

ATP binding cassette subfamily B member 9 (ABCB9) is a prognostic indicator of overall survival in ovarian cancer

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Abstract

Ovarian cancer (OC) is one of the most common gynecological malignancies and owns the highest mortality rate among all gynecological malignant tumors. ATP binding cassette subfamily B member 9 (ABCB9) is an antigen processing-like (TAPL) transporter that has been found to be involved in the development and progression of various malignant tumors in accumulating reports. However, the potential role of ABCB9 in OC has never been reported.

In this study, ABCB9 expression was evaluated in normal ovarian tissues and ovarian cancer tissues using The Cancer Genome Atlas (TCGA) database. And the associations between ABCB9 expression and clinical parameters of patients of OC were evaluated by Chi-square tests. Kaplan–Meier analysis and Cox regression analysis were performed to evaluate the prognostic significance of ABCB9. GSEA was performed to explore related signaling pathway.

ABCB9 expression levels were significantly decreased in OC compared with normal ovarian tissues ($P < .001$). Low ABCB9 expression was associated with survival status ($P = .0148$) in OC. Kaplan–Meier analysis showed that low ABCB9 expression was associated with poor overall survival in OC ($P = .0032$). Multivariable Cox regression analysis indicated that low ABCB9 expression was an independent prognostic factor (HR 0.64; $P = .01$) in OC patients. Besides, epithelial mesenchymal transition, UV response, and TGF- β signaling were enriched in low ABCB9 expression phenotype, respectively, examined by gene set enrichment analysis.

These results suggest that ABCB9 is an independent prognostic indicator in OC with certain clinical significance.

Abbreviations: ABCB9 = ATP binding cassette subfamily B member 9, GSEA = gene set enrichment analysis, NES = normalized enrichment score, OC = ovarian cancer, TCGA = The Cancer Genome Atlas.

Keywords: ABCB9, ATP binding cassette subfamily B member 9, ovarian cancer, prognosis, The Cancer Genome Atlas

1. Introduction

Ovarian cancer (OC) is the second most common gynecological malignancies in women, with a prevalence of 1.3%.^[1] Also it has the highest mortality rate among all gynecologic malignancies. Most women with OC are diagnosed at a late stage because the ovary is located deep in the pelvis, which should be highly vigilant.^[2] Besides, patients with OC present tumor relapse with chemoresistance, resulting in a poor prognosis with a 5-year

overall survival rate of ~30%.^[3] Therefore, it is essential to identify novel biomarkers of OC to help identify patients with poor prognosis.

Chemotherapy resistance is a main cause of low overall survival rate in clinical patients with cancer.^[4,5] Although chemoresistance has been effectively targeted in many other types of cancer, only a few medications have been approved for clinical use in targeting platinum-resistant OC.^[6] Previous studies have shown that ATP binding cassette (ABC) family participates in the development of multidrug resistance by the outflow of anticancer agents from a cancer cell as membrane drug transporters and have a regulatory effect on paclitaxel resistance in breast cancer, non-small cell lung cancer, nasopharyngeal cancer and so on.^[7–9] ABC family also plays an important physiological role in transporting various structurally diverse hydrophobic compounds across the cell membrane, including metabolic products, lipids, hormones, peptides, saccharides, amino acids, ions, vitamins, and xenobiotics.^[10,11] Unlike other ABC family members, the role of ATP binding cassette subfamily B member 9 (ABCB9), an important member of the multidrug (MDR)/transporter associated with antigen processing (TAP) subfamily of ABC genes located in chromosome 12q24.31, has little discussed in OC.^[12] So we hypothesize that ABCB9 may have the similar regulatory function in chemoresistance in OC, which further affects the prognosis of OC.

In the present study, we studied the association between ABCB9 expression and clinicopathologic characteristics of OC to help us better understand its role in tumor prognosis and finally evaluated the prognostic value of ABCB9 in OC. GSEA was performed to explore related signaling pathway.

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2. Materials and methods

2.1. Data mining of TCGA database

Data mining was performed in The Cancer Genome Atlas (TCGA) database (<https://cancergenome.nih.gov/>) and GTEx database (www.gtexportal.org/), in which ABCB9 expression was measured in a biopsy specimen of 308 ovarian cancer tissues and 88 normal ovarian tissues by RNAseq (IlluminaHiSeq).

2.2. Statistical analysis

Statistical analysis was performed using R (version 3.5.1). Chi-square tests assessed the association between ABCB9 expression and clinicopathological characteristics. The optic value of ABCB9 determined by ROC curve was used as a cut-off to divide high and low ABCB9 expression groups. Kaplan–Meier curve was used with the log-rank test to compare the overall survival between high and low ABCB9 expression groups. Univariate and multivariate Cox regression analyses were applied to estimate the independent prognostic value of the ABCB9 expression. $P < .05$ was considered statistically significant.

2.3. GSEA

Gene set enrichment analysis (GSEA) aims to use predefined gene sets to rank target genes according to the degree of difference between the two types of samples, and then to test whether the predefined gene sets are at the top or bottom of the sorting table.^[13,14] In this study, we used GSEA 3.0 software to analyze the data of ovarian cancer patients. We obtained normalized enrichment score (NES) by using permutation analysis 1000 times.

2.4. Ethical approval

No ethical approval is necessary because all clinical data we used in this study was from public database and available for research.

3. Results

3.1. Patient characteristics

From the TCGA database and GTEx database, 308 tumors with both clinicopathological parameters and gene expression data were analyzed. The demographic and clinicopathological parameters of the corresponding patients are described in Table 1.

3.2. ABCB9 expression and association with clinicopathological variables

Compared with in normal ovarian tissues ($n=88$), ABCB9 expression was significantly lower in OC tissues ($n=308$; $P < .05$). Also, significant differences in ABCB9 expression were observed according to patient age and the histological grade of OC (Fig. 1). OC patients were divided into high and low ABCB9 expression groups to evaluate the correlation between ABCB9 expression and clinicopathological parameters (Table 2). Moreover, the results show that low ABCB9 expression correlated significantly with survival status ($P = .0148$).

3.3. Low ABCB9 expression as an independent prognostic factor for poor survival

Low ABCB9 expression was found to be associated with poor overall survival ($P = .0032$; Fig. 2). Further subgroup analyses

Table 1

Clinical characteristics of the included patients with ovarian cancer.

characteristics	Number of cases
Age	
<55	113 (36.69)
≥55	195 (63.31)
Subdivision	
NA	17 (5.52)
Bilateral	212 (68.83)
Left	37 (12.01)
Right	42 (13.64)
Stage	
NA	2 (0.65)
I	1 (0.32)
II	22 (7.14)
III	245 (79.55)
IV	38 (12.34)
Longest dimension	
Large	124 (46.1)
Small	145 (53.9)
Lymphatic invasion	
NA	180 (58.44)
No	44 (14.29)
Yes	84 (27.27)
Histologic grade	
NA	2 (0.65)
G1	1 (0.32)
G2	37 (12.01)
G3	261 (84.74)
G4	1 (0.32)
GB	2 (0.65)
GX	4 (1.3)
New type	
NA	145 (47.08)
Locoregional	4 (1.3)
Metastatic	1 (0.32)
Progression	12 (3.9)
Recurrence	146 (47.4)
Sample type	
Primary tumor	303 (98.38)
Recurrent tumor	5 (1.62)
Vital status	
Deceased	184 (59.74)
Living	124 (40.26)
ABCB9	
High	94 (30.52)
Low	214 (69.48)

ABCB9=ATP binding cassette subfamily B member 9.

showed that low ABCB9 expression was associated with poor overall survival of patients with advanced stages ($P = .0021$) but not early stages ($P = .98$), G3 and G4 grade ($P = .0015$) but not G1 and G2 grade ($P = .55$), and young age ($P = .021$) but not old ($P = .11$; Fig. 2). Univariate analysis proved that patient age and ABCB9 expression were associated with poor overall survival (Table 3). Also multivariate analysis confirmed that low ABCB9 expression could be used as an independent prognostic factor for poor overall survival of OC (hazard ratio: 0.64, 95% confidence interval: 0.46–0.9, $P = .01$; Table 3).

3.4. ABCB9-related signaling pathway

As shown in Table 4, GSEA reveals significant differences in the enrichment of MSigDB Collection (NOM P -value <0.05). We

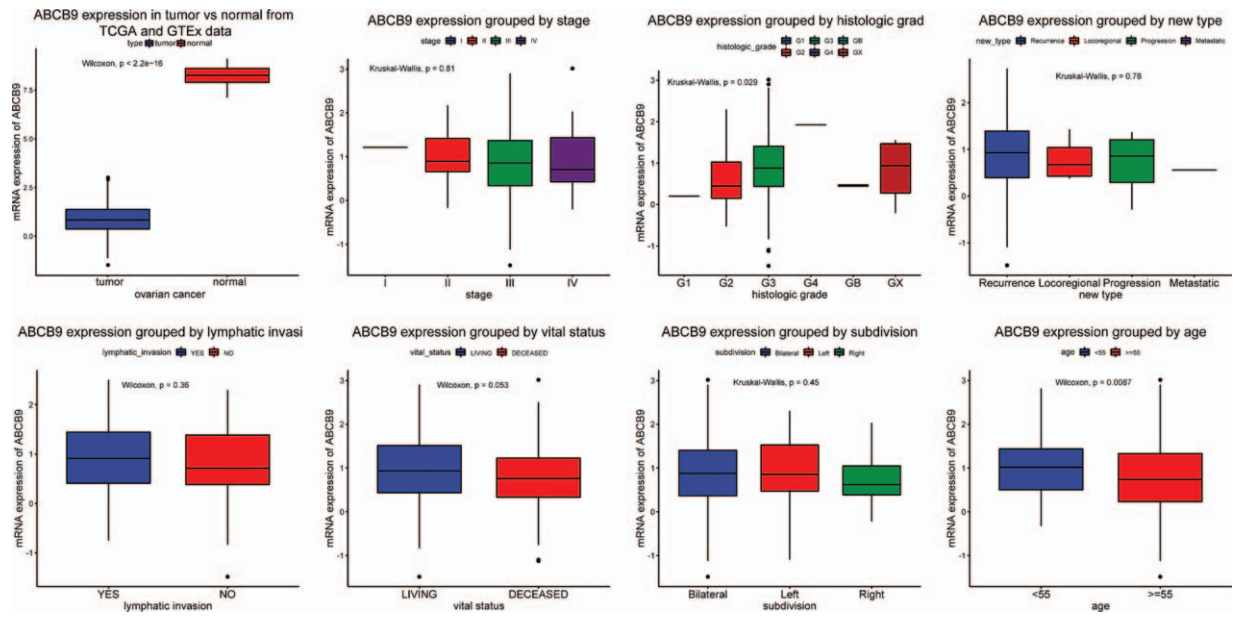


Figure 1. The different expression of ABCB9 in tumor vs normal, different clinical stage, histological type, new type, lymphatic invasion, subdivision, age and vital status. ABCB9=ATP binding cassette subfamily B member 9.

chose the most essential signaling pathways based on NES (Table 4; Fig. 3). Figure 3 shows that epithelial mesenchymal transition, UV response, and TGF-β signaling were enriched in low ABCB9 expression phenotype, respectively. In addition, we

have performed GSEA to analyze the WNT genes, and found that WNT signaling also increased in the ABCB9 low samples. However, the normalized P-value is .89749, which is not significant in statistics (Table 4; Fig. 3).

Table 2
Correlation between the clinical variables and ABCB9 expression in patients.

Parameter	Variable	N	ABCB9 mRNA expression		χ ²	P value		
			High	%			Low	%
Age	<55	113	39	(41.49)	74	(34.58)	1.0615	.3029
	≥55	195	55	(58.51)	140	(65.42)		
Subdivision	Bilateral	212	68	(75.56)	144	(71.64)	2.2114	.331
	Left	37	13	(14.44)	24	(11.94)		
	Right	42	9	(10)	33	(16.42)		
Stage	I	1	0	(0)	1	(0.47)	0.5898	.8988
	II	22	6	(6.38)	16	(7.55)		
	III	245	76	(80.85)	169	(79.72)		
	IV	38	12	(12.77)	26	(12.26)		
Longest Dimension	Large	124	36	(44.44)	88	(46.81)	0.05	.8231
	Small	145	45	(55.56)	100	(53.19)		
Lymphatic invasion	No	44	13	(30.23)	31	(36.47)	0.2548	.6137
	Yes	84	30	(69.77)	54	(63.53)		
Histologic grade	G1	1	0	(0)	1	(0.47)	10.0413	.0741
	G2	37	5	(5.32)	32	(15.09)		
	G3	261	86	(91.49)	175	(82.55)		
	G4	1	1	(1.06)	0	(0)		
	GB	2	0	(0)	2	(0.94)		
	GX	4	2	(2.13)	2	(0.94)		
New type	Locoregional	4	1	(2)	3	(2.65)	1.7684	.6218
	Metastatic	1	0	(0)	1	(0.88)		
	Progression	12	2	(4)	10	(8.85)		
	Recurrence	146	47	(94)	99	(87.61)		
Sample type	Primary tumor	303	93	(98.94)	210	(98.13)	0.0006	.9797
	Recurrent tumor	5	1	(1.06)	4	(1.87)		
Vital status	Deceased	184	46	(48.94)	138	(64.49)	5.9354	.0148
	Living	124	48	(51.06)	76	(35.51)		

ABCB9=ATP binding cassette subfamily B member 9.

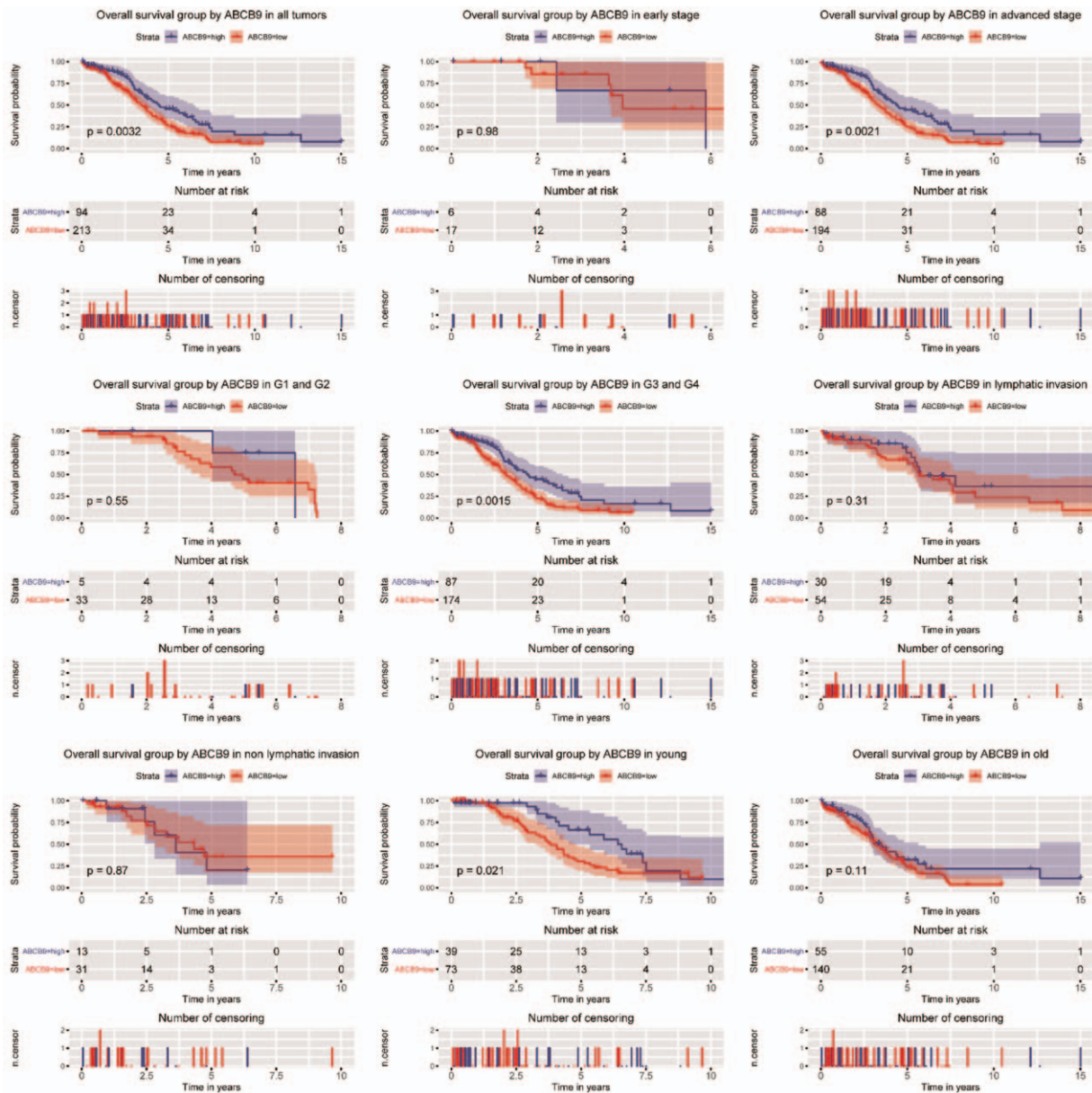


Figure 2. Survival curve in different groups of clinical stage, histological grade, lymphatic invasion, and age.

Table 3
Association between ABCB9 expression and overall survival.

Parameters	Univariate analysis			Multivariate analysis		
	Hazard ratio	CI95	P value	Hazard ratio	CI95	P value
Age	1.63	1.19–2.24	.003	1.54	1.12–2.12	.008
Subdivision	0.84	0.67–1.04	.101			
Stage	1.09	0.8–1.5	.581			
Longest dimension	1.12	0.82–1.52	.485			
Lymphatic invasion	1.02	0.85–1.23	.798			
Histologic grade	1.12	0.88–1.42	.349			
New type	0.99	0.63–1.55	.951			
sample type	0.43	0.11–1.73	.235			
ABCB9	0.6	0.43–0.85	.003	0.64	0.46–0.9	.01

ABCB9=ATP binding cassette subfamily B member 9.

Table 4
GSEA enrichment plot in low ABCB9 phenotype.

Gene set	ES	NES	NOM P-value
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	0.625434	1.71508	.037182
HALLMARK_UV_RESPONSE_DN	0.481323	1.670187	.017717
HALLMARK_TGF_BETA_SIGNALING	0.483673	1.587158	.033797
HALLMARK_WNT_BETA_CATENIN_SIGNALING	0.208170	0.65919	.89749

Gene sets with NOM P-value <.05 is considered as significant.
 FDR=false discovery rate, NES=normalized enrichment score, NOM=nominal.

4. Discussion

Limited screening methods and nonspecific symptoms cause most women with OC being diagnosed at an advanced stage.^[15,16] As a result, in the past 10 years, the survival rate of OC has little improved.^[17] Over 20 years ago, the occurrence of taxanes such

as paclitaxel had made a breakthrough in the treatment of OC. However, after clinical observation, more than 90% of patients who relapsed after first-line therapy within six months presented chemotherapy resistance after receiving the same treatment.^[5] Chemotherapy resistance is the main cause of chemotherapy

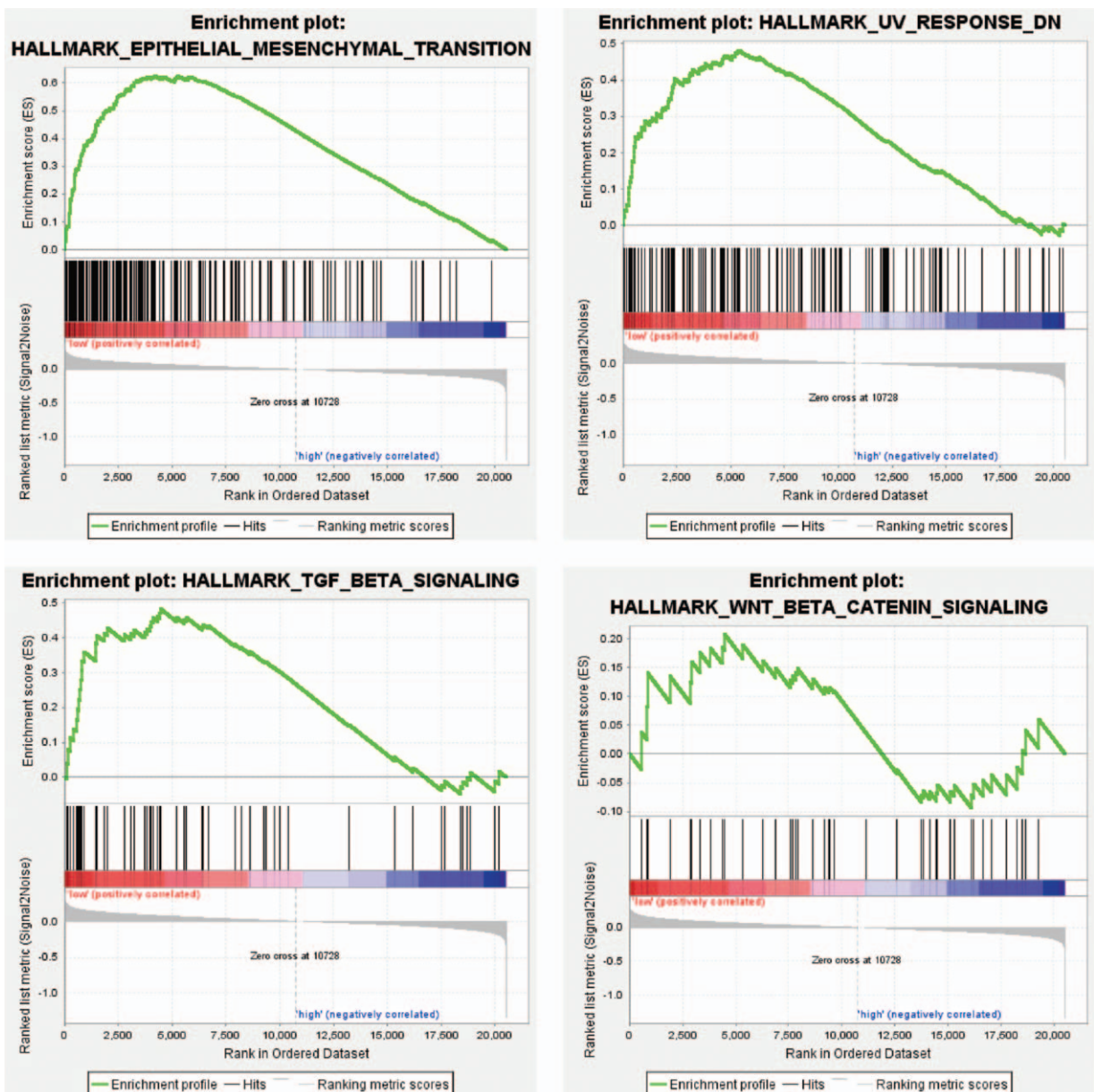


Figure 3. Enrichment plots from GSEA. GSEA = gene set enrichment analysis.

failure and the further poor prognostic outcomes. Recent years, there have been many reports focusing on the complex mechanism of chemoresistance in OC, including restoration of BRCA and DNA repair function, molecular subtype switching, evasion of apoptosis, increased drug efflux and so on.^[18–22] Although the mechanism of chemoresistance has been extensively studied, its clinical applications are still lacking. Thus, it would make sense to find a relevant molecular target to predict the patient's prognosis in advance quickly.

ABCB9 belongs to ABC transporter family, and in the previous reports, many genes of the ABC transporter family have been reported to participate in chemoresistance, such as ABCB1, ABCG2, and ABCC1.^[23] ABCB1 was the first discovered member of the ABC family and is known for its role in developing the resistance to cationic and neutral hydrophobic compounds.^[24,25] ABCG2 is a widely expressed transporter in human tissues and plays a key role in physiological regulation. The high expression of ABCG2 is an important factor in the decrease of intracellular chemotherapeutic drug concentration.^[26] ABCC1, the most studied protein associated with multidrug resistance in the ABCC subfamily, was demonstrated to be an active participant in many cancers including breast cancer, prostate cancer, OC and so on. Moreover, it is also studied to be associated with poor prognosis in patients with cancer.^[27] However, there is a significant difference in the expression of ABC genes between different individuals, thus affecting the effect of drug treatments and the different prognostic outcomes.

Despite the lack of systematic research, recent studies have provided evidence that ABCB9 might be targeted to different microRNAs and play a potential role in chemoresistance in various cancers. In breast cancer, ABCB9 was upregulated by miR-24 in paclitaxel-resistant breast cancer cells and patients.^[7] Similar to that in NSCLC, miR-31 plays an antiapoptotic role in cisplatin resistance by targeting the ABCB9 protein.^[8] Further in hepatocellular carcinoma, ABCB9 was found to be involved in the regulation of oxaliplatin-based chemosensitivity by miR-31-5p, which prevents the nuclear localization of PARP1.^[28] Conversely, I. Hlavata detected a significantly downregulated ABCB9 expression in colorectal tumor versus control mucosa tissues, which is consistent with our results that the ABCB9 expression was lower in OC tissues than in normal ovarian tissues.^[29] The difference between these findings may be related to the heterogeneity of tumor types and individual difference. But it suggested us that ABCB9 might play the same function in OC to be targeted by some certain genes in the regulation of chemoresistance and correlate to the prognosis of patients with OC.

Then, the dysregulated expression was observed to be associated with survival status by comparing the clinical parameters between high and low ABCB9 expression groups. Patients with lower expression of ABCB9 in OC tissues showed a poorer overall survival, especially those with advanced stages, G3 and G4 grade and young age. Clinically, most patients with OC are diagnosed at an advanced stage, so ABCB9 may be a useful indicator for contributing to early diagnosis, thus improve the prognosis of patients. OC includes numerous histological types and younger patients with lower expression of ABCB9 have a worse prognosis, which suggests that ABCB9 may be a helpful biomarker for poor prognosis of OC types more common in young women. Cox regression analysis indicated that low ABCB9 expression plays a significant prognostic value for prognosis of patients with OC.

Our team has been exploring the novel biomarkers for diagnosis and prognosis in the field of oncology.^[30–32] In this study, we have confirmed the hypothesis that ABCB9 expression is correlated with the overall survival of patients with OC and plays an independent role in the prognosis of OC. To the best of our knowledge, this is the first study to observe an association between low ABCB9 expression and poor survival in OC. These results have proved new evidence that ABC family members played a vital role in the prognosis of OC and laid a foundation for further studies to find more novel biomarkers of human cancers. A larger OC patient sample population is needed in our further studies to generate a proper predictive model for assessing the prognosis of patients with OC.

Author contributions

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Visualization: Yinuo Guan.

Writing – original draft: Lin Hou.

Writing – review & editing: Ziling Liu.

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