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Comprehensive analysis of the expression and prognosis for S100 in human ovarian cancer

A STROBE study

Hong-Yu Xu, MD[a], Hua-Mei Song, MD[b], Quan Zhou, MD[b,*]

Abstract

S100 family members are frequently deregulated in human malignancies, including ovarian cancer. However, the prognostic roles of each individual S100 family member in ovarian cancer (OC) patients remain elusive. In the present study, we assessed the prognostic roles and molecular function of 20 individual members of the S100 family in OC patients using GEPIA, Kaplan–Meier plotter, SurvExpress, GeneMANIA and Funrich database. Our results indicated that the mRNA expression levels of S100A1, S100A2, S100A4, S100A5, S100A11, S100A14, and S100A16 were significantly upregulated in patients with OC, and high mRNA expression of S100A1, S100A3, S100A5, S100A6, and S100A13 were significantly correlated with better overall survival, while increased S100A2, S100A7A, S100A10, and S100A11 mRNA expressions were associated with worse prognosis in OC patients. In stratified analysis, the trends of high expression of individual S100 members were nearly the same in different pathological grade, clinical stage, TP53 mutation status, and treatment. More importantly, S100 family signatures may be useful potential prognostic markers for OC. These findings suggest that S100 family plays a vital role in prognostic value and could potentially be an S100-targeted inhibitors for OC patients.

Abbreviations: BP = biological processes, CA125 = carbohydrate antigen 125, CC = cellular components, FIGO = the international federation of gynecology and obstetrics, GEPIA = gene expression profiling interactive analysis, GO = gene ontology, HE4 = human epididymal protein 4, HR = hazard ratio, MF = molecular functions, OC = ovarian cancer, TCGA = The Cancer Genome Atlas Program.

Keywords: Kaplan–Meier plotter, ovarian cancer, prognosis, S100 family, signature

1. Introduction

Ovarian cancer (OC) is the most common cause of cancer-related death among gynecological malignancies, and causes approximately 13,980 deaths annually worldwide.[1,2] During the past decade, there has been little improvement in survival rates of OC, due to the lack of specific symptoms and effective biomarkers. Over 75% of patients are not diagnosed until the disease is advanced (stages III and IV), and the 5-year survival rate is less than 30%.[3,4] Although cytoreductive surgery and platinum-based chemotherapy are applied routinely, most cases acquire platinum resistance and the disease progresses rapidly, with patients having poor long-term survival.[5] Many prognostic factors have been investigated in an attempt to better estimate outcomes in OC patients. Among them, FIGO stage, patient age, residual tumor after initial surgery, lymph node metastasis, vascular invasion, and cancer antigen 125 are consistently reported as important prognostic factors. However, testing these factors is time consuming and carries a steep cost, and they may have insufficient specificity or sensitivity for specific OC, which limits their extensive application in clinical settings.[4,6] It can also be difficult to obtain adequate tumor sample to perform prognostic analyses. Therefore, identification of more effective and minimally invasive prognostic markers is a matter of great clinical urgency for OC patients.

The S100 protein family, which comprises more than 20 known members in humans, is the largest subfamily of calcium-binding proteins of the EF-hand type, of which the first member was discovered in 1965.[7] Twenty-two of the S100 coding genes are clustered at chromosome locus 1q21, a region prone to chromosomal rearrangements and frequently rearranged in cancers.[8] There is growing evidence that deregulation of S100 expression is a common occurrence in several human malignancies, and previous reports demonstrate that S100 expression is associated with tumorigenesis and tumor progression, such as in

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[a] Department of Gynecology and Obstetrics, the Second People's Hospital of Yichang, China Three Gorges University, [b] Department of Gynecology and Obstetrics, the People's Hospital of China Three Gorges University/the First People's Hospital of Yichang, Yichang, Hubei, China.

[*] Correspondence: Quan Zhou, Department of Gynecology and Obstetrics, the People's Hospital of China Three Gorges University/the First People's Hospital of Yichang, 2#, Jie-fang Road, Yichang, 443000, Hubei, China (e-mail: zhouquan8519@163.com).

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head and neck cancer,[9,10] lung cancer,[11,12] breast cancer,[13–15] pancreatic cancer,[16,17] prostate cancer,[14,16,17] renal cancer,[18] cervical cancer,[19] gastric cancer[20] and OC.[21–25] These proteins are considered to have potential value as novel biomarkers in the detection and prediction of many kinds of tumors. Although the role of the majority of S100 family proteins has not been reported in OC, several S100 family members (S100A2, S100A4, S100A7, S100A10, and S100A11) have been shown to be related to poor prognosis in different studies.[23–25] However, the prognostic roles and molecular function of each individual S100 family member in OC, especially at the mRNA level, have not been determined.

In the current study, we assessed the expression patterns, prognostic roles and molecular function of each individual member of the S100 family in human OC patients using integrative bioinformatics analysis. The analysis process involves a series of databases such as the GEPIA, Kaplan–Meier plotter, SurvExpress, GeneMANIA and Funrich database. The results will help to provide perspectives on new biomarkers for predicting the prognosis of OC, and highlight the noteworthy S100-targeted inhibitors for OC treatment.

2. Materials and methods

2.1. Ethics approval and consent to participate

This study was approved by the Academic Committee of the People's Hospital of China Three Gorges University, and conducted according to the principles expressed in the Declaration of Helsinki. All the datasets were retrieved from the publishing literature, so it was confirmed that all written informed consent was obtained.

2.2. GEPIA dataset analysis

The online database Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/index.html) is an interactive web server for estimating mRNA expression data based on RNA sequencing expression data of 9,736 tumors and 8,587 normal samples from the TCGA and the GTEx projects.[26] It was used to investigate differential expression analysis, profiling according to pathological stages, patient survival analysis, and correlation analysis.

2.3. The Kaplan–Meier plotter analysis

The online Kaplan–Meier plotter (http://kmplot.com/analysis/) database, which is capable of assessing the effect of 54,675 genes on survival using 10,461 cancer samples, including 1,816 OC samples, was used to evaluate the effect of S100 family members mRNA expression on overall survival (OS) in human OC patients.[27] For each individual gene, patients were split into high and low expression groups by the median values of mRNA expression. The prognostic value of the mRNA expression of S100 family members was evaluated using the Kaplan-Meier survival plot, with a hazard ratio with 95% confidence intervals and log rank p-value. Subgroup analyses were performed by dividing patients based on pathological grade, clinical stage, TP53 mutation status, and treatment type. A P value $< .05$ was considered statistically significant to reduce the false positive rate.

2.4. SurvExpress analysis

SurvExpress (http://bioinformatica.mty.itesm.mx/SurvExpress), which is a web-based tool providing survival multivariate analysis and risk assessment based on genes expression.[28] In our analysis, SurvExpress was used to provide survival analysis and risk assessment for S100 family members signature in patients with OC. Patients of indicated datasets were stratified according to median value of prognostic index. High and low risk groups were divided based on the maximized risk algorithm. The log-rank test was used to evaluate statistically the equality of survival curves.

2.5. Interaction and functional enrichment analysis

GeneMANIA (http://www.genemania.org) provides a well-maintained, user-friendly gene-list analysis web interface for deriving hypotheses based on gene functions.[29] In this study, the GeneMANIA was adopted to construct a gene–gene interaction network for S100 family members in terms of physical interactions, co-expression, predictions, co-localization, and genetic interaction, as well as to evaluate their functions. FunRich was used to conduct pathway and process enrichment analysis of S100 family members and their closely related genes.[30] The Gene Ontology (GO) terms for biological process (BP), molecular function (MF) and cellular component (CC) categories, as well as biological pathways enrichment analyses were performed through FunRich.

3. Results

3.1. Transcription levels of S100 members in patients with OC

To determine differences in the mRNA expression of S100 member between tumor and normal tissues in OC, we performed a comprehensive analysis using the GEPIA databases. As shown in Figure 1, GEPIA analysis indicated that the expression levels of S100A1, S100A2, S100A4, S100A5, S100A11, S100A14 and S100A16 were higher in OC tissues than in normal tissues, whereas there were no significant difference in Other S100 member mRNA expression between OC and normal controls. We also analyzed the relationship between the transcription levels of S100 member and the tumor stage of patients with OC. As shown in Figure 2, the results demonstrated that S100A1, S100A11, S100A13, S100G and S100P mRNA expression was significantly associated with tumor stage for OC.

3.2. Prognostic ability of S100 members expression in OC patients

We respectively examined the prognostic ability of the mRNA expression of individual S100 family members in OC patients using www.Kmplot.com. Nine members were significantly associated with prognosis in OC patients (Fig. 3). We observed that high expression of S100A1, S100A3, S100A5, S100A6, and S100A13 were significantly correlated with better OS, while increased S100A2, S100A7A, S100A10, and S100A11 expression were associated with worse prognosis in OC patients. The mRNA levels of the other S100 family members were not correlated with OS, although the expression of S100A4 (HR = 1.14 95% CI: 1.00–1.30, $P = .055$) was modestly associated with poor survival.

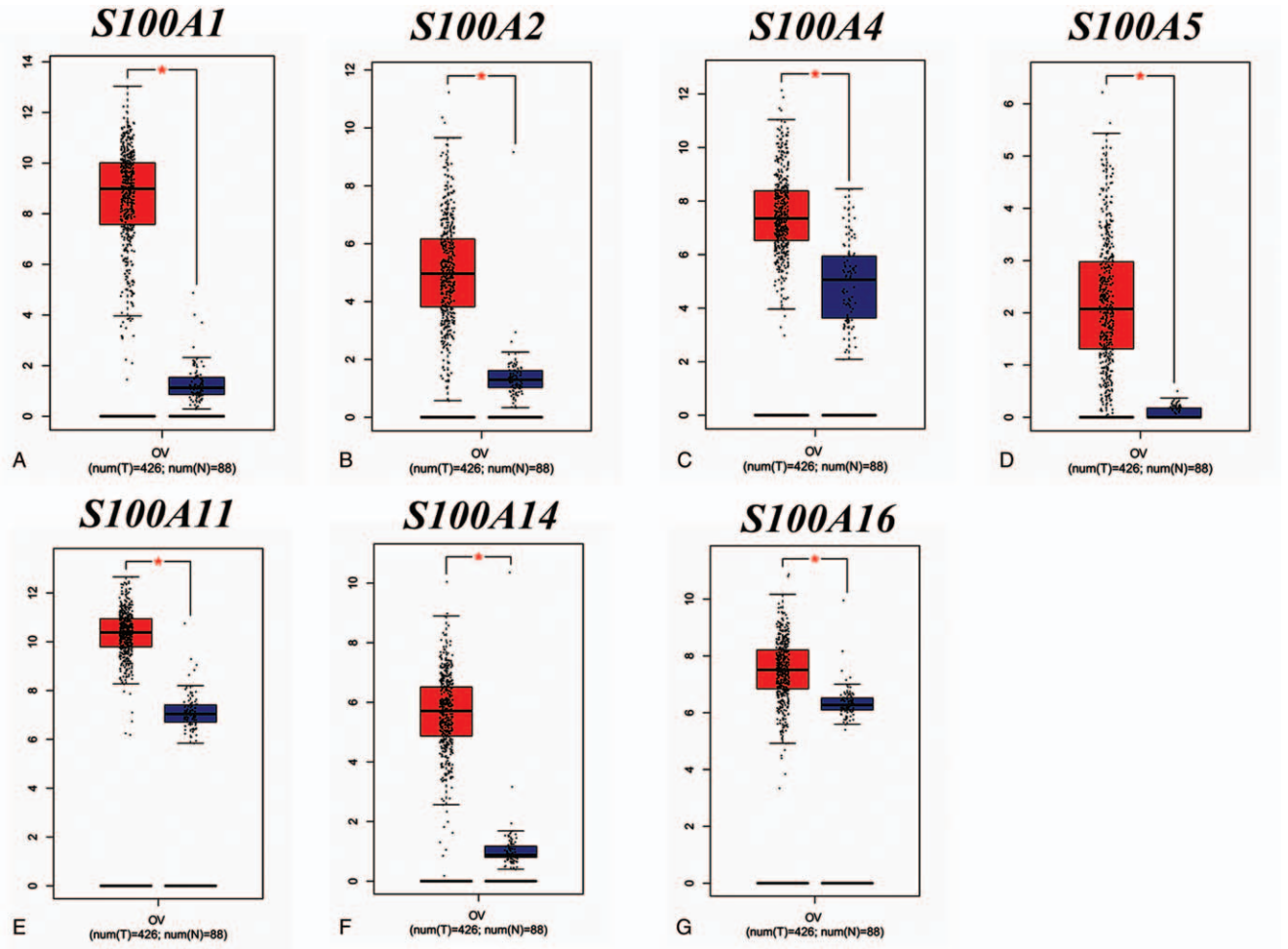

Figure 1. The expression of S100 family members in OC patients (GEPIA database). Note: Box plots derived from gene expression data in GEPIA comparing expression of a specific S100 family member in OC tissue and normal tissues, the *p* value was set up at 0.05. (A)-(G) The distribution of S100A1, S100A2, S100A4, S100A5, S100A11, S100A14, and S100A16 gene mRNA expression between OC tissue and normal tissues, respectively. (*, $P < .05$; **, $P < .01$; ***, $P < .001$).

3.3. Prognostic ability of S100 members expression in different OC subtypes

The prognostic ability of S100 family member expression was assessed in different pathological histological subtypes of OC, including serous and endometrioid. As shown in Table 1 and Figure 4, high expression of S100A5, S100A6, S100A8, and S100A13 were correlated with longer OS in serous OC patients. The expression of S100A10 and S100A11 were associated with poor OS in serous OC patients. S100A1 expression was modestly associated with OS, but without statistical significance. The remaining S100 family members were not related to prognosis in serous OC. In endometrioid OC, increased S100A12 and S100G expression were associated with better prognosis. The remaining S100 family members were not significantly associated with prognosis in endometrioid OC.

3.4. Prognostic ability of S100 members expression in OC patients with different clinicopathological features

To further assess the correlation of the expression of individual S100 family members with other clinicopathological features, we examined their correlation with pathological grade (Table 2), clinical stage (Table 3), and TP53 status (Table 4) in OC patients. As shown in Table 2, high expression of S100A2, S100A7A, and S100G were associated with better OS in pathological grade I OC patients. Increased S100A4, S100A6, S100A16, and S100B expression were associated with worse OS. However, elevated expression of S100A12 and S100Z were associated with better OS in grade II OC patients. In pathological grade III OC patients, high S100A2, S100A10, S100A11, and S100P expression were linked to shorter OS, but high S100A3, S100A5, S100A8, and S100B expression were correlated to longer OS. In addition, high expression of S100A1, S100A4, S100A6, S100A13, S100A14, and S100P were correlated with longer OS in grade IV OC patients.

As shown in Table 3, increased expression of S100A2 and S100B were associated with worse OS in clinical stage I patients, and only high expression of S100A13 was linked to better prognosis. For clinical stage II OC patients, high expression of S100A5 and S100G were associated with better OS, and high S100A6, S100A11, S100A16, and S100P expression correlated with poor prognosis in this subgroup. In clinical stage III OC patients, high expression of S100A1, S100A3, S100A5, S100A12, S100A14, and S100B correlated with better OS; in contrast, elevated S100A10, S100A11, and S100P expression were associated with worse OS. For clinical stage IV patients,

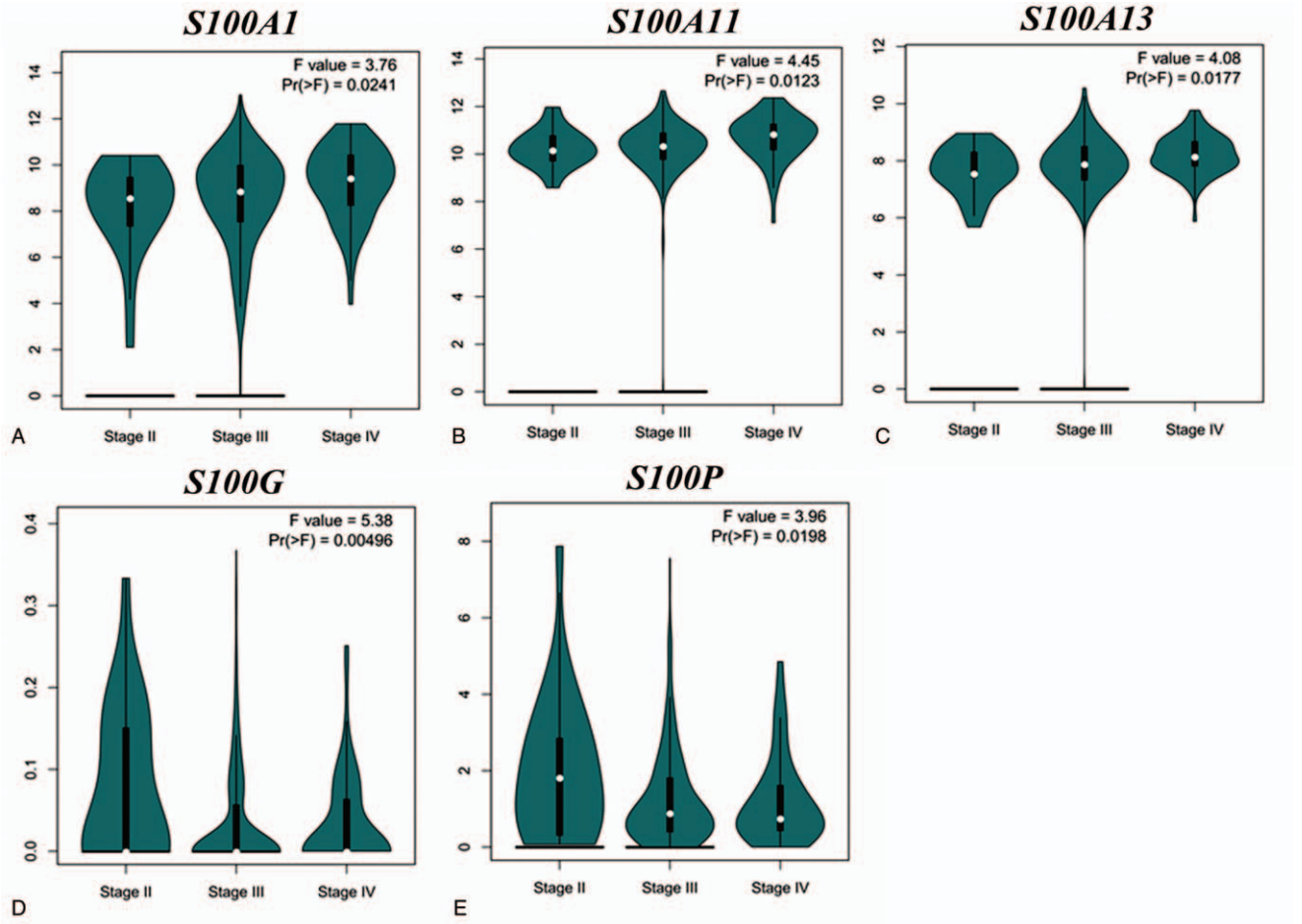

Figure 2. The expression levels of S100 family members in subgroups of different stage OC patients (GEPIA database). (A–E) Boxplot showing relative expression of S100A1, S100A11, S100A13, S100G and S100P in OC patients in stages, 2, 3, or 4 using GEPIA, respectively. (*, $P < .05$; **, $P < .01$; ***, $P < .001$).

high levels of S100A1, S100A4, and S100A5 were associated with worse OS, and only high S100A6 correlated with better OS in this subgroup.

Table 4 shows the correlation between S100 family member expression and TP53 status. Elevated expression of S100A1, S100A13, S100A16, S100G, and S100P were correlated with better OS in OC patients harboring mutated TP53. However, high expression of S100A7A, S100A11, S100A12, S100A14, and S100A16 were associated with poor OS in this subgroup. In contrast, increased S100A2, S100A3, S100A5, S100A13, and S100B expression were associated with worse OS in OC patients with wild-type TP53, and high expression of S100A8, S100A11, and S100B were linked to better prognosis.

3.5. Prognostic ability of S100 family members expression in OC patients according to treatment type

We examined the relationship between S100 family member expression and treatment in OC patients (Table 5). Elevated S100A2, S100A4, S100A7A, S100A10, S100A16, and S100B expression were associated with worse OS in OC patients who underwent optimal surgery, and high expression of S100A3, S100A7, S100A9, S100A12, and S100G were associated with outstanding OS in this subgroup. Increased S100A1, S100A6, S100A13, and S100A14 expression significantly correlated with longer survival in patients treated with suboptimal surgery. However, high expression of S100A11 was linked with worse OS in patients who underwent suboptimal surgery.

3.6. Prognostic ability of S100 family members signature in patients with OC

To further identify the prognostic values of S100 family members signature in patients with OC, the SurvExpress platform was used. A total of 1,902 patients from four datasets of large sample size ovarian cancer dataset in the SurvExpress platform were analyzed. High/low risk groups were divided by prognostic risk algorithms in each datasets. The survival analysis and Kaplan–Meier plotter between low risk (green) and high risk (red) groups were demonstrated in Figure 5. The results showed that the low risk group displayed a significant favorable OS outcome compared to the high risk group in ovarian serous cystadenocarcinoma TCGA (HR = 1.50, 95% CI = 1.19–1.88), ovarian Meta-base: 6 cohorts 22K genes (HR = 1.60, 95% CI = 1.32–1.94), Tothill Bowtell Survival Ovarian GSE9891 (HR = 2.25, 95% CI = 1.52–3.33) and Yoshihara Tanaka Ovarian GSE32062 (HR = 1.76, 95% CI = 1.22–1.54) datasets, respectively.

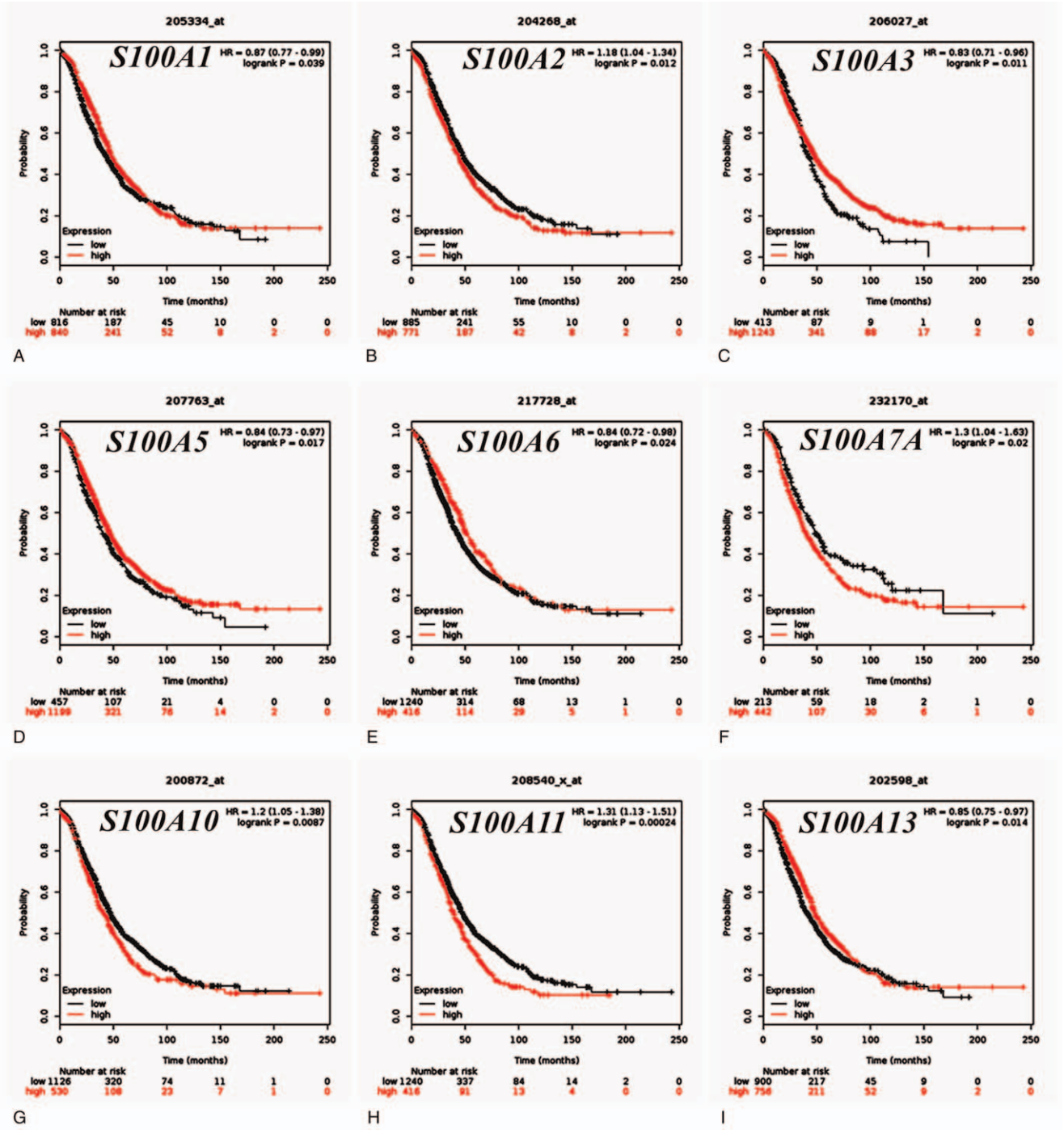

Figure 3. The prognostic value of the individual S100 family members (KM Plotter database). (A–I) Survival curves of S100A1, S100A2, S100A3, S100A5, S100A6, S100A7A, S100A10, S100A11, and S100A13 are plotted for all patients (n = 1,186), respectively.

3.7. Interaction and functions enrichment analysis of S100 family members in patients with OC

We ran GeneMANIA to analyze the S100 family members to further predict gene functions and network connections. As showed in Figure 6A, 19 genes closely related to the S100 family members are identified, such as CABP2, CABP7, CALN1, CAPSL, CRNN, EFCAB3, FLG, FLG2, GUCA1A, HRNR, KCNIP4, MICU3, MYL5, OCM, PVALB, RPTN, SNTN, TCHH, and TCHHL1. The co-expression interactions, co-localization interactions, physical interactions, prediction interactions, share protein domains interactions of the S100 family members were 197 pairs, 32 pairs, 8 pairs, 21 pairs and 1184 pairs, respectively.

The functions enrichment of S100 family members and their closely related genes were predicted by analyzing gene ontology (GO) and biological pathways enrichment analyses were performed through FunRich. As shown in Figure 6B–E, the biological process (BP) of S100 family members and their closely

Table 1

Correlation of S100 gene expression level with overall survival in ovarian cancer patients with different pathological histology.

S100 family	Affymetrix ID	Pathological grades	Cases	HR	95% CI	*P* value
S100A1	205334_at	Serous	1207	0.86	0.74–1.00	.055
		Endometrioid	–	–	–	–
S100A2	204268_at	Serous	1207	1.08	0.93–1.26	.31
		Endometrioid	47	4.9	0.82–29.32	.054
S100A3	206027_at	Serous	1207	0.86	0.73–1.01	.06
		Endometrioid	37	0.27	0.04–1.60	.12
S100A4	203186_s_at	Serous	1207	0.91	0.78–1.07	.24
		Endometrioid	37	4.79	0.53–42.98	.12
S100A5	207763_at	Serous	1207	0.83	0.70–0.98	**.025**
		Endometrioid	–	–	–	–
S100A6	217728_at	Serous	1207	0.80	0.67–0.95	**.013**
		Endometrioid	37	2.82	0.31–25.21	.33
S100A7	205916_at	Serous	1207	0.90	0.77–1.05	.19
		Endometrioid	37	0.17	0.02–1.48	.066
S100A7A	232170_at	Serous	1207	523	0.92–1.49	.20
		Endometrioid	–	–	–	–
S100A8	202917_s_at	Serous	1207	0.84	0.71–0.99	**.038**
		Endometrioid	37	0.41	0.05–3.66	.41
S100A9	203535_at	Serous	1207	0.87	0.74–1.01	.075
		Endometrioid	37	0.41	0.07–2.47	.32
S100A10	200872_at	Serous	1207	1.25	1.05–1.49	**.011**
		Endometrioid	–	–	–	–
S100A11	208540_x_at	Serous	1207	1.34	1.13–1.58	**.00079**
		Endometrioid	37	0.30	0.05–1.81	.16
S100A12	205863_at	Serous	1207	0.90	0.76–1.05	.18
		Endometrioid	37	0.10	0.01–0.89	**.011**
S100A13	202598_at	Serous	1207	0.80	0.68–0.94	**.0055**
		Endometrioid	37	0.16	0.03–0.09	**.022**
S100A14	218677_at	Serous	1207	0.89	0.76–1.04	.13
		Endometrioid	37	3.03	0.5–18.16	.20
S100A16	227998_at	Serous	523	1.21	0.97–1.52	.096
		Endometrioid	30	2.65	0.28–25.49	.38
S100B	209686_at	Serous	1207	1.13	0.95–1.33	.16
		Endometrioid	37	0.40	0.07–2.38	.29
S100G	207885_at	Serous	1207	0.90	0.76–1.06	.20
		Endometrioid	37	0.10	0.01–0.86	**.0092**
S100P	204351_at	Serous	1207	1.09	0.93–1.27	.28
		Endometrioid	47	0.38	0.06–2.29	.28
S100Z	1554876_a_at	Serous	523	1.16	0.93–1.46	.19
		Endometrioid	30	0.41	0.06–2.92	.36

The bold values indicate that the results are statistically significant.

related genes were mainly enrichment in the cell communication, signal transduction, learning and/or memory, calcium-mediated signaling, ion transport, cell growth and/or maintenance, transport and protein metabolism. The cellular components that these genes were involve in were the perinuclear region of cytoplasm, ruffle, cytoplasm, exosomes, extrinsic to internal side of plasma membrane, insoluble fraction, muscle myosin complex and cytoplasmic membrane-bounded vesicle. The molecular functions that these genes were mainly expressed in were calcium ion binding, channel regulator activity, heat shock protein activity, structural constituent of cytoskeleton and molecular function unknown; The top 8 results of the enriched biological pathways included endogenous TLR signaling, advanced glycosylation endproduct receptor signaling, visual signal transduction: cones, visual signal transduction: rods, mesenchymal-to-epithelial transition, validated transcriptional targets of TAp63 isoforms, validated targets of C-MYC transcriptional repression and p73 transcription factor network pathway.

4. Discussion

Accumulative studies have determined that deregulated S100 expression is a common feature in human cancers, and S100 expression is associated with tumorigenesis and progression.[7,8] However, the exact role of S100 expression in human tumors, including OC, is still controversial.[23–25] In the current study, we comprehensively examined the expression patterns, prognostic roles and molecular function of S100 family members in OC using integrated bioinformatical analysis. Among the members of the S100 family, the mRNA expression levels of S100A1, S100A2, S100A4, S100A5, S100A11, S100A14, and S100A16 were found to be significantly upregulated in patients with OC, and high mRNA expression of S100A1, S100A3, S100A5, S100A6, and S100A13 were significantly correlated with better overall survival, while increased S100A2, S100A7A, S100A10, and S100A11 mRNA expressions were associated with worse prognosis in OC patients. More importantly, S100

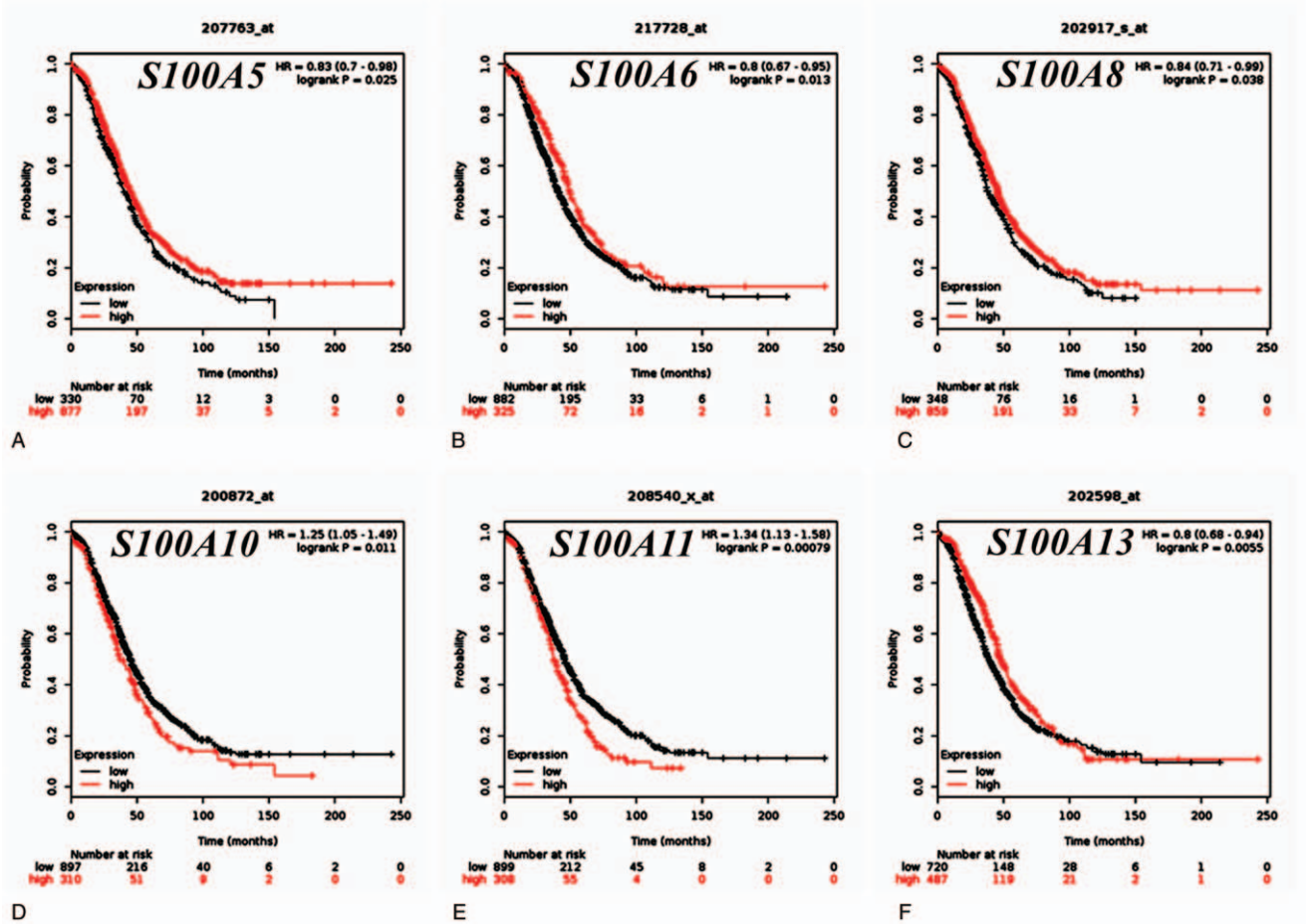

Figure 4. The prognostic values of individual S100 family members in serous ovarian cancer subtypes (KM Plotter database). (A)- (F) Survival curves of S100A5, S100A6, S100A8, S100A10, S100A11 and S100A13 are plotted for serous type OC patients (n=1,232), respectively.

family signatures may be useful potential prognostic markers for OC. Regrettably, to date, few studies have directly compared the prognostic value of S100 family members with other conventional markers, such as CA125 and HE4, and our study could therefore not elucidate whether S100 family members could improve the predictive accuracy of commonly used serum tumor markers for OC prognosis, either alone or in combination.

S100A1 is a member of the S100 family of calcium-binding proteins. It is involved in calcium signaling and neurotransmitter release and associated with cytoskeletal and filament-associated proteins, transcription factors and their regulators, enzymes, and other Ca_2^+-activated proteins.[31] However, its role in cancer has not yet been fully elucidated. Our results demonstrated that the mRNA expression levels of S100A1 were significantly upregulated in patients with OC, and increased expression of S100A1 was correlated with significantly better OS for all OC patients, but not in the serous or endometrioid subgroups. This may be due to the small sample size of these two subgroups. A previous study found that S100A1 expression was associated with clinicopathological features in OC patients, such as tumor grade, clinical stage, tumor differentiation, and lymph node metastasis.[32] Consistent with this result, we found that high expression of S100A1 indicated a better OS for OC patients with high grade (IV) and stage (IV). Furthermore, S100A1 expression was also associated with longer survival in OC patients who underwent suboptimal surgery.

S100A2 is considered a novel transcriptional target of the cellular calcium signaling and p53 signaling pathways,[33] and plays a pivotal role in regulating cell cycle progression and differentiation and triggering apoptotic programmed cell death in response to DNA damage or stress.[34] Decreased expression of S100A2 has been observed in several tumor types, such as oral cancer,[35] head and neck cancer,[9] breast cancer,[36] pancreatic cancer,[37] lung cancer,[38] bladder cancer,[9] gastric cancer,[20] and colorectal cancer,[39] leading to its designation as a potential tumor suppressor gene. Recent studies confirmed that S100A2 acts downstream of the BRCA1/ΔNp63 signaling axis in modulating transcriptional responses, and it participates in susceptibility to familial OC.[33] In our study, the mRNA expression levels of S100A2 were significantly increased in tumor compared to normal, and high expression of S100A2 was significantly associated with poor OS, especially in clinical stage I and pathological grade III OC patients. In addition, S100A2 was also found to be associated with decreased survival in OC patients who underwent optimal surgery in our analysis.

The biologic roles and prognostic effects of S100A3, S100A5, S100A7A, and S100A13 in OC are still ambiguous. S100A3 is a matricellular protein expressed in numerous tissues and cell types. It was reported to be associated with tumorigenesis in

Table 2

Correlation of S100 gene expression level with overall survival in ovarian cancer patients with different pathological grade.

S100 family	Affymetrix ID	clinical stage	Cases	HR	95% CI	*P* value
S100A1	205334_at	I	56	0.59	0.23–1.49	.25
		II	324	0.91	0.66–1.25	.54
		III	1015	0.89	0.75–1.05	.16
		IV	20	0.07	0.01–0.34	**3.2e−5**
S100A2	204268_at	I	56	0.14	0.02–1.04	**.026**
		II	324	1.30	0.91–1.86	.15
		III	1015	1.27	1.07–1.50	**.0051**
		IV	20	1.83	0.59–0.69	.29
S100A3	206027_at	I	56	2.22	0.73–6.77	.15
		II	324	1.26	0.93–1.71	.13
		III	1015	0.78	0.65–0.93	**.0056**
		IV	20	0.36	0.12–1.04	**.049**
S100A4	203186_s_at	I	56	0.63	0.21–1.93	.41
		II	324	1.46	1.06–2.03	**.0021**
		III	1015	1.09	0.92–1.29	.30
		IV	20	0.21	0.06–0.66	**.0036**
S100A5	207763_at	I	56	0.53	0.17–1.62	.26
		II	324	1.32	0.98–1.79	.071
		III	1015	0.79	0.66–0.95	**.011**
		IV	20	0.44	0.15–1.30	.13
S100A6	217728_at	I	56	0.41	0.14–1.19	.092
		II	324	1.40	1.02–1.93	**.038**
		III	1015	0.83	0.70–1.00	.051
		IV	20	0.58	0.37–0.90	**.015**
S100A7	205916_at	I	56	0.52	0.19–1.39	.18
		II	324	0.84	0.60–1.17	.30
		III	1015	0.90	0.76–1.06	.20
		IV	20	0.47	0.17–1.31	.14
S100A7A	232170_at	I	41	4.36	1.42–13.42	**.0051**
		II	162	1.39	0.90–2.17	.14
		III	392	0.81	0.63–1.04	.093
		IV	18	–	–	–
S100A8	202917_s_at	I	56	0.46	0.13–1.61	.22
		II	324	0.77	0.56–1.06	.11
		III	1015	0.75	0.63–0.89	**.0012**
		IV	20	0.55	0.17–1.73	.30
S100A9	203535_at	I	56	1.66	0.62–4.48	.31
		II	324	0.75	0.55–1.03	.071
		III	1015	0.85	0.72–1.00	.052
		IV	20	2.18	0.74–6.39	.15
S100A10	200872_at	I	56	0.56	0.21–1.48	.24
		II	324	1.34	0.97–1.84	.072
		III	1015	1.38	1.15–1.65	**.00058**
		IV	20	0.56	0.21–1.48	.24
S100A11	208540_x_at	I	56	0.55	0.22–1.42	.21
		II	324	0.74	0.53–1.03	.069
		III	1015	1.38	1.15–1.66	**.00051**
		IV	20	2.79	0.80–9.72	.094
S100A12	205863_at	I	56	1.91	0.73–4.99	.18
		II	324	0.56	0.41–0.78	**.00043**
		III	1015	0.90	0.76–1.06	.21
		IV	20	1.66	0.63–4.40	.30
S100A13	202598_at	I	56	1.60	0.59–4.33	.35
		II	324	0.31	0.09–1.14	.063
		III	1015	0.87	0.74–1.02	.096
		IV	20	1.34	0.90–1.99	.15
S100A14	218677_at	I	56	1.86	0.65–5.32	.24
		II	324	0.78	0.58–1.06	.11
		III	1015	0.87	0.74–1.03	.11
		IV	20	0.34	0.12–0.97	**.035**
S100A16	227998_at	I	41	0.53	0.17–1.63	.26
		II	162	1.75	1.02–3.01	**.04**
		III	392	1.29	1.00–1.67	.05
		IV	18	–	–	–
S100B	209686_at	I	56	2.05	0.76–5.50	.15
		II	324	1.41	1.02–1.94	**.036**
		III	1015	0.83	0.70–0.99	**.037**
		IV	20	0.46	0.14–1.47	.18
S100G	207885_at	I	56	0.27	0.09–0.87	**.019**
		II	324	0.77	0.55–1.08	.13
		III	1015	0.87	0.73–1.03	.11
		IV	20	0.71	0.26–1.94	.51
S100P	204351_at	I	56	0.65	0.25–1.72	.38
		II	324	0.87	0.64–1.20	.40
		III	1015	1.25	1.06–1.48	**.0096**
		IV	20	0.08	0.01–0.62	**.0023**
S100Z	1554876_a_at	I	41	–	–	–
		II	162	0.60	0.37–0.96	**.032**
		III	392	1.29	1.00–1.66	.051
		IV	18	–	–	–

The bold values indicate that the results are statistically significant.

Table 3

Correlation of S100 gene expression level with overall survival in ovarian cancer patients with different clinical stage.

S100 family	Affymetrix ID	clinical stage	Cases	HR	95% CI	*P* value
S100A1	205334_at	I	74	0.41	0.11–1.53	.17
		II	61	0.55	0.19–1.59	.26
		III	1044	0.80	0.68–0.94	**.0059**
		IV	176	1.48	1.03–2.14	**.034**
S100A2	204268_at	I	74	1.18	1.04–1.34	**.012**
		II	61	0.42	0.14–1.29	.12
		III	1044	1.08	0.91–1.28	.36
		IV	176	1.40	0.97–2.02	.069
S100A3	206027_at	I	74	0.36	0.11–1.20	.083
		II	61	0.74	0.37–1.51	.41
		III	1044	0.82	0.69–0.96	**.017**
		IV	176	0.79	0.54–1.15	.22
S100A4	203186_s_at	I	74	1.73	0.52–5.81	.37
		II	61	3.06	0.66–14.23	.14
		III	1044	0.88	0.74–1.05	.16
		IV	176	1.54	1.07–2.22	**.021**
S100A5	207763_at	I	74	0.48	0.14–1.59	.22
		II	61	0.12	0.02–0.95	**.017**
		III	1044	0.78	0.64–0.94	**.011**
		IV	176	1.69	1.17–2.45	**.0047**
S100A6	217728_at	I	74	0.38	0.12–1.18	.082
		II	61	3.27	1.00–10.73	**.04**
		III	1044	0.88	0.74–1.05	.16
		IV	176	0.58	0.37–0.90	**.015**
S100A7	205916_at	I	74	0.43	0.12–1.59	.19
		II	61	2.12	0.58–7.79	.25
		III	1044	0.87	0.73–1.03	.11
		IV	176	0.73	0.49–1.08	.12
S100A7A	232170_at	I	51	0.33	0.08–1.41	.12
		II	32	2.54	0.46–13.92	.27
		III	426	1.24	0.94–1.62	.12
		IV	61	1.74	0.95–3.16	.068
S100A8	202917_s_at	I	–	–	–	–
		II	61	2.04	0.66–6.27	.20
		III	1044	0.85	0.71–1.00	.056
		IV	176	0.76	0.53–1.09	.13
S100A9	203535_at	I	74	0.21	0.03–1.61	.096
		II	61	2.36	0.78–7.13	.12
		III	1044	0.90	0.76–1.06	.20
		IV	176	0.81	0.56–1.17	.26
S100A10	200872_at	I	74	0.16	0.02–1.22	.42
		II	61	2.47	0.77–7.94	.12
		III	1044	1.32	1.11–1.57	**.0014**
		IV	176	1.24	0.82–1.88	.31
S100A11	208540_x_at	I	74	0.36	0.11–1.15	.072
		II	61	4.55	1.00–20.78	**.033**
		III	1044	1.49	1.25–1.78	**7.9e−06**
		IV	176	1.1	0.77–1.59	.59
S100A12	205863_at	I	74	0.46	0.15–1.47	.18
		II	61	0.52	0.18–1.50	.220
		III	1044	0.83	0.70–0.98	**.027**
		IV	176	0.76	0.51–1.14	.18
S100A13	202598_at	I	74	0.11	0.01–0.84	**.0095**
		II	61	0.31	0.09–1.14	.063
		III	1044	0.87	0.74–1.02	.096
		IV	176	1.34	0.90–1.99	.15
S100A14	218677_at	I	74	2.24	0.49–10.25	.28
		II	–	–	–	–
		III	1044	0.85	0.72–1.00	**.046**
		IV	176	1.15	0.80–1.67	.45
S100A16	227998_at	I	51	2.42	0.58–10.21	.21
		II	32	0.35	0.07–1.85	.20
		III	426	1.42	1.05–1.93	**.022**
		IV	61	0.65	0.36–1.20	.17
S100B	209686_at	I	74	3.67	1.01–13.40	**.037**
		II	61	1.93	0.65–5.76	.23
		III	1044	0.83	0.70–1.00	**.048**
		IV	176	0.83	0.58–1.20	.33
S100G	207885_at	I	74	2.64	0.33–21.51	.34
		II	61	0.27	0.08–1.00	**.035**
		III	1044	0.84	0.70–1.01	.056
		IV	176	1.28	0.87–1.88	.20
S100P	204351_at	I	74	2.41	0.72–8.02	.14
		II	61	4.14	1.37–12.51	**.0063**
		III	1044	1.35	1.13–1.60	**.00074**
		IV	176	0.74	0.48–1.15	.18
S100Z	1554876_a_at	I	51	2.41	0.72–8.02	.14
		II	32	0.35	0.04–2.90	.31
		III	426	0.87	0.67–1.13	.29
		IV	176	0.63	0.35–1.14	.12

The bold values indicate that the results are statistically significant.

Table 4

Correlation of S100 gene expression level with overall survival in ovarian cancer patients with different TP53 mutation status.

S100 family	Affymetrix ID	TP53 mutation	Cases	HR	95% CI	*P* value
S100A1	205334_at	mutated	506	0.66	0.51–0.85	**.0011**
		wild type	94	0.65	0.36–1.17	.15
S100A2	204268_at	mutated	506	0.79	0.61–1.02	.069
		wild type	94	0.45	0.22–0.93	**.027**
S100A3	206027_at	mutated	506	1.22	0.96–1.56	.11
		wild type	94	0.41	0.23–0.74	**.0023**
S100A4	203186_s_at	mutated	506	0.82	0.64–1.03	.089
		wild type	94	0.62	0.35–1.13	.11
S100A5	207763_at	mutated	506	0.82	0.64–1.06	.14
		wild type	94	0.39	0.18–0.86	**.016**
S100A6	217728_at	mutated	506	0.79	0.62–1.02	.069
		wild type	94	0.63	0.36–1.10	.099
S100A7	205916_at	mutated	506	1.10	0.87–1.39	.42
		wild type	94	0.71	0.38–1.31	.27
S100A7A	232170_at	mutated	124	1.71	1.15–2.56	**.0079**
		wild type	19	–	–	–
S100A8	202917_s_at	mutated	506	0.80	0.63–1.03	.08
		wild type	94	1.84	1.05–3.23	**.031**
S100A9	203535_at	mutated	506	0.86	0.68–1.08	.20
		wild type	94	1.46	0.83–2.57	.19
S100A10	200872_at	mutated	506	1.26	0.94–1.64	.088
		wild type	94	0.61	0.33–1.11	.10
S100A11	208540_x_at	mutated	506	1.53	1.21–1.94	**.00031**
		wild type	94	2.14	1.17–3.91	**.011**
S100A12	205863_at	mutated	506	1.31	1.04–1.64	**.019**
		wild type	94	1.43	0.83–2.46	.20
S100A13	202598_at	mutated	506	0.75	0.60–0.94	**.013**
		wild type	94	0.16	0.03–0.09	**.022**
S100A14	218677_at	mutated	506	1.30	1.02–1.65	**.035**
		wild type	94	0.73	0.42–1.27	.27
S100A16	227998_at	mutated	124	0.64	0.42–0.98	**.038**
		wild type	19	–	–	–
S100B	209686_at	mutated	506	0.80	0.64–1.01	.055
		wild type	94	2.04	1.16–3.58	**.012**
S100G	207885_at	mutated	506	1.27	1.01–1.61	**.043**
		wild type	94	0.68	0.39–1.18	.17
S100P	204351_at	mutated	506	1.28	1.01–1.62	**.038**
		wild type	94	1.38	0.80–2.39	.25
S100Z	1554876_a_at	mutated	506	1.27	0.86–1.88	.22
		wild type	19	–	–	–

The bold values indicate that the results are statistically significant.

epidermoid cysts, pilomatrixoma, and digestive system tumors.[40,41] S100A5 is expressed in very restricted regions of the adult brain and regulates electrolyte metabolism.[42] S100A7A was demonstrated to be involved in the innate immune system and acts as a defense against epidermal differentiation and inflammation. However, its role in cancer has rarely been explored.[43] Unlike S100A5, the expression of S100A13 has been detected in multiple tissue types, with high expression in the thyroid gland. It plays essential roles in signal transduction for the modulation of tumor growth and invasion.[44] To the best of our knowledge, there are very few studies exploring the relationship between these four genes and outcomes of OC patients. Our analysis showed that the mRNA expression levels of S100A5 were significantly upregulated, and overexpression of S100A3, S100A5, and S100A13 were associated with better OS in OC patients, and S100A13 expression was also associated with better OS in early clinical stages, patients undergoing suboptimal surgery, and two pathological types of OC. In contrast, high expression of S100A7A was associated with worse OS in OC patients.

S100A6 is expressed in a limited number of cell types in adult normal tissues and in several tumor types. As an intracellular protein, S100A6 has been implicated in the regulation of several cellular functions, such as proliferation, cytoskeleton dynamics, apoptosis, and the cellular response to stress. It was reported to be inversely associated with the progression and invasion of several human carcinomas.[45] Moreover, a recent study indicated that serum S100A6 concentration predicts peritoneal tumor burden and correlates with clinical disease stage in OC patients.[46] Our results showed that increased expression of S100A6 was correlated with better prognosis, especially in serous type OC.

S100A10 is an integral part of the cellular structural scaffolding that interacts with plasma membrane proteins through its association with annexin II. S100A10 has been shown to be overexpressed in several human carcinomas, and knockdown of S100A10 significantly reduces the proliferation,

Table 5

Correlation of S100 gene expression level with overall survival in ovarian cancer patients with different treatment.

S100 family	Affymetrix ID	Treatment	Cases	HR	95% CI	*P* value
S100A1	205334_at	optimal	801	1.13	0.92–1.39	.26
		suboptimal	536	0.67	0.55–0.82	**9.1e−05**
S100A2	204268_at	optimal	801	1.24	1.01–1.52	**.039**
		suboptimal	536	1.19	0.98–1.46	.086
S100A3	206027_at	optimal	801	0.61	0.49–0.76	**1.1e−05**
		suboptimal	536	1.11	0.90–1.35	.33
S100A4	203186_s_at	optimal	801	1.26	1.01–1.56	**.039**
		suboptimal	536	0.84	0.66–1.06	.14
S100A5	207763_at	optimal	801	1.22	0.99–1.49	.057
		suboptimal	536	0.81	0.65–1.01	.066
S100A6	217728_at	optimal	801	0.88	0.70–1.10	.26
		suboptimal	536	0.78	0.62–0.99	**.043**
S100A7	205916_at	optimal	801	0.76	0.61–0.94	**.012**
		suboptimal	536	0.86	0.69–1.08	.20
S100A7A	232170_at	optimal	243	1.52	1.00–2.32	**.049**
		suboptimal	235	1.37	0.98–1.93	.065
S100A8	202917_s_at	optimal	801	0.83	0.68–1.02	0083
		suboptimal	536	0.91	0.73–1.33	.39
S100A9	203535_at	optimal	801	0.78	0.63–0.96	**.018**
		suboptimal	536	1.14	0.90–1.45	.26
S100A10	200872_at	optimal	801	1.42	1.15–1.76	**.0012**
		suboptimal	536	1.17	0.92–1.48	.21
S100A11	208540_x_at	optimal	801	1.23	0.98–1.55	.075
		suboptimal	536	1.42	1.15–1.76	**.0012**
S100A12	205863_at	optimal	801	0.71	0.57–0.90	**.0034**
		suboptimal	536	1.10	0.90–1.36	.36
S100A13	202598_at	optimal	801	0.84	0.66–1.06	.14
		suboptimal	536	0.75	0.61–0.93	**.0084**
S100A14	218677_at	optimal	801	0.86	0.70–1.06	.16
		suboptimal	536	0.81	0.66–1.01	**.058**
S100A16	227998_at	optimal	243	1.98	1.16–3.40	**.011**
		suboptimal	235	0.76	0.55–1.05	.091
S100B	209686_at	optimal	801	1.35	1.08–1.68	**.0077**
		suboptimal	536	0.82	0.67–1.01	.059
S100G	207885_at	optimal	801	0.69	0.55–0.86	**.0011**
		suboptimal	536	0.82	0.67–1.00	.055
S100P	204351_at	optimal	801	1.15	0.91–1.44	.24
		suboptimal	536	1.23	1.00–1.50	.05
S100Z	1554876_a_at	optimal	243	1.40	0.88–2.25	.16
		suboptimal	235	1.14	0.85–1.53	.40

The bold values indicate that the results are statistically significant.

migration, and invasion capacity of cancer cell lines.[47] Therefore, it has been implicated in tumor development and progression. Moreover, some studies reported that high S100A10 expression is a powerful predictor of poor chemotherapy response and/or poor outcome in ovarian serous carcinoma.[48,49] We found a similar result, with high S100A10 expression being related to poorer prognosis in OC patients.

S100A11 may function in motility, invasion, and tubulin polymerization. Chromosomal rearrangements and altered expression of S100A11 have been implicated in carcinogenesis, metastasis, and tumor progression.[50] S100A11 has been shown to promote the growth, invasion, and migration of OC cells, and its overexpression correlates with an aggressive malignant phenotype, suggesting it may be a novel prognostic factor for OC. Our results showed that increased expression of S100A11 might indicate worse outcome in serous OC patients, but not in endometrioid OC patients. In addition, high expression of S100A11 was correlated with a worse OS in grade III and stage III OC patients.

Mutations in tumor suppressor genes may be essential drivers in cancer onset and progression. p53, a transcriptional regulator, has been extensively studied, and is capable of inducing apoptosis, promoting genomic stability, and inhibiting angiogenesis.[51] Mutant p53 causes a gain-of-function phenotype, and is involved in tumorigenesis, invasion, and metastasis. Several S100 family members can directly bind to p53 and inhibit its expression and phosphorylation, which contributes to chemoresistance and leads to cancer progression.[52] Multiple studies have revealed a correlation between p53 function and OC stem cells; however, evidence on a prognostic association between TP53 status and S100 family members in OC remains to be clarified.[53] In our current analysis, we found that the mRNA

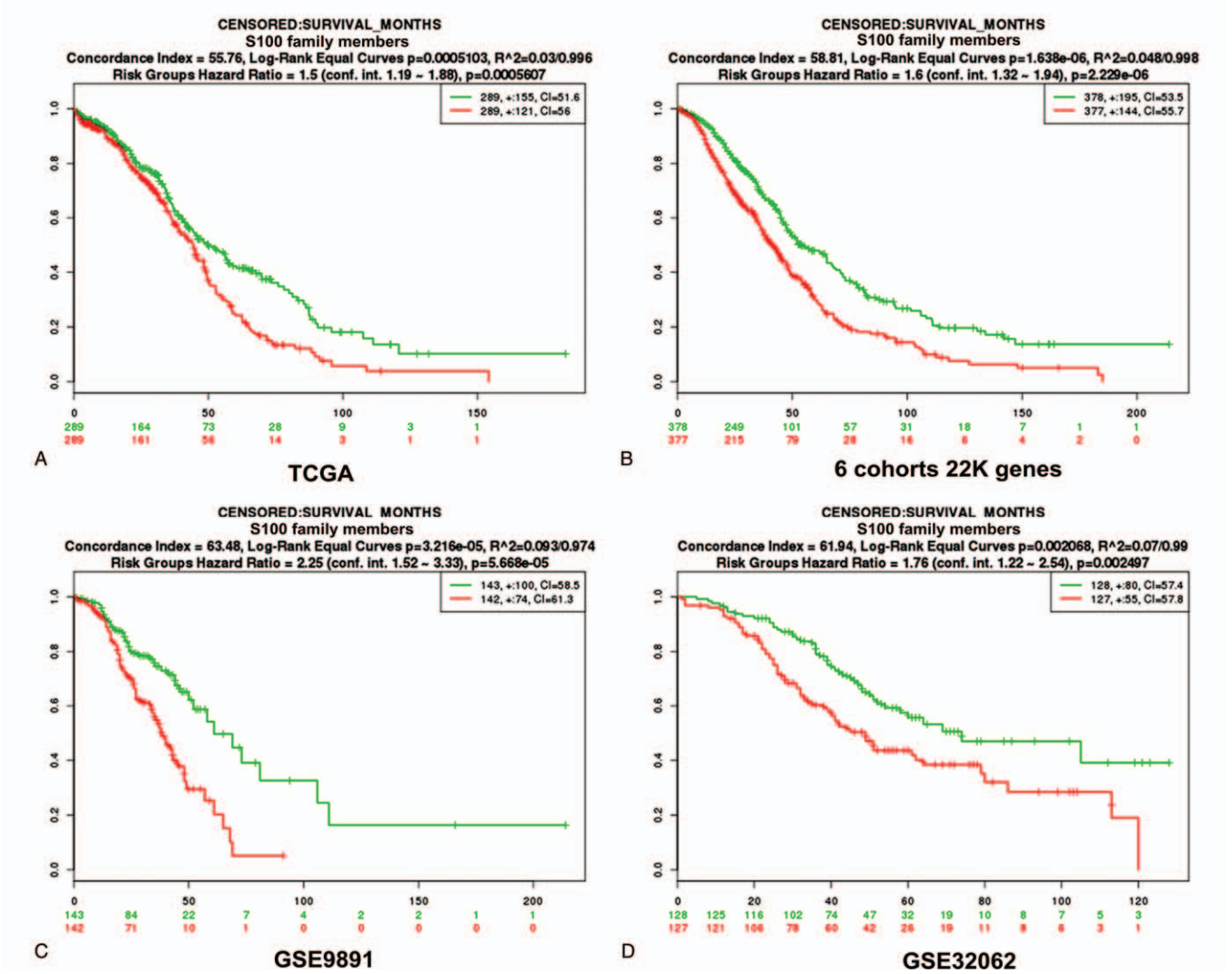

Figure 5. The genes signature of S100 family members in ovarian cancer (SurvExpress database). (A–D) Kaplan-Meier survival curves of S100 family members were explored in high risk and low risk group for ovarian serous cystadenocarcinoma TCGA, ovarian Meta-base: 6 cohorts 22K genes, Tothill Bowtell Survival Ovarian GSE9891 and Yoshihara Tanaka Ovarian GSE32062 datasets, respectively.

expression levels of S100A11, S100A14, and S100A16 were significantly increased, and increased S100A11, S100A14, S100A16, S100G, and S100P expression in TP53-mutated and S100A8, S100A11, and S100B expression in TP53-wild-type OC patients were correlated with poor OS, indicating that mutations in TP53 might regulate these S100 family members' expression and participation in the development and progression of OC.

In addition, S100 family, is composed of 20 members that exhibit a high degree of structural and function similarity in humans, the prognostic values of each gene don't fully reflect the intricacy of potential biomarkers and don't maximally distinguish the survival benefits in high/low expression group via the expression optimal cutoff. Therefore, we have identified the prognostic values of S100 family members signature in patients with OC using the SurvExpress platform. High/low risk groups were divided by prognostic risk algorithms, and the low risk group displayed a significant favorable OS outcome compared to the high risk group in four datasets. Our results indicating that S100 family signatures may be useful potential prognostic markers for OC. At last, we also carried out interaction and functions enrichment analysis of S100 family members in patients with OC by GeneMANIA and Funrich databases. 19 genes that are closely related with the S100 family members are identified, and dozens of gene ontology (GO) and biological pathways are enriched. Interestingly, the function and carcinogenesis of 19 closely related genes are currently less studied, but the involved pathways of their and S100 family members are closely related to the development and progression of various tumors. For example, TLR signaling pathway, p73 signaling pathway, p63 signaling pathway, C-MYC signaling pathway, Wnt signaling pathway, p53 signaling pathway, mTOR signaling pathway, c-Met signaling pathway, VEGF and VEGFR signaling network, immune System signaling pathway and CDC42 signaling events

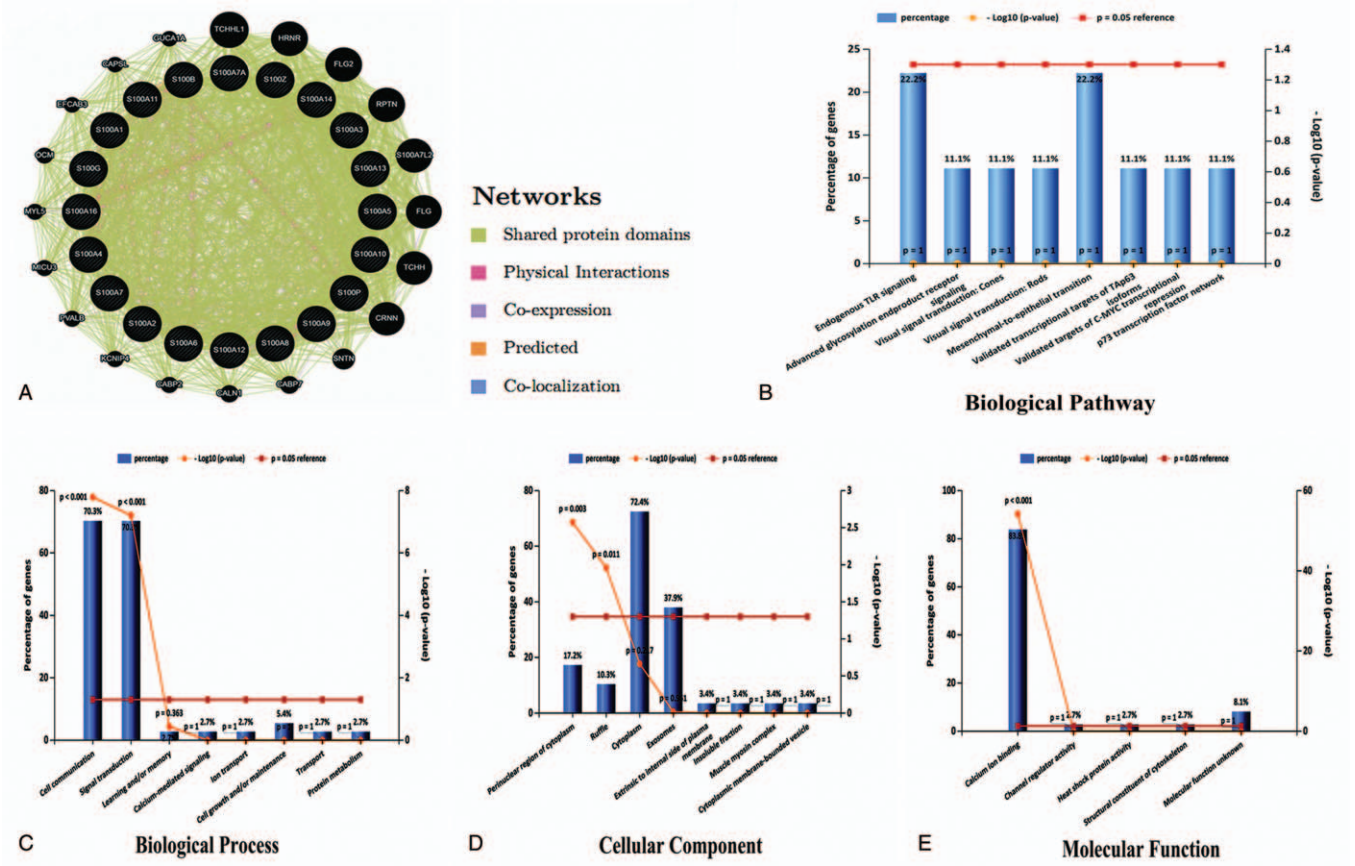

Figure 6. The interaction and functions enrichment analysis of S100 family members in ovarian cancer (GeneMANIA and Funrich database). (A) Network connections of S100 family members in patients with ovarian cancer by GeneMANIA; (B–E) The biological pathways and Gene Ontology (GO) terms for biological process (BP), molecular function (MF) and cellular component (CC) categories enrichment analyses were performed through FunRich, respectively.

signaling pathway. The above results provided a novel insight of S100 family members into OC pathogenesis, which might be helpful for better understanding the heterogeneity and complexity of the molecular biological properties of OC.

5. Conclusion

In conclusion, the mRNA expression levels of S100A1, S100A2, S100A4, S100A5, S100A11, S100A14, and S100A16 were significantly upregulated in patients with OC, and high mRNA expression of S100A1, S100A3, S100A5, S100A6, and S100A13 were significantly correlated with better overall survival, while increased S100A2, S100A7A, S100A10, and S100A11 mRNA expressions were associated with worse prognosis in OC patients. In addition, we also observed that specific S100 members were associated with prognosis when examining patients with different pathological histology, clinical stage, pathological grade, TP53 status, and treatment type. More importantly, S100 family signatures may be useful potential prognostic markers for OC. The associated results may be useful to develop tools to more accurately predict OC prognosis and promote development of S100-targeted inhibitors for the treatment of OC patients. However, due to the limitations of KM database mining, the above conclusions need to be interpreted cautiously in clinical practice. More large-scale and Cox-multivariate analysis are needed to be conducted to better validate the prognostic value of each individual member of the S100 family in patients with OC.

Supplementary Materials: Additional file: Table S1, http://links.lww.com/MD/F214. Interaction and functions enrichment analysis of S100 family members in patients with OC using GeneMANIA database.

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Author contributions

Conceptualization: Quan Zhou.
Data curation: Quan Zhou, Hong-Yu Xu.
Formal analysis: Hong-Yu Xu, Hua-Mei Song.
Funding acquisition: Quan Zhou.
Investigation: Quan Zhou, Hua-Mei Song.
Methodology: Hong-Yu Xu, Hua-Mei Song.
Project administration: Quan Zhou.
Resources: Hua-Mei Song.
Software: Hong-Yu Xu, Hua-Mei Song.
Visualization: Hong-Yu Xu.

Writing – original draft: Hua-Mei Song.
Writing – review & editing: Quan Zhou, Hua-Mei Song.

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