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Correlation Between Serum and Tissue SIRT1 Levels in Patients With Esophageal Squamous Cell Carcinoma

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Abstract. *Background/Aim: Identifying prognostic and molecular markers as therapeutic targets for esophageal squamous cell carcinoma (ESCC) could enhance the efficacy of multidisciplinary treatments. While tissue expression of sirtuin 1 (SIRT1) has been linked to tumor progression in ESCC, prognostic significance of serum SIRT1 levels and their correlation with tissue SIRT1 remains unexplored. This study aimed to investigate the correlation between serum and tissue SIRT1 levels in patients with ESCC. Patients and Methods: A total of 38 patients diagnosed with ESCC who were untreated preoperatively were recruited for this study. SIRT1 expression in the surgical specimens was assessed through immunostaining, while serum SIRT1 levels were measured using an enzyme-linked immunosorbent assay. We analyzed the association between tissue and serum SIRT1 levels, clinicopathological features, and patient prognosis. Results: Positive SIRT1 expression in tissue was significantly associated with deeper tumor depth (p=0.020). It was also significantly associated with poorer overall survival (OS) and relapse-free survival (RFS) (p=0.041 and p=0.012, respectively). Elevated serum SIRT1 levels were significantly correlated with increased tumor depth and weight loss (p=0.012 and p=0.030). While higher serum SIRT1 levels tended to be associated with poorer OS (p=0.069), no significant correlation was found between SIRT1 expression in tissue and its concentration in serum. Conclusion: SIRT1 tissue expression may be a valuable prognostic marker in ESCC. However, the clinical significance of serum SIRT1 levels appears to differ from that of its tissue expression. Future research is required to clarify the role of serum SIRT1 in ESCC.*

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Esophageal carcinoma is the sixth leading cause of cancer-related deaths and the seventh most common cancer worldwide (1). In Japan, the predominant histologic subtype is squamous cell carcinoma (ESCC), accounting for about 90% of cases, with adenocarcinoma being the other major subtype (2). Although a range of treatment options are available, including surgery, chemotherapy, and radiotherapy, the five-year survival rate for patients undergoing esophagectomy in Japan remains 59.3% (3, 4). Identifying prognostic and specific molecular markers as therapeutic targets for ESCC could enhance the effectiveness of multidisciplinary treatments and advance medical care.

The seven mammalian sirtuin deacetylases (SIRT1-7) are essential modulators of cellular signaling pathways. Among them, SIRT1, an NAD+-dependent deacetylase, is crucial for various biological functions, including stress response, apoptosis regulation, metabolism control, adaptation to caloric restriction, aging modulation, and cancer development (5, 6). SIRT1 has shown both tumor-promoting and tumor-suppressing effects in different cancers, but in ESCC, it is often associated with tumor promotion (7). Inhibiting SIRT1 reduces cell proliferation, migration, and epithelial-mesenchymal transition in ESCC cell lines (8, 9). We have reported that high SIRT1 expression in biopsy specimens correlates with poor prognosis and that SIRT1 suppression increases sensitivity to chemoradiotherapy (10). Furthermore, a meta-analysis found that high tissue expression levels of SIRT1 correlate with poorer overall survival (OS), deeper tumor invasion, and more advanced tumor, node, metastasis (TNM) stages in patients with ESCC (11). However, tissue expression of SIRT1 is heterogeneous and requires invasive procedures like biopsy or surgery for sample collection. This underscores the need for more precise and less invasive methods to assess SIRT1 expression.

We focused on serum SIRT1 levels, which can be measured from blood, which is a more convenient and less invasive laboratory sampling. Although serum SIRT1 has been studied in various cancer types, there is no consensus on whether its levels are elevated or reduced in patients with cancer compared to healthy controls (12-14). In our previous research on gastric cancer, we found no significant association between serum SIRT1 levels with clinicopathological features and prognosis (15). However, there are no reports on serum SIRT1 in ESCC, and clarifying the clinicopathological significance of serum SIRT1 could provide valuable insights into its role in cancer treatment.

In this study, we investigated the pathological features and prognostic significance of tissue SIRT1 expression and serum SIRT1 levels in patients with ESCC, as well as the relationship between these two variables.

Patients and Methods

Patients and materials. A total of 38 patients diagnosed with ESCC and untreated preoperatively at Chiba University Hospital between 2007 and 2017 were recruited for this study. Blood samples were collected during the patient's initial visit to our department. All patients underwent radical esophagectomy with lymph node dissection. Stage classification was performed according to the 12th edition of the Japanese Classification of Esophageal cancer (16), and clinical data were sourced from the clinical database. This study adhered to the principles outlined in the Declaration of Helsinki. It was approved by the Ethics Committee of the Graduate School of Medicine, Chiba University, Chiba, Japan (approval number: M10369). Informed consent for the use of anonymized data was provided via an opt-out method. This consent protocol was used for participant data in research. This consent procedure was reviewed and approved by the same Ethics Committee on August 30, 2022.

Immunohistochemistry. SIRT1 expression was analyzed immunohistochemically using the peroxidase-antiperoxidase complex method. Specimens were deparaffinized and incubated with Target Retrieval Solution (S2031; DAKO Japan, Tokyo, Japan) at 95˚C for 40 min. Endogenous peroxidase activity was blocked using methanol containing 3% hydrogen peroxide (S2023; DAKO Japan) at 24˚C for 30 min. Subsequently, the sections were incubated with a primary anti-SIRT1 monoclonal antibody with a dilution of 1:200 (1:200; ab110304; Abcam, Cambridge, UK) at 4˚C for 18 h (S0809; DAKO Japan). After washing with Tris-buffered saline (S3006; DAKO Japan), the sections were incubated with a secondary antibody (EnVision/HRP, anti-mouse/rabbit, K5001; DAKO Japan) at 37˚C for 60 min. After additional washes, the sections were treated with 3,3'-diaminobenzidine (S3468; DAKO Japan) for 2 min. Human colon tissues known to express SIRT1 were used as positive controls. Next, the sections were counterstained with hematoxylin (30002; Muto pure chemicals, Tokyo, Japan), dehydrated with ethanol (Kaneichi pharmaceutical, Osaka, Japan), and mounted. We classified SIRT1 expression into two groups based on staining intensity and percentage of staining. Staining intensity scores ranged from 0 (negative), 1 (weak staining), 2 (moderate), and 3 (strong), while the percent cell staining scores were 0 (no staining), 1 (1%-25%), 2 (26%-50%), 3 (51%-75%), and 4 (76%-100%). The staining index was obtained by summing these two scores, and if the staining index was more than four, the case was considered positive for SIRT1 expression, according to previous studies (8, 17, 18).

Measurement of SIRT1 serum concentration. Peripheral blood samples from patients were divided into serum and blood cells, and the serum used for analysis. Serum SIRT1 levels were measured using an enzyme-linked immunosorbent assay (ELISA) commercial kit for human SIRT1 (MBS2601311; MyBiosource, Inc., San Diego, CA, USA), following the manufacturer's protocol. All samples were analyzed in duplicate, and the average values were calculated. About 100 µl of samples or human SIRT1 standards with different concentrations were placed into the corresponding wells. Blank wells (0 ng/ml) were filled with the standard diluent. The ELISA plate was then covered with adhesive tape and incubated at 37˚C for 90 min. The plate was washed twice with wash buffer, and 100 µl of biotinylated human SIRT1 antibody solution was added to each well. The plate was covered with adhesive tape and incubated at 37˚C for 60 min. Then, the plate was washed thrice with wash buffer, and 100 µl of enzyme-conjugate liquid was added to each well. The plate was sealed with adhesive tape and incubated at 37˚C for 30 min. After incubation, the plate was washed five times with wash buffer, and 100 µl of color reagent solution was added to each well and incubated in the dark at 37˚C. The color change was observed, and the reaction stopped by adding 100 µl of color reagent C to each well when the standard curve showed a clear color gradient. The optical density was measured at 450 nm using a microplate spectrophotometer (xMark; Bio-Rad Laboratories Inc., Hercules, CA, USA). Protein concentrations were determined using Microplate Manager version 6 (Bio-Rad Laboratories Inc). All samples were analyzed in duplicate, and the average values were calculated. Standard curves prepared from known concentrations were used to determine SIRT1 levels in the serum samples.

Statistical analyses. The relationships between tissue SIRT1 expression, serum SIRT1 concentration, and clinicopathological characteristics of patients were analyzed using the chi-squared test and Wilcoxon rank-sum test. The correlation between tissue SIRT1 expression and serum SIRT1 concentration was analyzed using the Wilcoxon rank-sum test. For survival analysis, patients were categorized into two groups based on the median serum SIRT1 concentration. Survival rates were calculated using the Kaplan–Meier method, and the log-rank test was employed to evaluate differences. JMP data analysis software version 15 (SAS Institute Inc., Cary, NC, USA) was utilized for all statistical analyses, with statistical significance set at p-value <0.05.

Results

Patient characteristics. Patient characteristics are presented in Table I. The median patient age was 71.5 years. The majority of patients were male (31/38; 81.6%). "Weight loss" was defined as a loss of at least 2 kg in the month prior to the first visit; three patients experienced weight loss, while 13 did not. Half of the patients exhibited lymph node metastasis. Tumor depth ranged from T1a-T4 and stages varied from stage 0 to stage IV. The median serum SIRT1 concentration was 31.5 pg/ml.

Table I. *Patient characteristics*.

	N=38
Age, years; median (range)	71.5 (44-89)
Sex (male:female)	31:7
Weight loss	
(+)/(–)/unknown	3/13/22
Serum Alb levels; median (range) (g/dl)	4.4 (3.8-5.6)
Pathological T category	
T1a/T1b/T2/T3/T4	7/13/9/8/1
Pathological N category	
N(+)/N(-)	19/19
Tumor differentiation	
Well/moderate/poorly/unknown	8/15/12/3
Pathological stage	
0/I/II/III/IV	5/9/12/10/2
SIRT1 expression in tumor	
Positive/Negative	11/27
Serum SIRT1 (range), pg/ml	31.5(1.49-81.7)

Alb: Albumin.

Relationship between SIRT1 tissue expression and clinicopathological features. Among the 38 cases examined, 11 (28.9%) and 27 (71.1%) exhibited tumors with positive and negative SIRT1 expression. Representative images of SIRT1 expression are shown in Figure 1A. The correlation between SIRT1 tissue expression and clinicopathological characteristics is presented in Table II. Positive SIRT1 tissue expression was significantly correlated with deep tumor depth (p=0.020). All patients with positive SIRT1 statements were male (p=0.020). No significant relationship was observed between SIRT1 tissue expression and other clinicopathological factors, including age (p=0.198), weight loss (p=0.607), serum albumin levels (p=0.208), lymph node status (p=0.238), tumor differentiation (p=0.178) and stage (p=0.346).

Relationship between serum SIRT1 levels and clinicopathological features. The serum levels of SIRT1 for each clinicopathological feature are shown in Table III. Serum SIRT1 levels were significantly higher in the group with tumor depth greater than T1b (p=0.012) and weight loss (p=0.030). However, serum SIRT1 concentrations did not show significant differences based on age (p=0.693), sex (p=0.118), serum albumin levels (p=0.701), lymph node status (p=0.815), tumor differentiation (p=0.958), and stage (p=0.188).

Correlation between serum SIRT1 levels and the expression of SIRT1 in tumor tissue. Figure 1B shows a comparison of serum SIRT1 concentrations and SIRT1 expression in tumor tissues. The average serum SIRT1 concentration was 32.61±10.06 pg/ml in patients with SIRT1-positive tumors and 30.82±15.44 pg/ml in patients with SIRT1-negative tumors. However, this difference was not statistically significant (p=0.221).

Survival analyses. An analysis of the relationship between SIRT1 expression in tumor tissue and prognosis revealed that high SIRT1 expression was significantly associated with poorer overall survival (OS) (p=0.045) and relapse-free survival (RFS) (p=0.011) relative to low SIRT1 expression (Figure 2). Furthermore, the group with high serum SIRT1 levels tended to have poorer OS than the group with low levels (p=0.069). In contrast, there were no significant differences in RFS between the high-and-low serum SIRT1 groups (p=0.233).

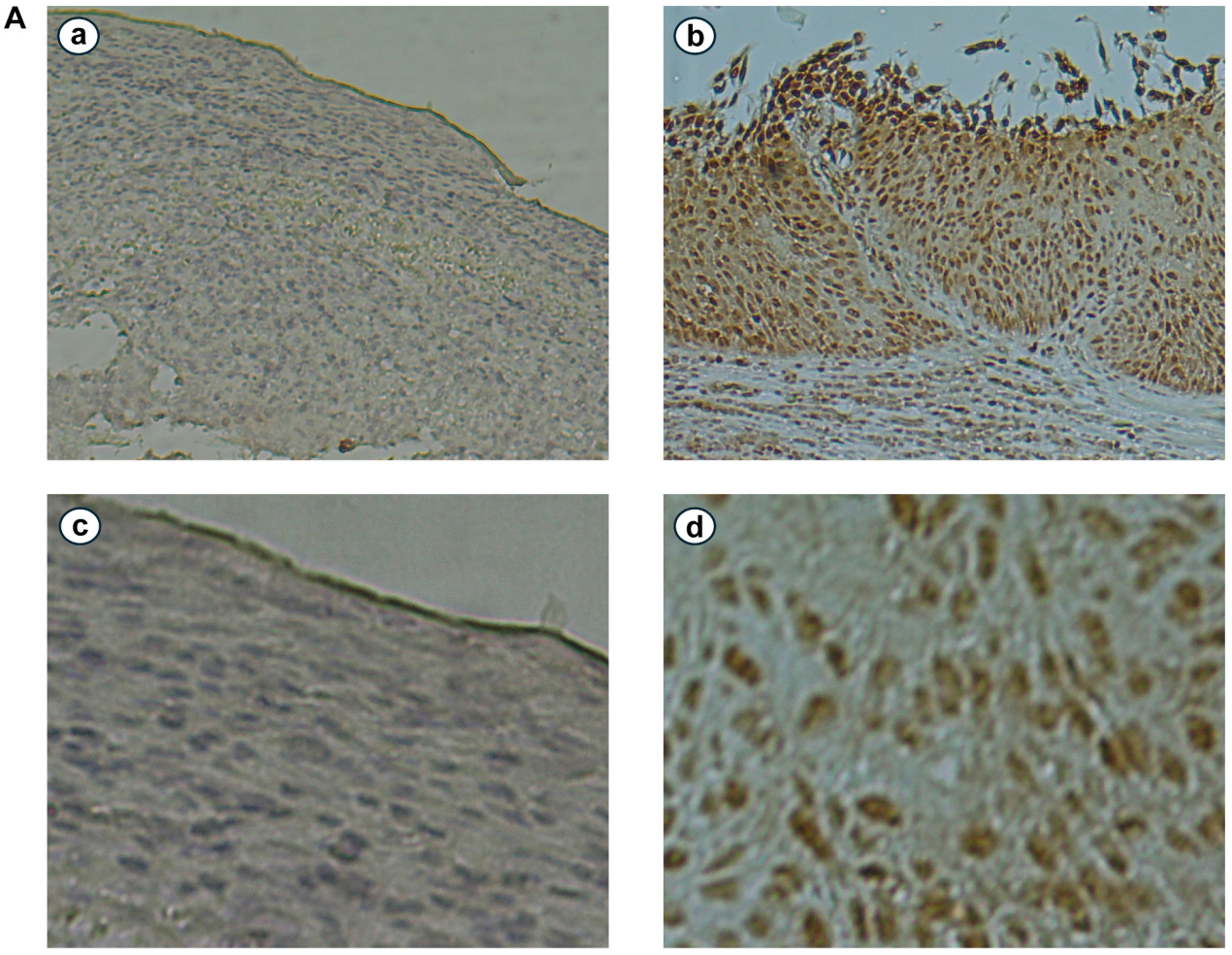
Discussion

ESCC stands out as one of the most aggressive cancers, characterized by poor prognosis (1). Therefore, identifying valid prognostic biomarkers and therapeutic targets is crucial for improving patient outcomes. In this study, we focused on the potential of SIRT1, a gene associated with longevity, that has gained increasing interest in cancer research (5). We elucidated the clinicopathological significance of serum SIRT1 and examined its association with SIRT1 tissue expression.

Our findings revealed that positive SIRT1 tissue expression was significantly associated with deeper tumor depth (p=0.020). There was a significant relationship between positive tissue SIRT1 expression and poorer OS and RFS (p=0.041 and p=0.012). Elevated serum SIRT1 levels were also significantly correlated with deeper tumor depth and weight loss (p=0.012 and p=0.030). The group with high serum SIRT1 levels tended to have poorer OS (p=0.069). However, no significant correlation was observed between tissue SIRT1 expression and serum SIRT1 concentration. These results suggest that tissue expression of SIRT1 may be a more valuable prognostic biomarker for patients with ESCC than serum SIRT1 levels but that serum SIRT1 levels may also have distinctive characteristics. This study is the first to elucidate the relationship between SIRT1 tissue expression and serum levels.

SIRT1 has been implicated in promoting tumor growth in ESCC (7), with high SIRT1 expression in tumors correlating with poor prognosis (10, 11). Our results align with previous reports reinforcing the idea that SIRT1 tissue expression is a promising prognostic biomarker in patients with ESCC.

In this study, serum SIRT1 levels were not associated with tissue expression, which mirrors our early findings in gastric cancer (15). Therefore, serum SIRT1 levels may not reflect tissue expression but may be strongly influenced by various *in vivo* conditions. The primary source of serum SIRT1 and the mechanisms underlying its regulation or secretion from tissues remain unclear (19). In this study, we observed that patients with weight loss at the initial diagnosis had significantly higher serum SIRT1 concentrations (p=0.030).



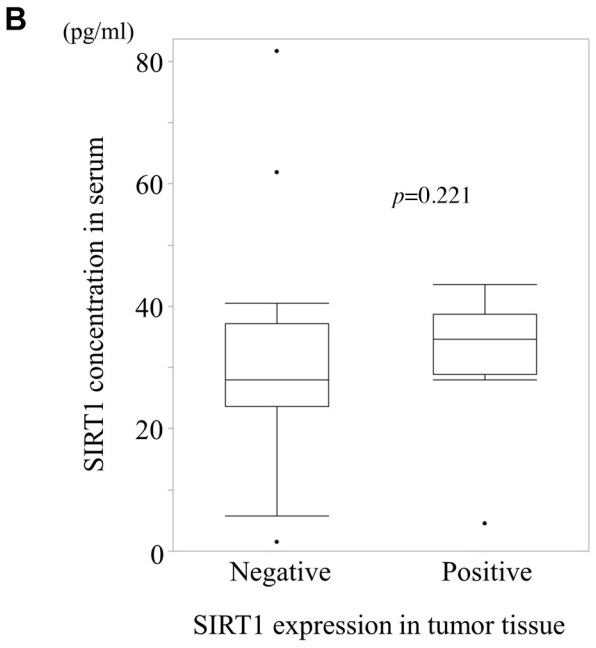


Figure 1. *Immunochemical images and correlation between serum and tissue SIRT1 expression. (A) Immunohistochemical images of sirtuin 1 (SIRT1) expression in tissue. Images of low expression (a and b) and high expression (c and d) are shown (100× in the upper section, 400× in the lower section). (B) Correlation between serum SIRT1 concentration and SIRT1 tissue expression in the surgical specimens.*

Table II. *Association between SIRT1 tissue expression and clinicopathological characteristics.*

Characteristics	SIRT1 expression		*p*-Value
	Positive	Negative	
Age			
Over 70 years	4	16	0.198
Under 70 years	7	11	
Sex			
Male	11	20	0.020
Female	0	7	
Weight loss			
(+)	1	2	0.607
(–)	3	10	
Serum Alb level			
Over 4.4 g/dl	3	13	0.208
Under 4.4 g/dl	8	14	
Pathological T category			
T1a	0	7	0.020
T1b/T2/T3/T4	11	20	
Pathological N category			
N(+)	7	12	0.238
N(–)	4	15	
Tumor differentiation			
Well/moderate	9	14	0.178
Poorly	2	10	
Pathological stage			
0/I	3	11	0.346
II/III/IV	8	16	

Alb: Albumin.

Table III. *Relationship between serum SIRT1 levels and clinicopathological factors.*

Variables	N	Average serum SIRT1 (pg/ml)	*p*-Value
Age			
Over 70 years	20	32.02±11.10	0.693
Under 70 years	18	30.58±16.82	
Sex			
Male	31	32.80±10.67	0.118
Female	7	24.89±14.40	
Weight loss			
(+)	3	43.76±17.93	0.030
(–)	13	30.19±14.12	
Serum Alb level			
Over 4.4 g/dl	16	30.04±13.67	0.701
Under 4.4 g/dl	22	32.29±14.36	
Pathological T category			
T1a	7	24.08±25.04	0.012
T1b/T2/T3/T4	31	32.98±14.12	
Pathological N category			
N(+)	19	30.94±9.15	0.815
N(–)	19	31.74±17.74	
Tumor differentiation			
Well/moderate	23	31.67±14.21	0.958
Poorly	12	32.52±14.80	
Pathological Stage			
0/I	14	28.89±18.60	0.188
II/III/IV	24	32.77±14.12	

Alb: Albumin.

There have been several reports, such as increased serum SIRT1 concentrations after weight loss, caloric restriction, or nutritional status (20-24). The elevated SIRT1 levels in patients experiencing weight loss at the initial visit, which is consistent with these results, may reflect the nutritional status of the patients. In patients with ESCC, malnutrition is a poor prognostic factor (25). In the present study, we observed a trend toward poorer OS in patients with higher SIRT1 serum concentrations. Given that serum levels were not associated with tissue expression, this finding could be due to poor nutritional status in the group with higher SIRT1 serum levels, resulting in a relatively poor prognosis. Nevertheless, the number of cases in this study was minimal, and further studies are needed to verify these hypotheses.

The strength of this study lies in its rare approach of measuring both tissue and serum SIRT1 expression in patients with ESCC while also exploring their characteristics and associations with clinical outcomes. This comprehensive approach was facilitated by integrating examinations, surgeries, and laboratory experiments conducted at our department. However, the study has certain limitations. The retrospective design may introduce selection bias, and the relatively small sample size from a single East Asian country necessitates broader studies in other regions to generalize the findings.

Conclusion

We found that positive SIRT1 tissue expression was associated with more advanced tumor depth and a poorer prognosis in patients with ESCC. Elevated serum SIRT1 levels were also significantly associated with deeper tumor depth and weight loss and showed a tendency toward poorer OS. However, there was no significant correlation between SIRT1 expression in tissue and its serum levels. These findings suggest that while tissue SIRT1 expression may be a valuable novel prognostic biomarker, serum levels could be influenced by other factors, such as nutritional status, and may hold different clinicopathologic significance than tissue expression. Further studies are needed to better understand the role of serum SIRT1 levels in ESCC.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

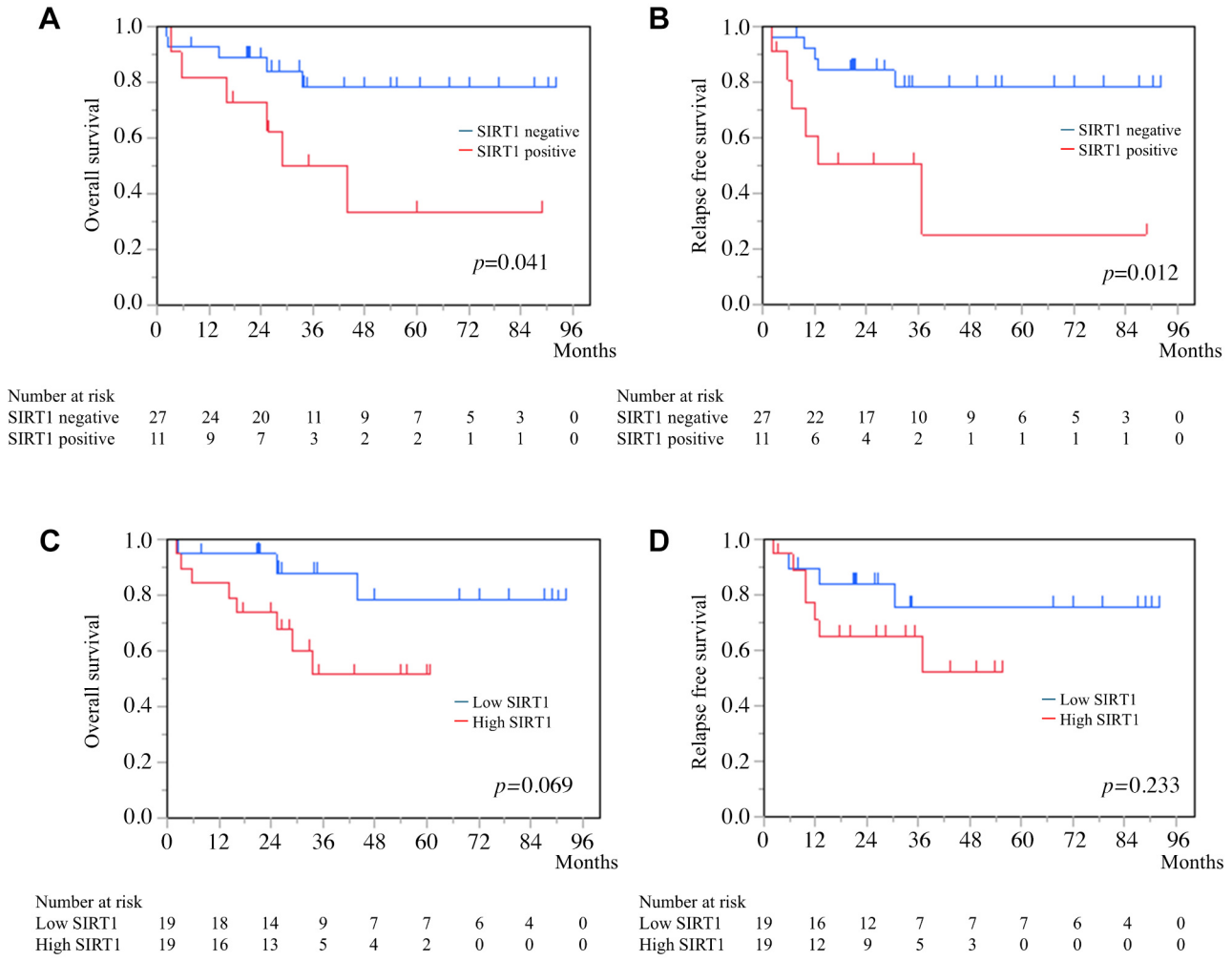


Figure 2. *Comparison of overall survival (OS) and relapse-free survival (RFS) according to tissue and serum sirtuin 1 (SIRT1) expression. (A) OS according to SIRT1 tissue expression. (B) RFS according to SIRT1 tissue expression. (C) OS according to serum SIRT1 levels. (D) RFS according to serum SIRT1 levels.*

Authors' Contributions

All Authors contributed to conceptualization. H.Mo. performed almost all experiments with advice from R.O. and H.Ma. T.T., N.S., and T.K. contributed to data collection. R.O., T.T., Y.M., and H.Ma. conducted project administration. R.O., Y.M., and H.Ma. supervised the study. H.Mo. prepared the manuscript under the supervision of K.O., T.S., S.I., T.M., Y.N, and M.Y. All Authors provided critical feedback and approved the final manuscript.

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