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Gene expression and prognosis of sirtuin family members in ovarian cancer

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Abstract

Sirtuins (SIRTs), a class of nicotinamide-adenine dinucleotide (NAD)+-dependent deacetylases, involve in modulating carcinogenesis and progression of various malignancies through their regulation of the cancer metabolism. However, the expression profiles and prognostic roles of SIRTs in ovarian cancer (OC) remain unclear. We underscore the transcriptional expression and prognostic significance of SIRTs in OC patients using online databases. Gene Expression Profiling Interactive analysis (GEPIA) was applied to analyze mRNA expression, and Kaplan–Meier plotter was used to evaluate prognostic value. In patients with OC, *SIRT1/2/3* were significantly down-regulated, while rest of *SIRTs* were not significantly changed. High SIRT2/5/6/7 expression was correlated with favorable overall survival (OS), while high SIRT1/4 expression was correlated with poor OS. Additionally, aberrant SIRTs mRNA levels were related to the prognosis of OC patients with different clinicopathological characteristics. This is the first study to integrate bioinformatics approaches intended to identify the expression profiles and prognostic value of SIRTs in OC. These results suggest that SIRTs is related to the prognosis of OC and may be the potential therapeutic interventions in OC.

Abbreviations: BP = biological process, CC = cellular component, DAVID = Database for annotation, Visualization and integrated Discovery, GO = gene ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, MF = molecular function, OC = ovarian cancer, OS = overall survival, PFS = progression-free survival, PPS = post-progression survival, SIRT = sirtuin.

Keywords: gene expression, ovarian cancer, prognosis, sirtuin

1. Introduction

Ovarian cancer (OC) is a common gynecological tumor with approximately 204,000 cases worldwide each year.[1] Despite advances in treatment of OC, the survival of OC patients still remains limited with a 5-year survival rate of 10% to 30%.[2] Therefore, it is crucial to identify the predictive and prognostic biomarkers in OC and thus develop more effective individualized therapy and provide better prognosis.

The sirtuin (SIRT) family consists of 7 members, SIRT1 to SIRT7, which is a class of nicotinamide-adenine dinucleotide (NAD)+-dependent deacetylases.[3] The SIRT family members exhibit distinct expression patterns and have different biological functions.[4] It is well-established that SIRT family are involved in stress resistance, genome stability, energy metabolism, and longevity.[5] Additionally, accumulating evidence has demonstrated that SIRT family members are involved in carcinogenesis, progression, and survival.[6] To date, some studies have noted that SIRTs are associated with tumorigenesis and progression of OC and its clinicopathological stages.[7,8] However, the expression profiles and prognostic role of SIRTs in OC patients remain ill-defined.

Recently, gene microarray and bioinformatics analysis were widely used to identify the potential biomarkers and functional pathways involved in the carcinogenesis and progression of cancer.[9] In the current study, we intended to explore the expression patterns and prognostic roles of SIRTs in patients with OC using online databases, and thus accelerate the establishment of potential prognostic biomarkers for OC patients.

2. Materials and methods

2.1. Gene expression profiles

SIRTs mRNA levels in patients with OC were analyzed by Gene Expression Profiling Interactive analysis (GEPIA) online platform (http://gepia.cancer-pku.cn/)[10] Additionally, we performed tumor differential expression analysis according to pathological stages, and P-value $<.01$ was considered significant. In addition,

Editor: Lanjing Zhang.

Statement of Ethics: There are no ethical requirements for this article, because our study was based on the results of online databases.

The work is supported by the Youth Science Funds of Department of Science and Technology in Jiangxi Province (no.20192BAB215017), and the National Natural Science Funds of China (no.81760351 and no.81460015).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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How to cite this article: Zeng Z, Huang Y, Li Y, Huang S, Wang J, Tang Y, Jiang Y. Gene expression and prognosis of SIRT family members in ovarian cancer. Medicine 2020;99:24(e20685).

Received: 6 November 2019 / Received in final form: 3 April 2020 / Accepted: 12 May 2020

http://dx.doi.org/10.1097/MD.0000000000020685

SIRT protein levels were analyzed using the Human Protein Atlas database (HPA) (https://www.proteinatlas.org/) to confirm whether the expression at the mRNA and protein levels matched.

2.2. Prognostic analysis

The prognostic significance of SIRTs was assessed by Kaplan–Meier Plotter (www.kmplot.com), which includes survival data of 1816 OC patients downloaded from GEO, EGA, and TCGA.[11] Samples were divided into high and low expression groups according to median expression to analyze prognosis of OC patients, namely overall survival (OS), progression-free survival (PFS), and post-progression survival (PPS). Univariate cox analysis was performed with adjustments to pathological grade, clinical stage, and TP53 mutation of OC. *P* value <.05 was considered significant.

2.3. Frequency of genetic alteration analysis

Genetic alteration of SIRT genes in patients with OC was downloaded from CBioPortal for Cancer Genomics (http://www.cbioportal.org).[12] The genomic profiles, such as mutations, copy-number alteration, and mRNA expression were selected for querying SIRT family members.

2.4. Functional analysis

Functional network integration for SIRT genes prioritization and function was performed in GeneMANIA (http://www.genemania.org).[13] DAVID was used to performed biological enrichment analysis for SIRT family members including gene ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway.[14,15]

2.5. Ethical statement

All the data of this paper were obtained from the open-access database, we did not get these data from patients directly, nor intervene these patients. So the ethical approval was not necessary.

3. Results

3.1. SIRT mRNA levels in OC patients

We firstly checked relative SIRT mRNA levels in OC compared with that in healthy ovarian tissue using GEPIA. SIRT1, SIRT2, and SIRT3 mRNA levels were significantly lower in OC tissues compared with healthy ovarian tissue (Fig. 1), and SIRT1 as well as SIRT3 mRNA levels matched their reported protein levels (Fig. 2). Differences in mRNA and protein expression between OC and healthy ovarian tissue were not observed for other SIRTs. Moreover, we investigated the SIRT expression in different stages of OC. SIRT1 and SIRT5 mRNA levels changed significantly in various tumor stages, whereas the rest of SIRT expression was not differential (Fig. 3).

3.2. Prognostic value of SIRT mRNA levels in OC patients

We next evaluated the prognostic roles of SIRT level in all OC patients using Kaplan–Meier plotter. High SIRT3, SIRT5, SIRT6, and SIRT7 mRNA levels were significantly related to the favorable OS, while high SIRT1 and SIRT4 levels were related to the poor OS (Fig. 4). Additionally, increased mRNA levels of SIRT2, SIRT6, and SIRT7 or decreased levels of SIRT1, SIRT4, and SIRT5 were correlated with favorable PFS (Fig. 5). High SIRT3 and SIRT5 mRNA levels or low SIRT2 and SIRT4 levels were associated with favorable PPS for OC patients (Fig. 6). The prognostic significance of SIRT levels were also evaluated in the serous and endometrioid subtypes. As shown in Table 1, increased SIRT3, SIRT5, SIRT6, SIRT7, and decreased SIRT4 mRNA levels were linked to longer OS in patients serous OC. In patients with endometrioid OC, only decreased SIRT5 mRNA levels were associated with worsen OS.

3.3. Prognostic roles of SIRT levels in OC patients with different clinicopathological features

Furthermore, we assessed the correlation between SIRT expression and other clinicopathological features for OC patients including grades, stages, and TP53 status. As shown in Table 2, elevated SIRT2 and SIRT4 levels were linked to poor OS in OC patients with grade I and grade III, respectively. High SIRT3 as well as SIRT6 and SIRT7 levels were correlated with better OS in OC patients with grade II and grade III, respectively. In grade IV, only high SIRT4 level was related with poor OS. In all stages of OC patients, elevated SIRT6 and SIRT7 levels were related to favorable OS. In advanced stages (III and IV), elevated SIRT5 level was linked to better OS, while elevated SIRT1 and SIRT4 levels were related with poor OS. Moreover, high SIRT2 and SIRT3 levels were correlated with unfavored OS, whereas high SIRT5 level was linked to longer OS in OC patients with TP53 mutation.

3.4. SIRT genetic alterations in OC

We evaluated the genetic alterations of SIRTs in OC using cBioPortal. The frequency gene alterations ranged from 16.7% (94/563) to 31.02% (188/606) including mutation, amplification, and deep deletion among the 4 datasets (Fig. 7A). The percentages of genetic alterations in specific SIRTs varied from 1.4% to 10.0% (SIRT1, 1.4%; SIRT2, 10%; SIRT3, 2.3%; SIRT4, 1.7%; SIRT5, 8%; SIRT6, 1.9%; SIRT7, 5%), and amplification was the most common alteration (Fig. 7B). In addition, we accessed the prognostic roles of SIRTs in OC patients with or without alterations, and did not observe any significant correlation between the presence of alterations and OS and PFS (*P*-values, .885 and .896, respectively) (Fig. 7C, D).

We then used GeneMANIA to construct a network of SIRTs and their functionally related genes. The results exhibited that 20 genes-DHPS, ETFA, ILVBL, HACL1, NNT, ETFB, AASS, PGAP1, SCCPDH, GLUD1, CMYA5, DNAJB8, MCF2L2, CTC-435M10.3, BCKDHA, PDHA1, PDHA2, ELF5, IDE, and UGDH were closely correlated with SIRTs (Fig. 7E). Moreover, all SIRTs share protein domains; SIRT2 and SIRT3, SIRT3 and SIRT5, SIRT6 and SIRT7 are coexpressed; SIRT1 and SIRT2, SIRT3 and SIRT4, SIRT3 and SIRT5 have physical interactions.

3.5. Functional enrichment analysis of SIRTs in OC

We used the DAVID for GO and KEGG pathway enrichment analysis. The top 5 GO terms of SIRTs are shown in Table 3. Biological process associated with SIRTs was enriched in rNAD+ binding, peptidyl-lysine deacetylation, NAD-dependent histone

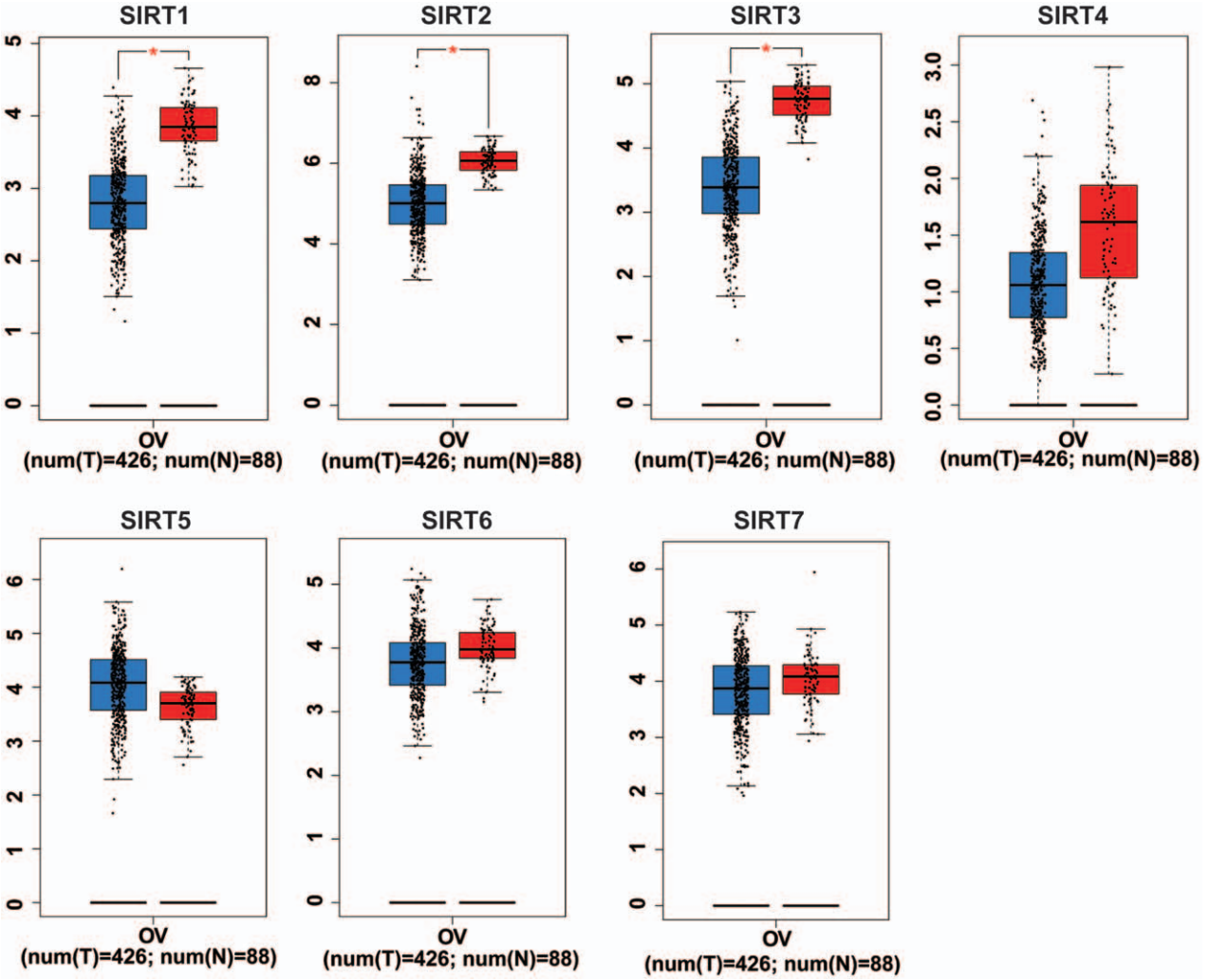

Figure 1. SIRT mRNA levels in OC patients. OC = ovarian cancer; SIRT = sirtuin.

deacetylase activity (H3-K9 specific), protein destabilization, and negative regulation of fat cell differentiation. For cellular component, SIRTs were mainly enriched in positive regulation of transcription from RNA polymerase II promoter, positive regulation of endothelial cell proliferation, PML body, cholesterol homeostasis, and positive regulation of phosphatidylinositol 3-kinase signaling. Molecular function associated with SIRTs was enriched in mitochondrion, angiogenesis, protein ubiquitination, mitochondrial inner membrane, and spermatogenesis. In addition, the most enriched KEGG pathway term was central carbon metabolism in cancer.

4. Discussion

In the present study, we investigated the expression profiles, prognostic roles, genetic alterations, and biological functions of SIRTs using bioinformatic analysis. Our results revealed that SITR1/2/3 mRNA levels were significantly lower in OC. All SIRT levels were correlated with the prognosis, whereas, genetic alterations of SIRTs were not linked to prognosis of OC patients. Furthermore, the biological function of SIRTs is mainly enriched in metabolism-related pathways in cancer.

Previous studies have shown that SIRT1 negatively regulates estrogen receptor beta and stimulates reactive oxygen species formation,[16,17] suggesting an oncogenic role in OC. On the other hand, SIRT1 may server as a suppressor in OC through inhibiting epithelial to mesenchymal transition.[18,19] Shuang et al[20] and Mvunta et al[8] reported that overexpression of SIRT1 indicates poor prognosis in patients with OC. Consistent with these publications, our results demonstrated that high SIRT1 level was significantly associated with poor OS and FPS, especially patients with advanced stage, and was not correlated with histology subtypes, pathological grades, and TP53 mutation in OC patients. These findings indicate that SIRT1 could be a prognosis indicator for the patient's survival outcome and as a novel therapeutic target.

Our finding demonstrated that SIRT2 mRNA level was lower in patients with OC, which was consistent with the report by Du et al[21] that protein expression of SIRT2 was down-regulated in OC. In addition, high SIRT2 level was correlated with favorable PFS, whereas worsen PPS in OC patients, specifically in grade I and TP53 mutation patients. These results indicated that SIRT2 could suppress carcinogenesis, and its underlying mechanisms are maintaining genome integrity and inhibiting cell cycle.[22,23]

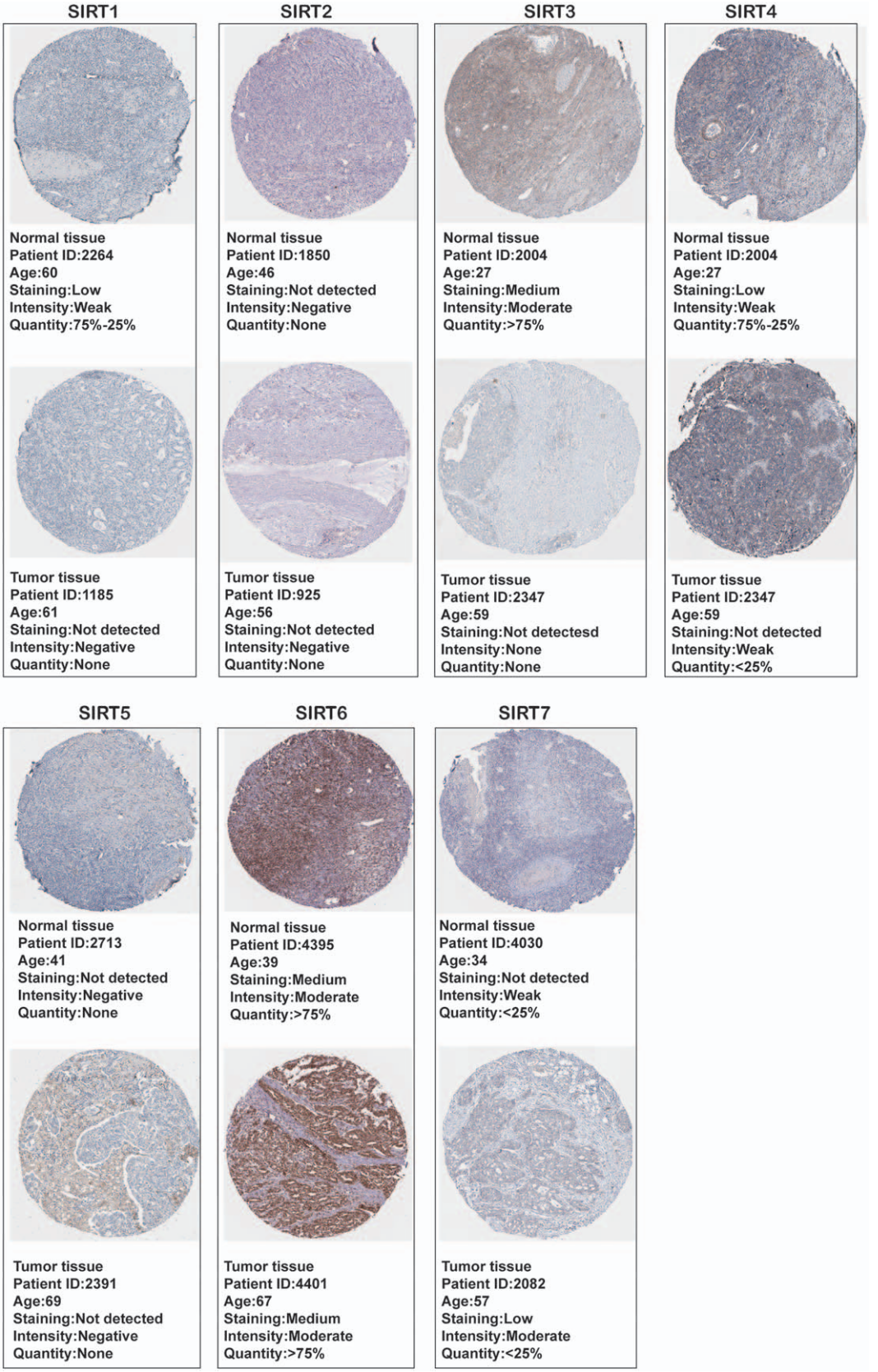

Figure 2. SIRT protein levels in OC patients. OC = ovarian cancer; SIRT = sirtuin.

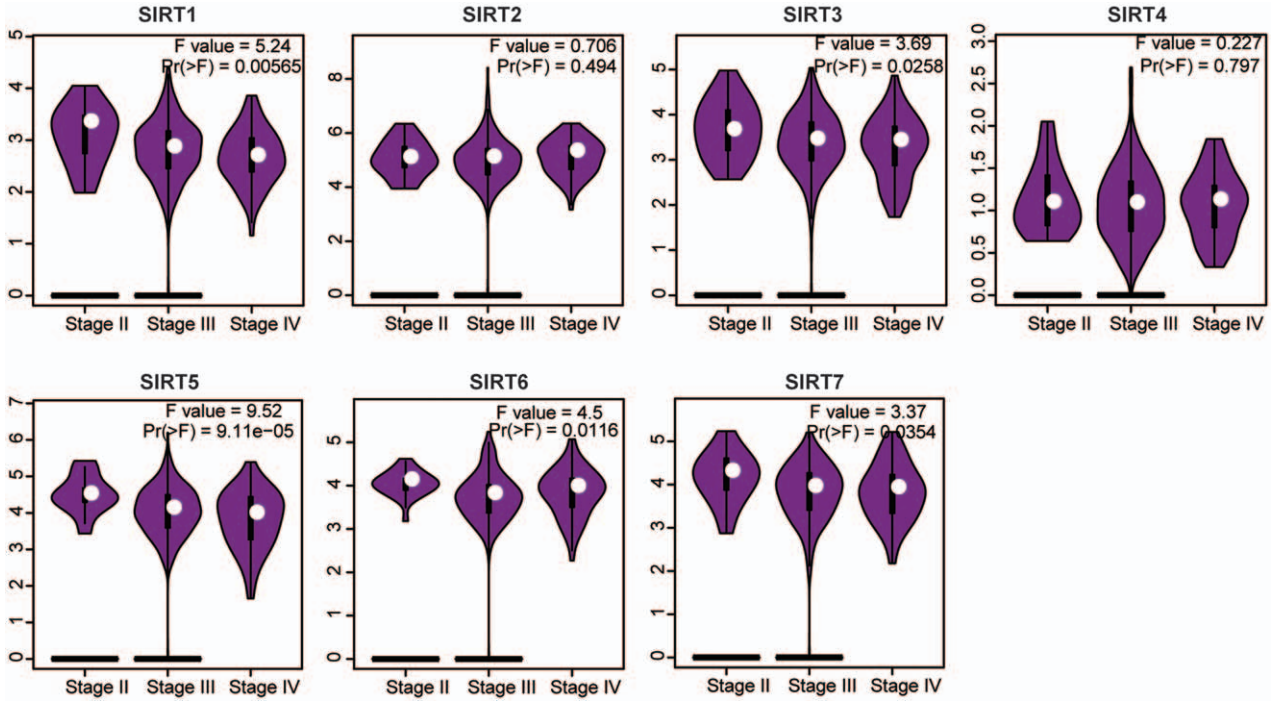

Figure 3. SIRT mRNA levels in different tumor stages of OC patients. OC = ovarian cancer; SIRT = sirtuin.

Yang et al[24] noted that SIRT3 expression was decreased in OC patient tissues. Coinciding with the aforementioned data, low SIRT3 level was observed in patients with OC, and high SIRT3 level was correlated with longer OS and PPS, especially in grade II and serous OC. Mechanistically, SIRT3, a mitochondrial stress deacetylase, regards as a tumor suppressor through involving in cancer metabolism and apoptosis and inhibiting epithelial to mesenchymal transition.[25–28] These results revealed that SIRT3 could serve as potential prognostic role in OC patients.

Similarly, SIRT4 is another mitochondrial stress member of the SIRT family and shown to be involved in tumor formation and growth with its tumor suppressor functions.[29,30] SIRT4 were reported to be down-regulated in a various type of cancers such as breast and endometrioid adenocarcinoma.[31,32] However, the

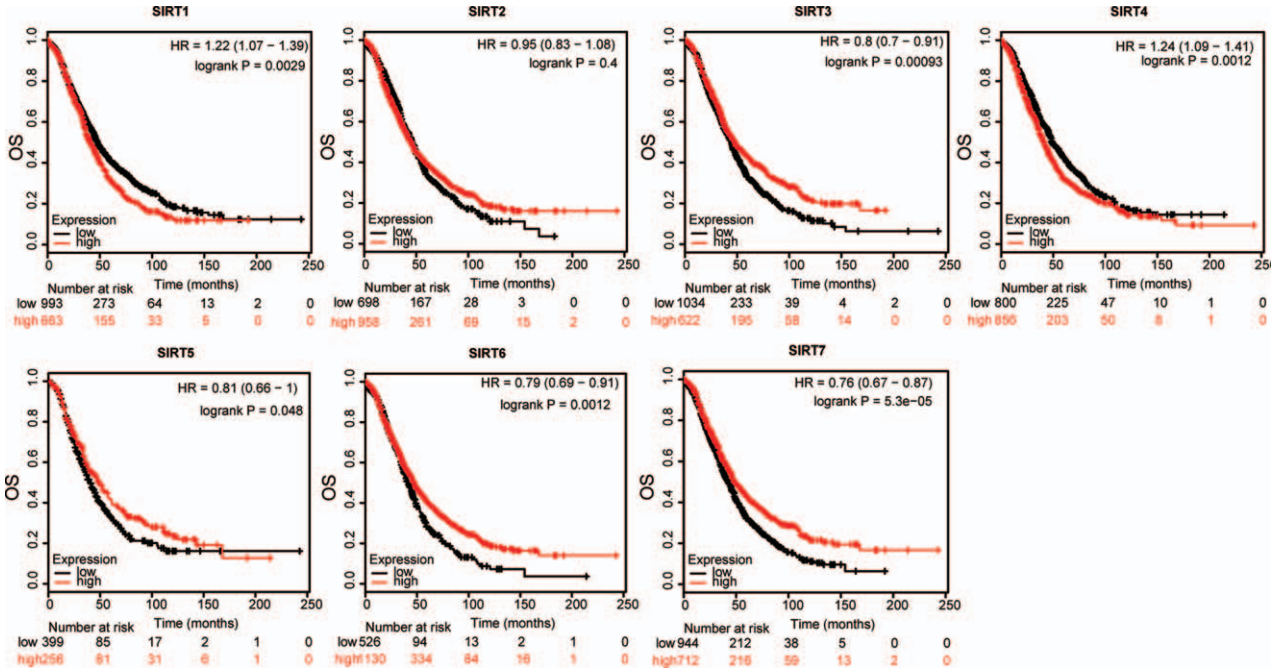

Figure 4. Correlation between SIRT mRNA levels and OS in OC patients. OC = ovarian cancer; OS = overall survival; SIRT = sirtuin.

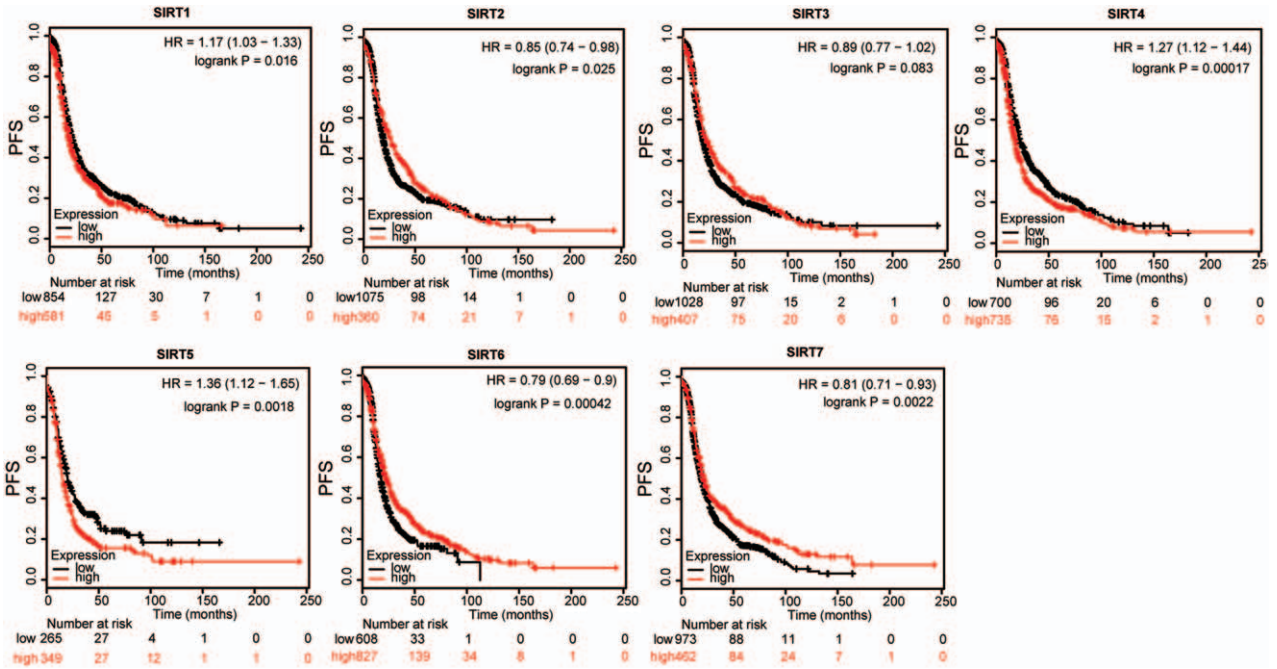

Figure 5. Correlation between SIRT mRNA levels and PFS in OC patients. OC = ovarian cancer; PFS = progression-free survival; SIRT = sirtuin.

prognostic role of SIRT4 in OC patients has not been appreciated. Our findings exhibited that elevated SIRT4 level was related to unfavorable OS, PFS, and PPS in patients with OC, especially in different histology subtypes, grades, and stages.

Although a growing body of work now links many sirtuins to cancer,[33] survival and tumorigenic roles for SIRT5 in neoplasia have not fully been addressed. Our results showed that overexpression of SIRT5 were correlated with favorable OS, PPS, and poor PFS in OC patients. According to clinicopathological features, high level of SIRT5 predicted worsen OS in advanced stages and mutated-TP53-type serous OC patients, whereas better OS in endometrioid OC. This implies that SIRT5 likely exerts differing biological effects in the same cell type in different states through distinct lysine modifications.

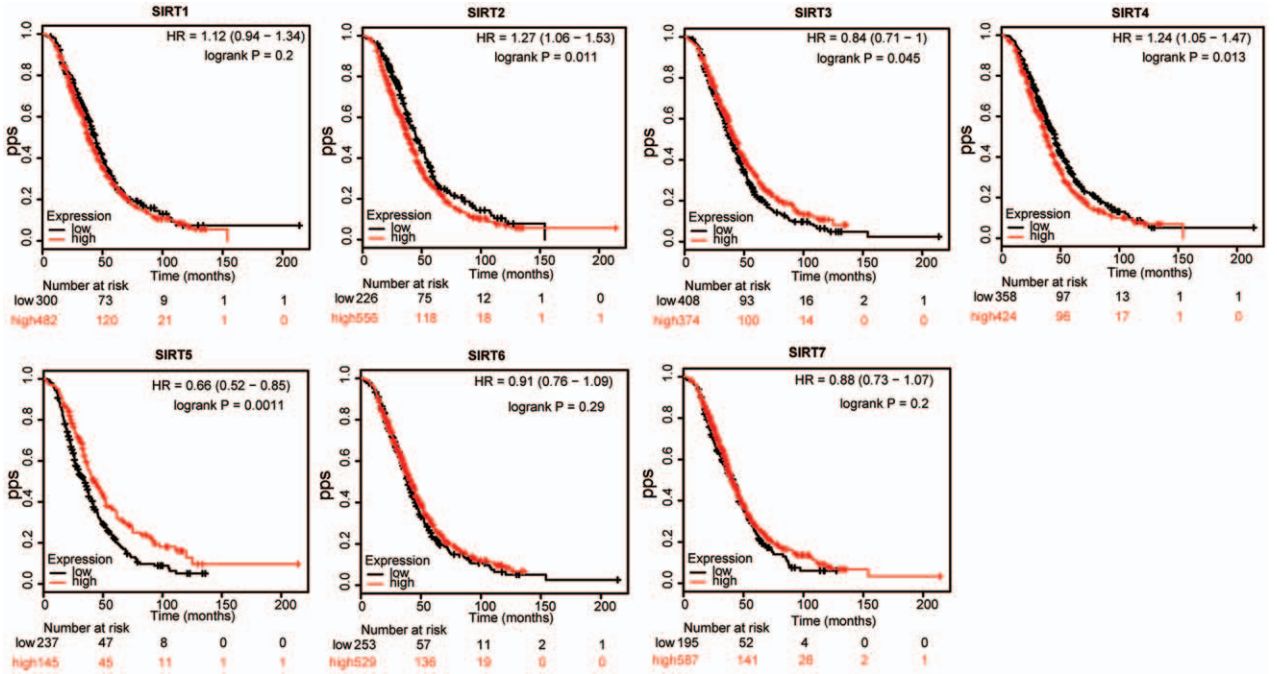

Figure 6. Correlation between SIRT mRNA levels and PPS in OC patients. OC = ovarian cancer; PPS = post-progression survival; SIRT = sirtuin.

Table 1

The OS of SIRTs in different pathological subtypes OC patients.

SIRTs	Histology	Cases	HR	95%CI	*P*-value
SIRT1	Serous	1207	1.15	0.99–1.34	.074
	Eendometrioid	37	4.94	0.82–29.69	.053
SIRT2	Serous	1207	1.13	0.95–1.33	.17
	Eendometrioid	37	3.84	0.43–34.41	.19
SIRT3	Serous	1207	0.82	0.7–0.95	**.0096**
	Eendometrioid	37	0.46	0.08–2.75	.38
SIRT4	Serous	1207	1.22	1.03–1.4	**.02**
	Eendometrioid	37	415840481.25	0-inf	.071
SIRT5	Serous	1207	0.79	0.66–0.94	**.0085**
	Eendometrioid	37	6.99	0.78–62.62	**.043**
SIRT6	Serous	1207	0.81	0.69–0.94	**.0062**
	Eendometrioid	37	0.17	0.02–1.5	.069
SIRT7	Serous	1207	0.8	0.69–0.93	**.0044**
	Eendometrioid	37	294193658.36	0-inf	.18

P-value was analyzed using the survival analysis test. The bold font indicates that the difference was statistically significant.
OC = ovarian cancer, OS = overall survival, SIRT1 = sirtuin-1, SIRT2 = sirtuin-2, SIRT3 = sirtuin-3, SIRT4 = sirtuin-4, SIRT5 = sirtuin-5, SIRT6 = sirtuin-6, SIRT7 = sirtuin-7.

Table 2

The OS of SIRTs in OC patients with different clinicopathological features.

SIRTs	Clinicopathological features	Cases	HR	95%CI	*P*-value
Grades					
SIRT1	I	56	0.68	0.25–1.86	.45
	II	324	1.29	0.95–1.77	.1
	III	1015	1.18	0.99–1.41	.072
	IV	20	2.74	0.93–8.02	.056
SIRT2	I	56	3.04	0.98–9.38	**.043**
	II	324	0.82	0.58–1.15	.25
	III	1015	1.1	0.92–1.33	.3
	IV	20	0.06	0.25–1.77	.4
SIRT3	I	56	1.75	0.67–4.55	.24
	II	324	0.58	0.43–0.79	**.00049**
	III	1015	0.84	0.7–1.00	.052
	IV	20	1.66	0.64–4.32	.29
SIRT4	I	56	0.71	0.28–1.81	.48
	II	324	1.24	0.91–1.69	.18
	III	1015	1.32	1.1–1.58	**.0026**
	IV	20	4.15	0.92–18.71	**.047**
SIRT5	I	41	2.06	0.71–5.96	.17
	II	162	0.71	0.44–1.13	.15
	III	392	0.81	0.61–1.08	.16
	IV	18	2.07	0.72–5.96	.17
SIRT6	I	56	0.43	0.16–1.13	.079
	II	324	0.61	0.45–0.83	**.0013**
	III	1015	0.82	0.69–0.97	**.018**
	IV	20	2.61	0.72–9.48	.13
SIRT7	I	56	0.63	0.24–1.64	.34
	II	324	0.78	0.57–1.05	.11
	III	1015	0.73	0.61–0.88	**.00075**
	IV	20	1.96	0.75–5.18	.17
Stage					
SIRT1	I + II	135	1.96	0.9–4.28	.086
	III + IV	1220	1.18	1.02–1.37	.03
SIRT2	I + II	135	0.5	0.23–1.09	.076
	III + IV	1220	1.11	0.94–1.31	.23
SIRT3	I + II	135	0.51	0.23–1.14	.093
	III + IV	1220	0.9	0.77–1.04	.15
SIRT4	I + II	135	0.52	0.2–1.4	.19
	III + IV	1220	1.26	1.07–1.49	**.0052**
SIRT5	I + II	83	1.93	0.7–5.36	.2

(*continued*)

Table 2

(continued).

SIRTs	Clinicopathological features	Cases	HR	95%CI	*P*-value
	III + IV	487	0.68	0.4–0.87	**.0015**
SIRT6	I + II	135	0.23	0.07–0.77	**.009**
	III + IV	1220	0.77	0.67–0.9	**.00084**
SIRT7	I + II	135	0.37	0.17–0.81	**.0097**
	III + IV	1220	0.83	0.71–0.96	**.013**
TP53 mutations					
SIRT1	Mutated	506	1.21	0.95–1.53	.13
	Wild type	94	1.53	0.85–2.76	.15
SIRT2	Mutated	506	1.55	1.22–1.97	**.00025**
	Wild type	94	0.64	0.37–1.12	.12
SIRT3	Mutated	506	1.42	1.1–1.84	**.0072**
	Wild type	94	0.54	0.29–0.99	.043
SIRT4	Mutated	506	1.19	0.94–1.49	.14
	Wild type	94	1.69	0.95–3.02	.072
SIRT5	Mutated	124	0.5	0.32–0.77	**.0015**
	Wild type	19	0.51	0.16–1.64	.25
SIRT6	Mutated	506	1.17	0.92–1.49	.21
	Wild type	94	0.67	0.38–1.18	.17
SIRT7	Mutated	506	1.19	0.94–1.5	.15
	Wild type	94	1.3	0.72–2.34	.38

P-value was analyzed using the survival analysis test. The bold font indicates that the difference was statistically significant.
OC = ovarian cancer, OS = overall survival, SIRT1 = sirtuin-1, SIRT2 = sirtuin-2, SIRT3 = sirtuin-3, SIRT4 = sirtuin-4, SIRT5 = sirtuin-5, SIRT6 = sirtuin-6, SIRT7 = sirtuin-7.

Zhang et al[34] reported that decreased expression of SIRT6 correlates closely with poor prognosis of OC patients, and another study shown that SIRT6 inhibits ovarian cancer cell proliferation via down-regulation of Notch 3 expression.[35] Similarly, increased expression of SIRT6 was related to favorable OS and PFS, particularly in serous OC patients with state III. These results suggest that SIRT6 might serve as a protective role against OC. However, Bae et al[36] demonstrated that SIRT6 is involved in the progression of OC via β-catenin-mediated epithelial to mesenchymal transition. These controversial results may be owing to various study design, detection method, and sample size. The biological function of SIRT7 is still in its infancy. Current evidences suggest that SIRT7 over-expression might have some tumorigenic potential in OC through inhibiting apoptosis.[37] Although differential SIRT7 expression was not found in tumor tissues in our analysis, its increased level was related to favorable OS and PFS, particularly in serous OC patients with state III. Thus, the role of SIRT7 in OC is still needed to be explored.

We constructed a network of SIRTs and their functionally related genes to illuminate the biological mechanism of SIRT in OC. Functional enrichment results indicated that *SIRTs* are mainly enriched in metabolism pathways. It is well established that tumorigenesis is dependent on the reprogramming of cellular metabolism as both direct and indirect consequence of oncogenic mutations.[38]

Admittedly, our research has some limitations. Firstly, all clinical data were analyzed by Kaplan–Meier survival curves, and logistic or COX regression could not be performed due to limited data. Thus, variable factors such as age, grade, stage, surgery etc

Table 3

The GO function enrichment analysis of SIRTs and neighbor genes in OC.

Category	Description	Count	Gene ratio	*P*-value
GOTERM_BP	GO:0070403~NAD+ binding	4	0.3108	2.04E–09
GOTERM_BP	GO:0034983~peptidyl-lysine deacetylation	3	0.2331	9.72E–05
GOTERM_BP	GO:0046969~NAD-dependent histone deacetylase activity (H3-K9 specific)	3	0.2331	.0001
GOTERM_BP	GO:0031648~protein destabilization	2	0.1554	.0009
GOTERM_BP	GO:0045599~negative regulation of fat cell differentiation	2	0.1554	.0009
GOTERM_CC	GO:0045944~positive regulation of transcription from RNA polymerase II promoter	2	0.1554	.0016
GOTERM_CC	GO:0001938~positive regulation of endothelial cell proliferation	2	0.1554	.0033
GOTERM_CC	GO:0016605~PML body	2	0.1554	.0053
GOTERM_CC	GO:0042632~cholesterol homeostasis	2	0.1554	.0070
GOTERM_CC	GO:0014068~positive regulation of phosphatidylinositol 3-kinase signaling	2	0.1554	.0091
GOTERM_MF	GO:0005739~mitochondrion	8	0.6216	4.50E–22
GOTERM_MF	GO:0001525~angiogenesis	3	0.2331	8.57E–07
GOTERM_MF	GO:0016567~protein ubiquitination	2	0.1554	.0011
GOTERM_MF	GO:0005743~mitochondrial inner membrane	3	0.2331	.0014
GOTERM_MF	GO:0007283~spermatogenesis	3	0.2331	.0111

BP = biological process, CC = cellular component, DAVID = Database for annotation, Visualization and integrated Discovery, GO = gene ontology, MF = molecular function.

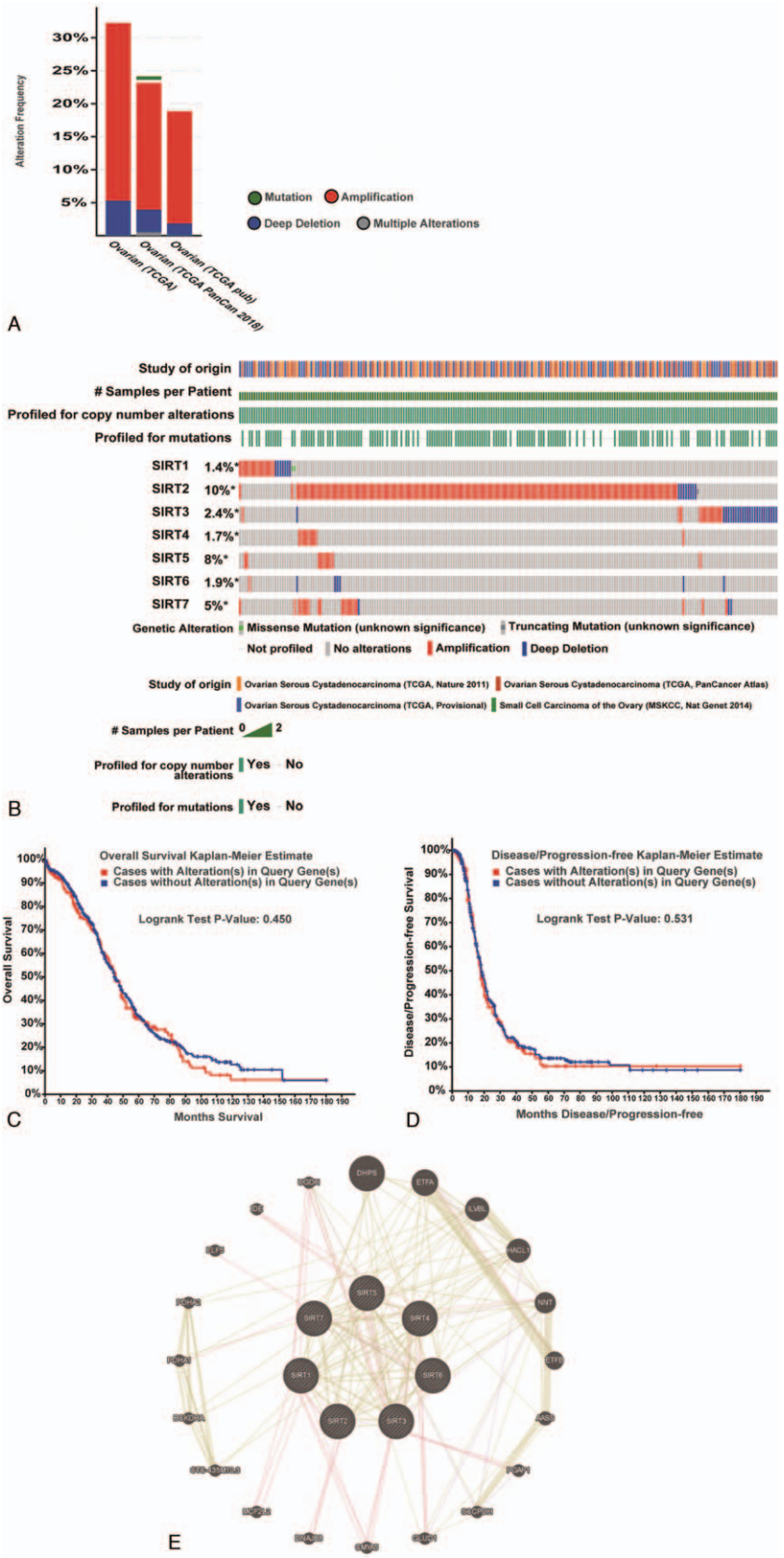

Figure 7. SIRT alteration frequencies in OC and SIRT functional network. (A) Summary of SIRT alterations. (B) OncoPrint visual summary of SIRT alterations. (C) Kaplan–Meier plots comparing OS in cases with or without SIRT alterations. (D) Kaplan–Meier plots comparing DSF in cases with or without SIRT alterations. (E) functional network among SIRTs. DSF = Disease Free Survival, OC = ovarian cancer; OS = overall survival; SIRT = sirtuin.

may influence the survival analysis of SIRTs expression in OC patients. Secondly, Kaplan–Meier Plotter database still use silverberg grading system based on differentiation degree, while the low-grade serous carcinoma and high-grade serous carcinoma were recommended to classify ovarian serous cancer and FIGO grade was recommended to classify ovarian endometrioid cancer for the superiority that can be simple and easy to use, high repeatability, better able to guide the clinical treatment. Thirdly, one clear weakness of bioinformatics analysis is the background heterogeneity.

5. Conclusion

This is the first study to integrate bioinformatics approaches intended to identify the expression profiles and prognostic value of SIRTs in OC. SIRT1/2/3 mRNA levels were significantly down-regulated in OC, and aberrant SIRTs levels were correlated with the prognosis of patients with OC. These results suggest that SIRTs is related to the prognosis of OC and may be the potential therapeutic interventions in OC.

Author contributions

ZZ wrote the manuscript, carried out the research methodology and acquired the data. HS, YH, YL, JW, and YT performed the data analysis and provided the technical support. YJ conceived and designed the study. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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