



Prognostic and clinical significance of Solute Carrier Family 7 Member 1 in ovarian cancer

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Background: Members of the solute carrier (SLC)7 family are known to play important roles in tumorigenesis and development. However, the prognostic significance of the SLC7 family in ovarian cancer (OC) remains unknown.

Methods: Expression patterns of SLC7 family members in OC were analyzed using gene expression profiling interactive analysis (GEPIA). The Kaplan-Meier plotter was applied to evaluate associations of the *SLC7* gene family with prognosis of OC. *SLC7A1* expression was additionally analyzed via immunohistochemical staining. χ^2 , Kaplan-Meier and Cox regression analysis were used to evaluate the relationship between *SLC7A1* expression and clinicopathological features, platinum resistance and prognosis in patients with high-grade serous ovarian cancer (HGSOC).

Results: The GEPIA dataset revealed the abundant expression of *SLC7A1*, *SLC7A4*, and *SLC7A7*, and conversely, the low expression of *SLC7A2* and *SLC7A8* in OC relative to normal tissue samples. Kaplan-Meier survival analysis further indicated that high *SLC7A1* and low *SLC7A2* mRNA levels were significantly associated with overall survival ($P < 0.05$). Positive *SLC7A1* expression was detected in 65 (58.1%) HGSOC tissue samples, but not in all normal ovarian tissue samples (100%), indicating that the expression of *SLC7A1* in HGSOC tissues was significantly higher than that in normal ovarian tissues ($P < 0.001$). Additionally, expression of *SLC7A1* was negatively associated with relapse-free survival (RFS; $P < 0.05$).

Conclusions: *SLC7A1* is a potential prognostic biomarker of OC.

Keywords: Ovarian cancer (OC); *SLC7A1*; relapse-free survival

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Introduction

Ovarian cancer (OC) is one of the most common gynecological malignancies, accounting for the highest mortality rates among gynecological cancers. Moreover, it has a significant negative impact on the lives of women worldwide (1). Approximately 152,000 women die from OC every year, with a reported overall five-year survival rate of approximately 30% (2,3). Since OC is difficult to diagnose at the early stages, more than 75% cases are not detected

until advanced disease and recurrence presents a common problem (4). Therefore, the identification of effective prognostic biomarkers remains an urgent requirement to improve management and prognosis of OC.

The solute carrier (SLC) transporter superfamily includes multiple membrane-binding proteins and participates in transmembrane transport of numerous substrates. Members of this protein family play critical physiological roles and therefore serve as potential therapeutic targets for many diseases (5). The SLC7 family

consists of 13 genes and is divided into two subfamilies: (I) cationic amino acid transporters (CAT, SLC7A1-4) and (II) l-type amino acid transporters (LAT, SLC7 5-14) (6). Amino acids are essential for growth of living cells, in particular, abnormally proliferating tumor cells. Consequently, compared with normal cells, expression of amino acid transporters in cancer cells is usually upregulated (7). Multiple studies have confirmed that dysfunction of SLC family 7 genes is associated with the incidence of human diseases, in particular, the occurrence, development, metastasis, and drug resistance of different cancer types (8-10). For instance, SLC7A5 overexpression in invasive cancers is significantly correlated with expression of c-Myc, a key regulatory factor of tumor cell metabolism. SLC7A5 is upregulated with tumor progression and thus relatively increased in high-grade and metastatic tumors (11-13). Similarly, SLC7A11 is abundantly expressed in a variety of tumor types. For example, the overexpression of SLC7A11 in glioblastoma enhances the migration and invasion of tumor cells, and patients with high expression of SLC7A11 have poor prognosis (14,15).

However, to our knowledge, no studies regarding the overall expression pattern and prognostic value of SLC7 genes have been documented in the literature. The associations among the clinicopathologic characteristics of OC and the SLC7 gene family remain unknown at present. In the current study, we focused on the expression patterns of individual SLC7 genes in OC and explored their prognostic significance. Our collective findings provide novel insights into the roles of the SLC7 gene family in OC that may be effectively applied for diagnostic treatment and prognostic purposes. In particular, our study aims to explore the relationship between the expression of SLC7A1 and platinum resistance and prognosis in patients with HGSOc, and to provide a possible theoretical basis for improving the treatment and prognosis of OC.

We present the following article in accordance with the REMARK reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-2744>).

Methods

cBioportal for Cancer Genomics

The relationship between *SLC7* genes and OC and alterations in expression were analyzed using data from cBioportal (<http://www.cbioportal.org/>) for Cancer Genomics, an open-access resource for interactive

exploration of multiple Cancer Genomics datasets (16). cBioPortal currently stores data on DNA copy number (assumptions for each gene, discrete values such as "deep deletion" or "amplification," and log2 levels), mRNA and microRNA expression, non-synonymous mutations, protein and phospholipid levels reverse-phase protein arrays (RPPA) and DNA methylation.

GEPIA validation of differential expression of SLC family 7 genes

GEPIA (<http://gepia.cancerpku.cn/>) is a multi-functional network database that collects RNA sequencing expression data from 9,736 tumor samples and 8,587 normal samples from TCGA and GTEx databases (17). GEPIA provides a variety of functions, including evaluation of tumor/normal differential expression profiles, analysis according to cancer type or pathological stage, patient survival analysis, similarity analysis, and so on. Then, the expression of SLC7 family in OC was analyzed in GEPIA database.

Kaplan-Meier plotter database analysis

As a tool for biomarker assessment, the Kaplan–Meier plotter (<http://kmplot.com>) was applied to analyze 54,675 genes and 10,188 tumor tissue samples (including breast, ovarian, lung, and gastric cancer types). The prognostic value of SLC7 mRNA transcript levels was additionally measured using the Kaplan–Meier plotter, which included gene expression profiles and survival information from 1,657 OC patients based on mRNA chip analysis (18). Patients were separated into two groups based on median gene expression of SLC7 family members (high *vs.* low). OS values of the two groups were compared using a Kaplan–Meier survival plot. Hazard ratio (HR) values with 95% CI, and log-rank P values were calculated. Data were considered significant at P values of <0.05.

Patient selection

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and it was conducted with approval from the Ethics Committee of Zhejiang Cancer Hospital (No. IRB-2015-175). Written informed consent was obtained from the participants. The 128 frozen tissue samples (collected between 2008 and 2014 and maintained at –80 °C) were provided by the Biobank of Zhejiang Cancer Hospital. All samples were fixed and

paraffin-embedded. The samples for study included 112 HGSOc and 16 normal ovarian tissue samples. The tumor staging and histological grading were evaluated according to the staging criteria of the International Federation of Obstetrics and Gynecology (FIGO) (19).

All patients enrolled in the study received standard chemotherapy after operation. According to the recurrence of platinum treatment, the patients who relapsed or did not relapse after 6 months were platinum sensitive group, and those who relapsed less than 6 months were platinum resistant group. RFS was calculated from the date of diagnosis to the date of recurrence.

Immunohistochemical staining

Rabbit anti-SLC7A1 polyclonal antibody [14195-1-AP] was purchased from Proteintech. The second antibody (PV-9000) and Diaminobenzidine (DAB) kit were purchased from Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd. The sample was embedded in paraffin, cut into a thickness of 4 μ m, dewaxed with xylene and then hydrated. High pressure repair was performed with citrate buffer for 2.5 min. Wash three times with phosphate buffer saline (PBS) for two min each, soak in 3% hydrogen peroxide solution for 10 min, and wash with PBS three times for two min each time. The slices were incubated overnight with the primary antibody (1:100 dilution) at 4 °C. Rinse with running water for 15 min, then rinse with PBS for 3 times for 5 min each time. Add the second antibody, incubate at room temperature for 20 min, and rinse with PBS for 3 times for 5 min each time. Diaminobenzidine (DAB) was used to staining at room temperature, and observed under microscope, then re-stained with hematoxylin and sealed.

Evaluation of immunohistochemical data

The expression of SLC7A1 detected by immunohistochemistry was evaluated by staining index, staining index = staining intensity + positive staining ratio of tumor cells (20). The staining intensity was divided into four grades: 0 points (negative), 1 points (weakly positive), 2 points (moderately positive) or 3 points (strongly positive). The scores for the percentage of positive area are as follows: 0 points <5%, 1 point, 5–25%, 2 points, 26–50%, 3 points, 51–75%, and 4 points, >75%. Cases in which the sum of two scores was <5 points were classified as low expression, 0 points as no expression and \geq 5 points as high expression.

Western blot analysis

RIPA reagent (Beyotime Institute of Biotechnology) containing protease inhibitor mixture (Beyotime) was used to lyse the tissue. After that, the total protein was quantified by BCA Kit (Beyotime Institute of Biotechnology). Twenty-five micrograms protein was separated in 10% polyacrylamide gel (Beyotime Institute of Biotechnology) and then transferred to nitrocellulose membrane (Thermo Fisher Scientific, Inc.). At room temperature, the membrane was blocked with 5% non-fat milk powder in PBST for 1 hour, and then incubated with the primary antibody against SLC7A1 (1:1,000; cat. no. ab14195-1-AP; Proteintech) at 4 °C overnight. After washing the membrane with PBST, the anti-rabbit secondary antibody (1:3,000; cat. no. 170-6515; Bio-Rad Laboratories, Inc.) was incubated for 1 hour. SuperSignal West Pico substrate and CL-Xposure film (Thermo Fisher Scientific, Inc.) were used to develop the film. Image Lab 3.0 (Bio-Rad Laboratories, Inc.) was used to analyze the results of Western blotting. β -actin is an internal reference protein.

Statistical analysis

The chi-square test (χ^2) was used to analyze the correlation between SLC7A1 expression and clinicopathological features. The correlations between platinum resistance and SLC7A1 expression as well as clinical features were further analyzed with chi-square test (χ^2). Kaplan-Meier and Cox proportional hazard regression tests were employed for univariate and multivariate survival analyses. All analyses were performed using SPSS PASW Statistics v18.0 (IBM, Chicago, IL, USA). Data were considered significant at $P < 0.05$ and highly significant at $P < 0.01$.

Results

Genetic differences in SLC7 family genes in OC

The database of cBioPortal OC (TCGA, Provisional) <http://www.cbioportal.org> was used to analyze the relationship between SLC7 genes and OC. Our results suggest that DNA amplification is one of the most important single factors displaying alterations in different histological types of OC (*Figure 1A*). We further analyzed the genetic alteration rates of single SLC7 genes; DNA amplification was the most common type of alteration, accounting for more than half of all genetic variation. Notably, genetic variation of SLC7A2 was predominantly attributed to DNA

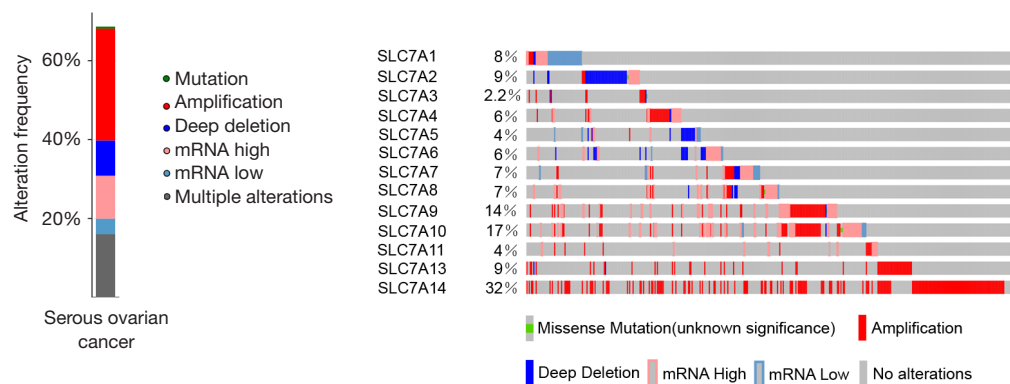


Figure 1 Different genetic alterations of SLC7 family members in OC. SLC7, solute carrier 7; OC, ovarian cancer.

deep deletion (*Figure 1B*).

mRNA expression of SLC7 family members in OC patients

We used the Gene Expression Profiling Interactive Analysis (GEPIA) dataset (<http://gepia.cancer-pku.cn/>) to evaluate expression of SLC7 mRNAs in OC. Our results showed that levels of SLC7A1, SLC7A4, SLC7A5, SLC7A7, SLC7A10, and SLC7A11 were higher in OC compared with normal tissues, among which SLC7A1, SLC7A4 and SLC7A7 levels were significantly elevated. Conversely, SLC7A2, SLC7A3, SLC7A6, SLC7A8, SLC7A9, and SLC7A14 levels were lower in OC compared with normal tissues, among which SLC7A2, and SLC7A8 levels were significantly decreased. SLC7A13 was the only gene for which expression data were lacking in OC patients (*Figure 2*).

Prognostic value of the SLC7 expression in OC

Kaplan–Meier plotter analysis showed that high expression of SLC7A1 (OS HR =1.14, 95% CI, 1.0 to 1.3, P=0.045), SLC7A3 (OS HR =1.38, 95% CI, 1.12 to 1.69, P=0.00018), and SLC7A14 (OS HR =1.31, 95% CI, 1.06 to 1.63, P=0.0014) was associated with poor prognosis in patients with OC. Conversely, low expression of SLC7A2 (OS HR =0.79, 95% CI, 0.69 to 0.9, P=0.00048), SLC7A4 (OS HR =0.82, 95% CI, 0.71 to 0.94, P=0.0052), SLC7A5 (OS HR =0.80, 95% CI, 0.69 to 0.93, P=0.0036) and SLC7A11 (OS HR =0.70, 95% CI, 0.61 to 0.79, P=3.9e-08) was correlated with poor prognosis (*Figure 3*). We further used the Kaplan–Meier plotter to determine the correlations among overall survival (OS), first progression (FP), post-progression survival (PPS) and SLC7 gene expression in

OC patients, determined via Forest plot (*Figure 4*). SLC7A1 had significant prognostic value in OS, FP, and PPS and was therefore selected for further in-depth analysis.

SLC7A1 expression in relation to clinicopathological characteristics of patients with HGSOc

Immunohistochemistry was used to detect the expression of SLC7A1 protein in 112 HGSOc and 16 normal ovarian tissues (*Figure 5*). The results disclosed expression of SLC7A1 in 65 of the HGSOc samples (58.1%) but not the remaining 47 HGSOc samples (41.9%). Notably, SLC7A1 was not detected in all 16 normal ovarian tissue samples (100%). The results showed that the expression level of SLC7A1 in HGSOc tissues was significantly higher than that in normal ovarian tissues (P<0.001; *Table 1*). Among the 112 HGSOc samples, we observed no distinct correlation between SLC7A1 expression and age of patients, FIGO stage, histologic grade, CA-125, lymph node metastasis or postoperative residual tumor size (P>0.05), while platinum resistance was strongly correlated with SLC7A1 expression (P=0.043; *Table 2*). At the same time, Western blotting was used to detect the expression of SLC7A1 in 4 cases of HGSOc and 4 cases of normal ovarian tissues. The results showed that the expression of SLC7A1 in HGSOc tissues was significantly up-regulated compared with normal tissues (*Figure S1*).

Prognostic value of SLC7A1 in OC

As shown in *Table 3*, Kaplan–Meier univariate analysis showed that there was a significant correlation between SLC7A1 expression and RFS in patients with HGSOc

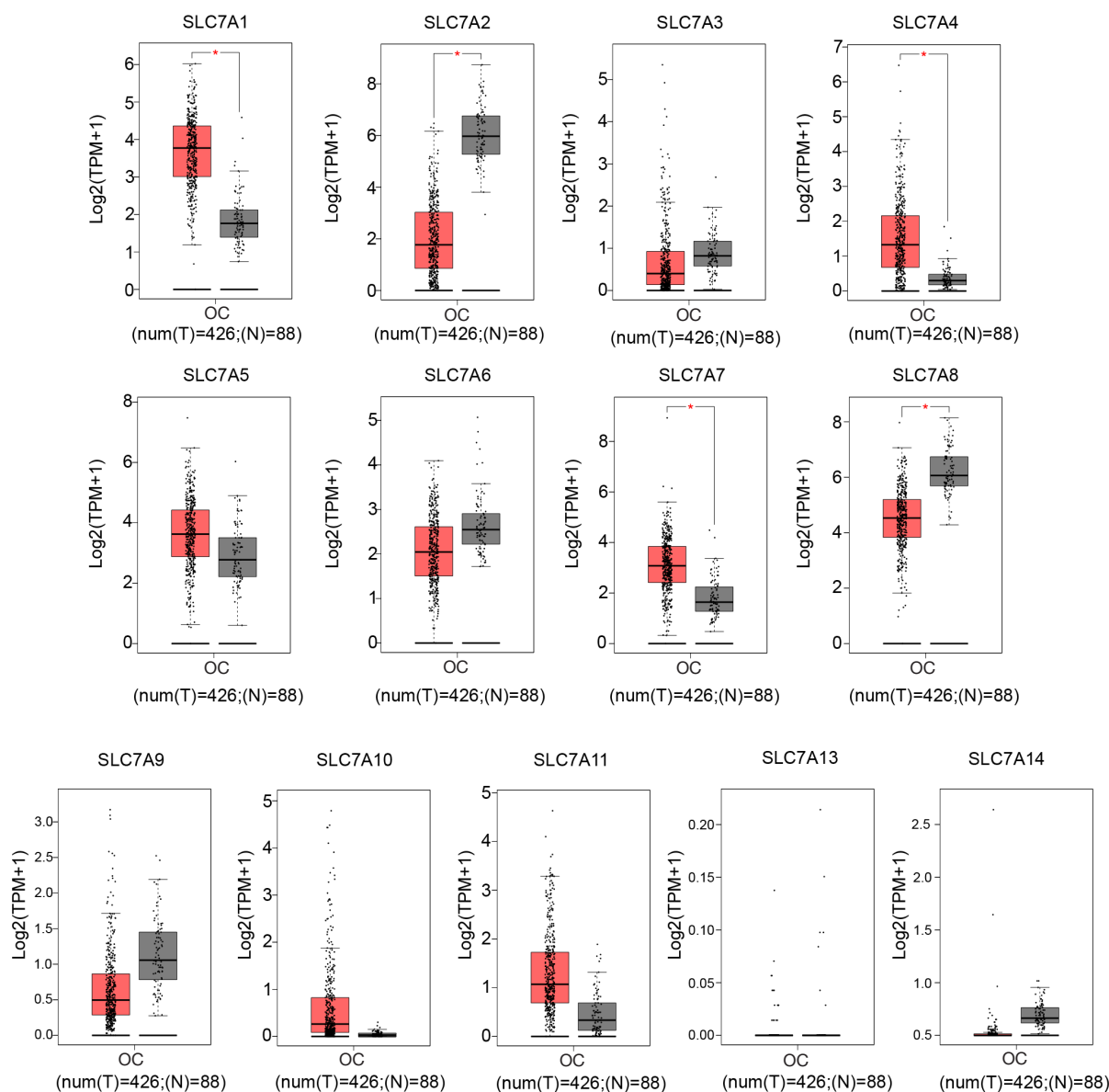


Figure 2 Levels of SLC7 family members in OC evaluated using GEPIA. *, P<0.05. SLC7, solute carrier 7; OC, ovarian cancer; GEPIA, Gene Expression Profiling Interactive Analysis.

(P<0.05). FIGO stage, CA-125, lymph node metastasis and residual tumor size were also correlated with RFS (P<0.05). As shown in *Table 4*, multivariate Cox regression analysis further confirmed FIGO stage (HR =5.141; 95% CI, 1.531 to 17.260; P=0.008), CA-125 (HR =1.831; 95% CI, 1.062 to 3.155; P=0.029), lymph node metastasis (HR =1.673; 95% CI, 1.057 to 2.648; P=0.028) and SLC7A1 expression (HR =1.617; 95% CI, 1.045 to 2.504; P=0.031) were significantly associated with RFS. Accordingly, late-stage FIGO, CA-

125 >500, lymph node metastasis and high expression of SLC7A1 were identified as risk factors for recurrence of HGSOc.

Discussion

In the present study, we focused on the expression profiles of SLC7 family members and their associations with survival outcomes in patients with OC. Our results

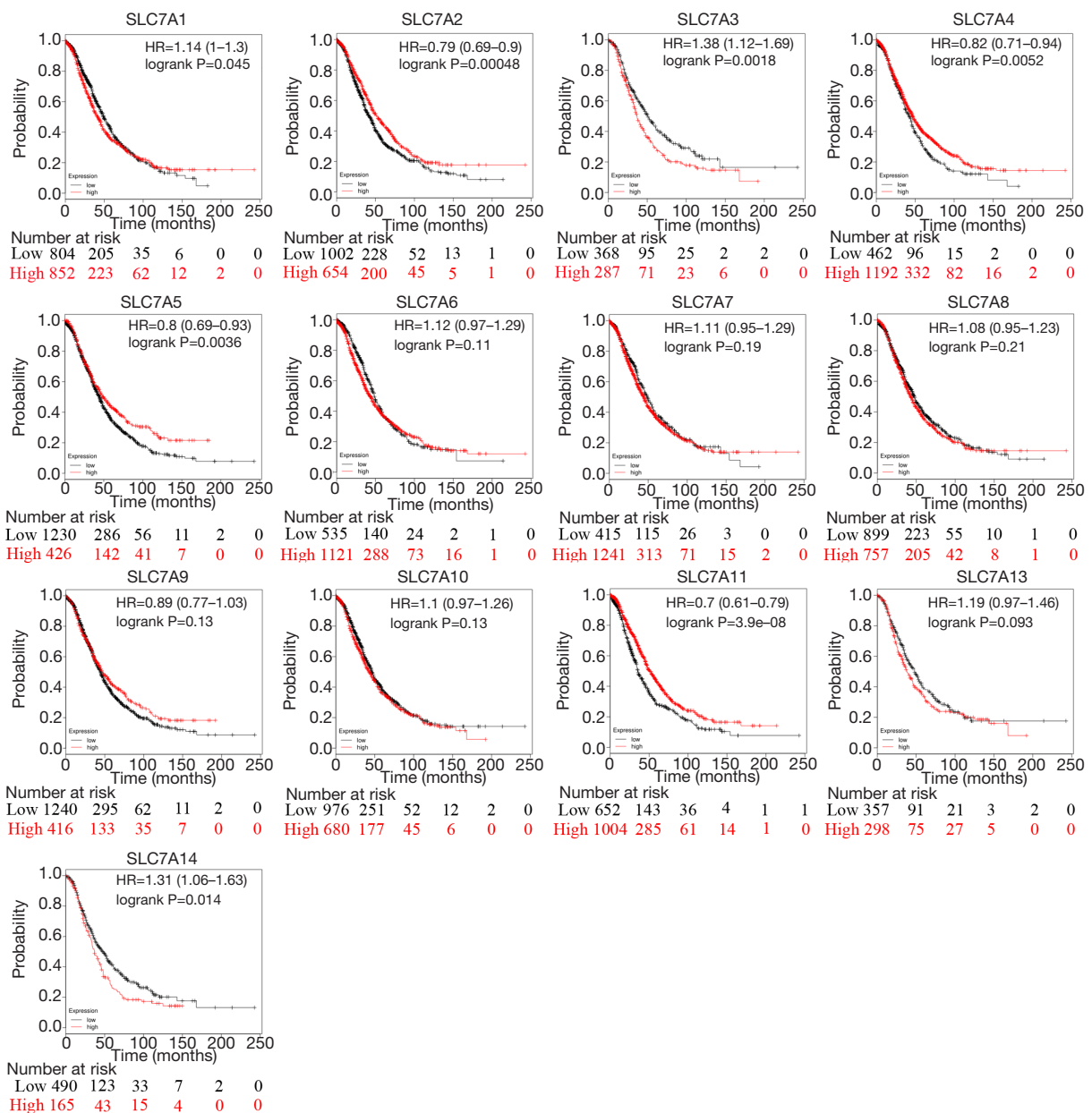


Figure 3 Analysis of OS in relation to SLC7 family members in OC patients using the Kaplan-Meier plotter. P values were calculated using the log-rank test. OS, overall survival; SLC7, solute carrier 7.

showed that SLC7A1, SLC7A4, and SLC7A7 levels were significantly higher whereas those of SLC7A2 and SLC7A8 were significantly lower in OC relative to normal tissues. Kaplan-Meier Plotter survival analysis further indicated that increased SLC7A1 and decreased SLC7A2 mRNA levels were highly associated with OS ($P < 0.05$).

SLC7A1, also known as CAT-1, is a cationic amino acid transporter (CAT) whose main function is to mediate

arginine uptake (21). The growth of several cancer cell lines, including acute myeloid leukemia, breast cancer, and colorectal cancer, is highly dependent on arginine (22-24). Compared with normal breast cells, the human breast cancer cell lines, T47D and MDA-MB-231, are reported to overexpress SLC7A1. Knockout of the SLC7A1 gene resulted in a significant increase in apoptosis of MCF-7 and T47D cells *in vitro* (23). Other studies have demonstrated

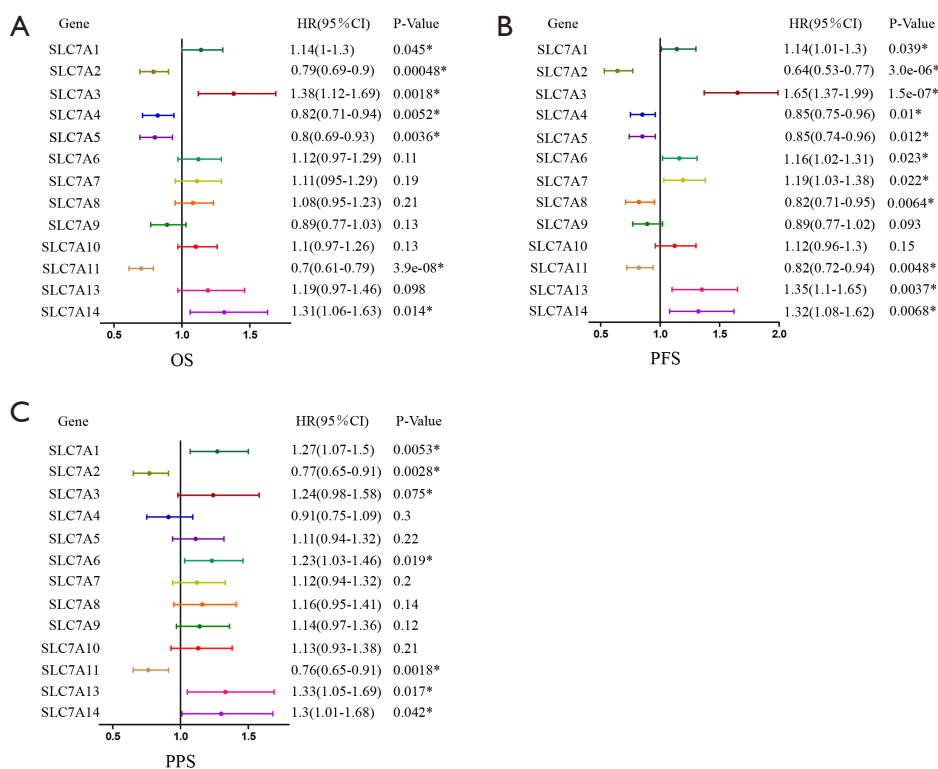


Figure 4 Correlation of OS, FP and PPS with SLC7 gene family expression in OC patients. *, $P < 0.05$. OS, overall survival; FP, first progression; PPS, post-progression survival; SLC7, solute carrier 7; OC, ovarian cancer.

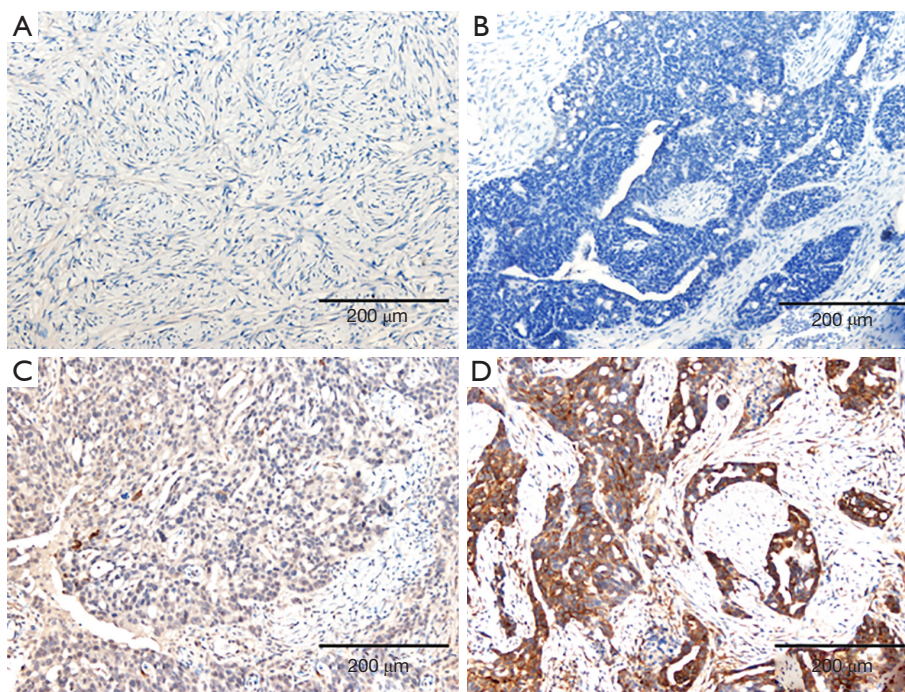


Figure 5 Immunohistochemical detection of SLC7A1. Negative expression of SLC7A1 in (A) normal ovarian and (B) HGSOC tissues. (C) Low expression of SLC7A1 in HGSOC tissues. (D) High expression of SLC7A1 in HGSOC tissues. HGSOC, high-grade serous ovarian cancer.

Table 1 Expression of SLC7A1 in HGSOC and normal ovarian tissue samples

Variables	SLC7A1 expression		P value
	Low	High	
HGSOC	47	65	<0.001
Normal	16	0	

Statistical analysis was performed with a Fisher's exact test. HGSOC, high-grade serous ovarian cancer.

the abundant expression of CAT-1 mRNA and protein in colorectal cancer tissue relative to normal tissue. Apoptosis of colorectal cancer cells could be induced by knockout of SLC7A1, supporting its utility as a unique molecular biomarker and therapeutic target for colorectal cancer (25). Another recent investigation showed that SLC7A1 is highly expressed in tumors and involved in the central mechanism of tumor evasion against the T-cell-mediated anti-tumor immune response, leading to poor prognosis (25). Our finding that overexpression of SLC7A1 in OC patients is correlated with poor OS is consistent with previous results. In Kaplan-Meier Plotter Database, the OS, FP and PPS time of high expression of SLC7A1 in patients with OC was short, and $P < 0.05$, showing a good prognostic value. In the follow-up verification experiment, we collected 112 patients with OC and found that patients with high expression of SLC7A1 were more likely to develop drug resistance and more likely to relapse than patients with low expression.

In our study, 22.4% patients developed platinum resistance, in keeping with previous reports (26). Some studies have shown that MIR-122 is the highest expression of miRNA, in normal liver, but significantly decreased in hepatoma cells resistant to sorafenib. On the other hand, SLC7A1 has been found to be the direct target of miR-122. MIR-122 promotes the sensitivity of hepatocellular carcinoma cells to sorafenib by targeting and inhibiting SLC7A1 (27). The results of this study suggest that the up-regulation of SLC7A1 is related to the platinum resistance in HGSOC, but further research is needed to clarify this mechanism.

Another important finding of this study is that recurrence of HGSOC is associated with several factors, such as late FIGO stage, lymph node metastasis, and high SLC7A1 expression. Several researchers have confirmed that postoperative recurrence of HGSOC increases with more advanced clinical stage. Late clinical stage is an independent risk factor for postoperative recurrence of OC, in accordance

Table 2 Associations between the expression level of SLC7A1 and clinicopathological characteristics

	SLC7A1 expression		P value
	Low	High	
Age, years			
≤54	25	35	0.945 ^a
>54	22	30	
FIGO stage			
I-II	5	6	0.999 ^b
III-IV	42	59	
Histological grade			
G2	26	34	0.404 ^a
G3	17	31	
CA-125, U/mL			
≤500	10	16	0.680 ^a
>500	37	49	
Lymph node metastasis			
No	22	28	0.695 ^a
Yes	25	37	
Residual tumor size, cm			
≤1	34	44	0.598 ^a
>1	13	21	
Platinum resistance			
Present	6	18	0.043 ^a
Absent	40	43	

Statistical analysis was performed with ^a χ^2 test or ^b Fisher's exact test.

with our results (28). Advanced clinical stage is associated with promotion of intraperitoneal tumor implantation and metastasis and potential invasion of blood or lymphatic vessels, resulting in distant metastasis (29). The rate of lymph node metastasis in advanced OC is considerably higher. Intraoperative pelvic and para-aortic lymphadenectomy have been shown to significantly reduce tumor metastasis and recurrence (30,31). Data from the present study consistently demonstrated that lymph node metastasis is a risk factor for recurrence of HGSOC (32). Lymphadenectomy is one of the known factors affecting recurrence of OC. Therefore, extensive dissection of pelvic and celiac lymph nodes could reduce the possibility of postoperative recurrence of

Table 3 Univariate survival analysis of relapse-free survival of patients with ovarian cancer

Variable	n	Mean ± SE	95% CI	P value
Age, years				
≤54	60	21.617±3.157	15.429–27.806	0.725
>54	47	23.402±3.543	16.457–30.346	
FIGO stage				
I–II	11	66.455±9.978	46.898–86.011	<0.001
III–IV	96	17.801±1.893	14.092–21.510	
Histological grade				
G2	57	25.591±3.775	18.567–33.364	0.177
G3	46	19.364±2.927	13.628–25.101	
CA-125, U/mL				
≤500	25	30.568±5.744	19.310–41.826	0.041
>500	82	19.536±2.363	14.904–24.169	
Lymph node metastasis				
No	47	32.120±4.516	23.269–40.971	0.001
Yes	60	14.994±1.918	11.234–18.755	
Residual tumor size, cm				
≤1	76	26.643±3.206	20.359–32.926	0.004
>1	31	13.645±2.664	8.823–18.867	
SLC7A1 expression				
Low	46	29.177±4.327	20.696–37.658	0.031
High	61	16.917±2.183	12.638–21.196	

Analysis was performed with a log-rank test.

Table 4 Multivariate survival analysis of relapse-free survival of patients with ovarian cancer

Variable	β	SE	HR	95% CI	P value
FIGO stage (III–IV)	1.637	0.618	5.141	1.531–17.260	0.008
CA-125 (>500)	0.605	0.278	1.831	1.062–3.155	0.029
Lymph node metastasis (Yes)	0.515	0.234	1.673	1.057–2.648	0.028
Residual tumor size (>1 cm)	0.439	0.238	1.551	0.973–2.472	0.065
SLC7A1 expression (High)	0.481	0.223	1.617	1.045–2.504	0.031

According to Cox regression analysis.

OC (33,34). CA-125 is the most commonly used tumor marker for diagnosis of OC recurrence. More than 90% of patients presenting with advanced OC, especially HGSOc, experience remission or deterioration of the disease. In our experiments, postoperative CA-125 >500 U/L was

determined as a high risk factor for HGSOc recurrence. Additionally, SLC7A1 was identified as an independent prognostic factor for RFS in HGSOc.

To our knowledge, this is the first report to demonstrate that platinum resistance and prognosis are associated with

SLC7A1 expression in patients with HGSOC. However, our study has a number of limitations that should be considered, such as its small sample size and single-center nature. In conclusion, the high expression of SLC7A1 is associated with poor prognosis and platinum resistance in patients with HGSOC. SLC7A1 may therefore serve as an effective potential biomarker for HGSOC.

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Footnote

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Data Sharing Statement: Available at <http://dx.doi.org/10.21037/tcr-20-2744>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-2744>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) with approval from the Ethics Committee of Zhejiang Cancer Hospital (No. IRB-2015-175). Written informed consent was obtained from all participants.

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Supplementary

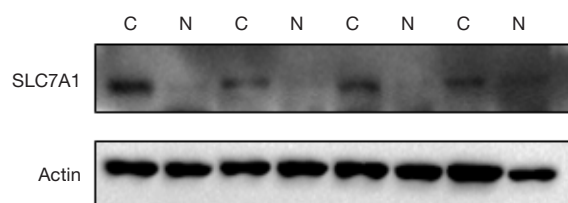


Figure S1 Western blotting (WB) analysis was used to detect the expression of SLC7A1 in HGSOC and normal ovarian tissues. HGSOC, high-grade serous ovarian cancer.