunostaining of GATA6 was verified using PBS on TMA slides. Intestinal glands were stained for use as a positive control, while the intestinal smooth muscle was used for the negative control.

2.4. Immunohistochemical evaluation

All the sections were analyzed under a light microscope (Olympus), with the subcellular localization and intensity of staining assessed by two independent pathologists. In general, GATA6 was mainly expressed in the nucleus. As described by Elisa Specht et al [22], IRS was applied for the IHC staining evaluation. The score was calculated as Staining Intensity (SI) × Percentage of positive cells (PP). Staining intensity and positive percentage were classified into four and five grades, respectively:

SI value: 3 points, dark brown; 2 points, light brown; 1 point, yellow; 0 point, negative; PP value:4 points, >80%; 3 points, 50%-80%; 2 points, 10%-50%; 1 point, <10%; 0 point, 0%; an IRS value ≥3 points was considered as positive.

2.5. Statistical analysis

Data was analyzed by SPSS 17.0 software. For categorical data, chi-square analysis or Fisher exact test was used. Kaplan–Meier and Cox analysis were applied for survival analysis, including OS and DFS. Statistical significance was set at $P < .05$.

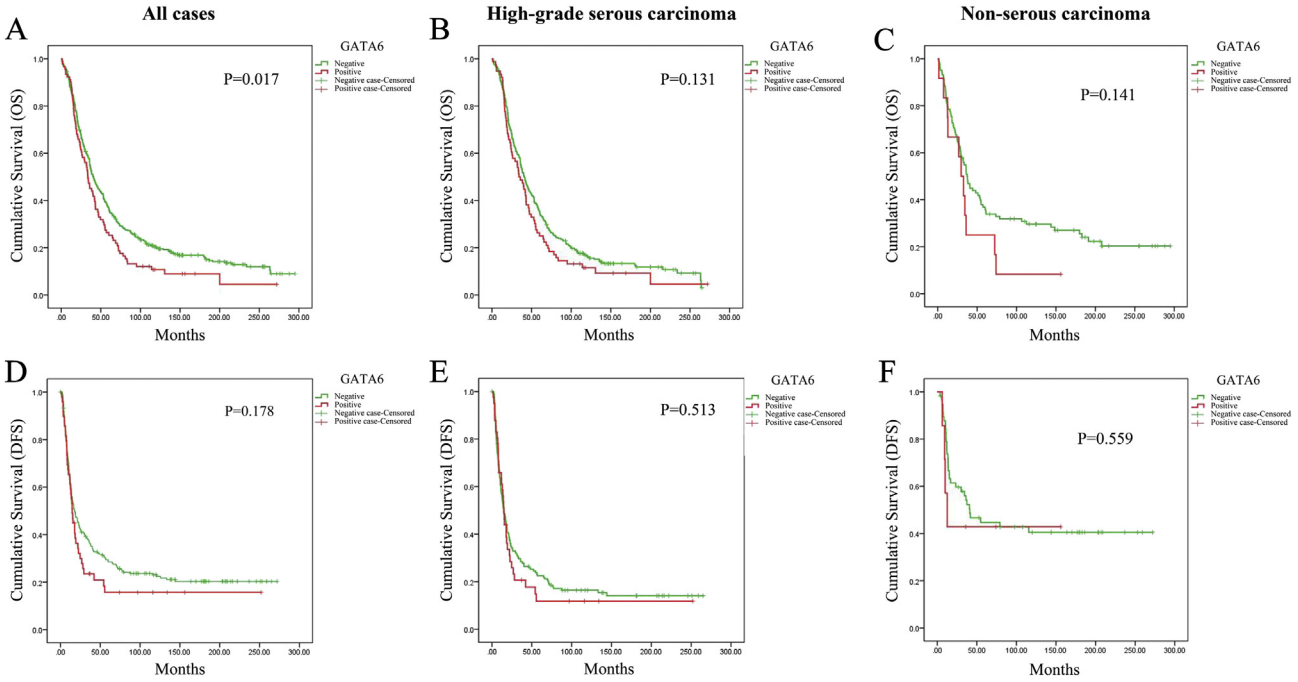

Fig. 2 Kaplan–Meier curves showing correlation between GATA6 expression and survival in OC. A, OS versus GATA6 expression in all patients ($P = .017$). B, OS versus GATA6 expression in high-grade serous carcinoma patients ($P = .131$). C, OS versus GATA6 expression in non-serous carcinomas ($P = .141$). D, DFS versus GATA6 expression in all patients ($P = .178$). E, DFS versus GATA6 expression in high-grade serous carcinoma patients ($P = .513$). F, DFS versus GATA6 expression in non-serous carcinomas ($P = .559$).

3. Results

3.1. Expression of GATA6 in OCs

By IHC, 94 of 521 ovarian cancer tissues (18.0%) were verified as GATA6 positive by IHC staining (Table 1). The positive control and negative control is shown in Fig. 1. Generally, expression of GATA6 in normal ovarian tissue was mainly located in the epithelial cells and displayed negative or weak positive staining (Fig. 1A). However, in OC tissues, GATA6 expression varied from negative to strong positive (Fig. 1C). The majority of the positive samples exerted staining in the tumor cells, while some cases showed stromal expression of GATA6 (Fig. 1B). These data demonstrated that GATA6 expression was heterogeneous in different OC tissues.

3.2. Expression of GATA6 was negatively associated with prognosis in OC patients

The OS of OC patients was associated with the GATA6 expression. Patients with OS ≤5 years had a higher rate of GATA 6 positivity than those with OS greater than 5 years (20.3% versus 13.1%, $P = .041$, Table 1), suggesting that GATA6 may indicate a poor prognosis in OCs. To validate this finding, survival analysis was performed in the 521 OC cases collected.

Kaplan-Meier analysis showed a negative correlation between GATA6 expression and OS (P = .017, Fig. 2A), as positive expression of GATA6 had a worse prognosis. As the main histopathological subtype, high-grade serous carcinoma was analyzed independently. As shown in Fig. 2B, there was an trend between GATA6 expression and OS in this specific subgroup ($P = .131$). There was a propensity for higher GATA6 expression accompanied by a shorter DFS in all ovarian cancer cases ($P = .178$, Fig. 2D), expression of GATA6 did not predict DFS in high-grade serous carcinoma cases ($P = .513$, Fig. 2E). All non-serous carcinomas were also analyzed as a group, with GATA6 showing a trend for OS although it did not reach statistical significance ($P = .141$, Fig. 2C) but did not predict DFS in the non-serous carcinoma group ($P = .559$, Fig. 2F). Histopathological type, histological grade, primary tumor stage, debulking status, clinical response to chemotherapy, relapse, and occurrence of ascites were all significantly associated with OS ($P < .05$, Table 2). To avoid confounder effects, Multivariate Cox analysis was applied. First, the interrelated factors were screened out by correlation analysis. Age, expression of GATA6, primary tumor stage, histological grade, clinical response to chemotherapy, and occurrence of ascites were included in the Cox analysis. Positive staining of GATA6 emerged as an independent predictor for poor overall survival ($P = .007$; Table 3). Meanwhile, primary tumor stage, clinical response to chemotherapy and occurrence of ascites were all independent predictors for prognosis ($P < .05$). In all, data revealed expression of GATA6 was a risk factor that can predict poor prognosis in OC patients.

Table 2 Univariate survival analysis of clinicopathological parameters of patients with ovarian cancer

Features	Overall survival (months, mean ± SE)		*P*
Age	<55	≥55	.052
	85.2 ± 7.2	68.1 ± 4.5	
Histological type	Serous carcinoma	Endometroid adenocarcinoma	<.0001
	69.1 ± 3.9	145.8 ± 20.0	
	Mucinous adenocarcinoma	Clear cell carcinoma	
	110.8 ± 30.6	79.5 ± 28.0	
	Undifferentiated carcinoma	MMMT[#]	
	47.5 ± 16.4	45.0 ± 14.4	
	Mixed type carcinoma	Other	
	19.1 ± 4.5	52.1 ± 15.2	
Location	Unilateral	Bilateral	.055
	111.5 ± 12.0	80.9 ± 6.1	
Grade	Low grade	High grade	.02
	113.0 ± 19.9	69.2 ± 3.8	
Primary tumor stage	T1&T2	T3&T4	<.0001
	152.5 ± 14.5	63.4 ± 3.7	
Ascites	Yes	No	.005
	66.7 ± 4.6	101.0 ± 12.6	
Relapse	No	Yes	<.0001
	217.8 ± 12.3	55.1 ± 3.1	
Debulking status	Optimal	Sub-optimal	<.0001
	104.7 ± 6.9	51.6 ± 5.4	
Clinical Response	Yes	None	<.0001
	87.9 ± 4.7	18.6 ± 3.0	
GATA6	Negative	Positive	.017
	79.3 ± 4.6	55.1 ± 7.0	

[#] Malignant mixed mÜllerian tumor.

Table 3 Cox analysis for overall survival of ovarian cancer

Factors	Overall survival	*P*
	Hazard ratio (95% confidence interval(CI))	
Age (<50/≥55)	1.106 (0.864–1.415)	.425
GATA6 (Negative/positive)	1.482 (1.116–1.968)	.007
Primary tumor stage (I–II/III–IV)	1.915 (1.143–3.210)	.014
Histological grade (high/low)	1.326 (0.733–2.399)	.350
Occurrence of ascites(yes/no)	1.488 (1.066–2.079)	.02
Clinical response (yes/no)	0.199 (0.141–0.280)	<.0001

Table 4 Correlation between GATA6 expression and the histopathological subtype of ovarian cancer

Histological type	GATA6		$P^{\#}$
	Negative	Positive	
Serous carcinoma	323 (80.0%)	81 (20.0%)	.032
Mucinous carcinoma	9 (69.2%)	4 (30.8%)	
Endometroid adenocarcinoma	40 (97.6%)	1 (2.4%)	
Undifferentiated carcinoma	10 (90.9%)	1 (9.1%)	
Clear cell carcinoma	12 (100%)	0 (0.0%)	
MMMT (malignant mixed mÜllerian tumor)	13 (92.9%)	1 (7.1%)	
Other	20 (80.0%)	5 (20.0%)	

[#] *P* is for χ^2 or Fisher exact test, $P < .05$ regarded as statistically significant.

3.3. Expression of GATA6 was correlated with histological type

χ^2/Fisher exact test revealed a close relationship between expression of GATA6 and some certain clinical features in OC patients (Table 1). Among serous carcinoma cases, GATA 6 was expressed in 20.0% of cases, compared with 10.3% positive in non-serous carcinoma cases (Table 1, $P = .019$). Of non-serous carcinoma cases, mucinous carcinoma had the highest positive rate of GATA6 expression (30.8%, Table 4). Given that GATA6 is involved in lineage differentiation, this data suggests GATA6 may be involved in the histological differentiation of OC.

4. Discussion

As a transcription factor, GATA6 exerts its function by binding to the gene promoter. It can bind to the GATA consensus element directly, or interact with the other transcription factors, such as Sp1 and hepatocyte nuclear factor−1α [12,23]. Downstream genes involved in tumor progression include 67LR [14], urokinase plasminogen activator [12], slug [24], REG4 [18], LGR5 [17], and BMP4 [25]. Notably, in addition to tumor progress, GATA6 was reported to play an important role in self-renewal of cancer stem cells. Whissell et al [25] reported that GATA6 directly promoted the expression of LGR5 in adenoma stem cells but suppressed BMP signaling to differentiated tumor cells, establishing an environment facilitating colorectal cancer initiation. Similar roles were also reported in esophageal adenocarcinoma [15]. GATA 6 expression has been reported to be modified indifferent ways. Kwei et al [13] showed that an increased gene copy number of GATA 6 can contribute to its overexpression. Taken together, GATA6 was not only a promoter, but also an initiator in some cancers.

Transcription factor-mediated reprograming might be a potential and powerful mechanism accounting for refractory cases, especially in cases of recurrence and drug-resistance. Wamaitha et al demonstrated that GATA6 was able to initiate reprograming of multiple cell types to induce extraembryonic endoderm stem cells by inhibiting pluripotency gene expression and activating extraembryonic endoderm gene [26]. This role of GATA6 in mediating cell fate switch was demonstrated 10 years ago [27,28]. Therefore, GATA6 is regarded as a member of transcription factors that are involved in cellular reprograming. Other similar examples of proteins involved in cellular reprogramming include overexpression of Cdx2 has been shown to convert mouse embryonic stem cells to trophectoderm-like cells [29], induction of MyoD can induce fibroblasts transformation to myogenic cells [30], and upregulating the SRY homeobox gene Sox17 can reprogram mouse embryonic stem cells to extraembryonic endoderm cells [31,32].

Our study showed that expression of GATA6 has a significant correlation with poor OS, histopathological subtype and 5-year survival rate. Our data showed a correlation between GATA6 and the histopathological subtype of the OC. Clinical stage, clinical response to chemotherapy, and occurrence of ascites, and GATA6 expression were all shown to be independent risk factors for predicting the prognosis. Taken together, our study demonstrated that GATA6 presents a novel prognostic factor for ovarian cancer and may represent an important gene in ovarian cancer development.

Conflict of interest

The authors declare no conflict of interest.

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