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*Original Article*

# Increased SIRT7 protein levels predict a poor prognosis for patients with esophageal squamous cell carcinoma

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**Abstract:** Background: Several members of the SIRT family (SIRT1-7), a highly conserved family of $NAD^+$-dependent enzymes, play an important role in tumor formation. Recently, several studies have suggested that SIRT7 is abnormally expressed in several tumor types. However, no studies have assessed its clinical significance in esophageal squamous cell carcinoma (ESCC). Method: We investigated SIRT7 protein expression levels in ESCC and its potential association with selected clinico-pathological parameters and overall survival of 93 ESCC patients by immunohistochemical staining on a tissue microarray. Results: SIRT7 expression was higher in ESCC compared with non-neoplastic tissues ($P<0.001$). In addition, higher SIRT7 expression levels were observed at the later American Joint Committee on Cancer stage ($P = 0.049$). In addition, the average survival time of patients with high SIRT7 expression in esophageal tumors was lower than that of patients with low SIRT7 expression, especially in patients with a tumor size larger than 5 cm ($P = 0.003$). Conclusions: SIRT7 may participatein the development of ESCC and may be a promising target for the diagnosis and treatment of esophageal cancer.

**Keywords:** SIRT7, carcinogenesis, esophageal squamous cell carcinoma

## Introduction

Esophageal cancer is the sixth leading cause of cancer-related death worldwide. There were 400,200 patient deaths because of esophageal cancer in 2012 globally [1]. The prognosis of patients with esophageal squamous cell carcinoma (ESCC) is poor, and the postoperative 5-year survival rate is only about 15% [2]. The etiology and pathogenesis of esophageal cancer is very complex, including many risk factors and a variety of genetic and epigenetic alterations. Over the past few decades, many key genes and signaling pathways were found to play a role in the pathogenesis of esophageal cancer. These include tumor suppressor gene TP53, CDKN2A, RTK-MAPK-PI3K and the Notch signaling pathway [3]. To discover potentially useful targets to aid diagnosis and therapeutic strategies, a better understanding of the molecular mechanisms involved in altered gene expression and pathological changes in esophageal cancer is necessary.

The SIRT family (SIRT1-7) is a group of $NAD^+$-dependent acetylases, deacetylases and ADP-ribosyltransferases, which are involved in pressure resistance, genome stability, energy metabolism and aging [4]. SIRT7 is mainly expressed in the nucleus and interacted with polymerase I RNA to regulate the transcription of ribosomal genes (rDNA) [5]. SIRT7 is considered to play an important role in the transcription of RNA Pol I [6]. Furthermore, SIRT7 inhibited tumor growth in several murine cell lines [7]. In contrast, another study also showed that SIRT7 inhibited tumor suppressor gene transcription to promote tumor growth [8]. To date, no studies have reported the relationship between SIRT7 expression and the clinico-pathological parameters of ESCC.

By high-throughput tissue microarray and immunohistochemistry, we investigated the expression of SIRT7 in ESCC, and further analyzed the relationship between SIRT7 expression and the clinical pathological parameters and prognostic value of ESCC.

**Table 1.** Correlation between the SIRT7 expression and clinicopathologic variables in ESCC

| Clinicopathologic parameters | SIRT7 expression | | | $X^2$ | *P*-value[a] |
|---|---|---|---|---|---|
| | All cases | Low | High | | |
| Age (years) | | | | 0.019 | 0.889 |
| ≤60 | 27 | 18 | 9 | | |
| >60 | 66 | 43 | 23 | | |
| Gender | | | | 0.747 | 0.387 |
| Male | 77 | 52 | 25 | | |
| Female | 16 | 9 | 7 | | |
| Tumor size (cm) | | | | 0.058 | 0.810 |
| ≤5 | 51 | 34 | 17 | | |
| >5 | 42 | 27 | 15 | | |
| Differentiation | | | | 1.887 | 0.170 |
| I-II | 74 | 46 | 28 | | |
| III-IV | 19 | 15 | 4 | | |
| Stage (T) | | | | 0.550 | 0.458 |
| T1-T2 | 22 | 16 | 6 | | |
| T3-T4 | 64 | 41 | 23 | | |
| Stage (N) | | | | 2.961 | 0.085 |
| N0 | 45 | 33 | 12 | | |
| N1-N3 | 48 | 27 | 21 | | |
| AJCC stage | | | | 3.884 | **0.049** |
| I-II | 48 | 36 | 12 | | |
| III-IV | 40 | 22 | 18 | | |

Bold values are statistically significant ($P<0.05$). [a]Chi-square test.

## Materials and methods

The current study was approval by the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China) ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

*Patients and tissue samples*

This study investigated 93 cases that providing individual samples. The age range of the patients was 49-85 years with a mean age of 65.8 years. The study was from January 2009 to 2010 in December, and the follow-up started at September 2014. The follow-up time was from 3.8-5.7 years. Overall survival time was defined from the time of receiving radical surgery to the time of death from any cause. Patients did not receive preoperative chemotherapy or radiotherapy before surgery. The clinico-pathologic parameters included the following: the age, gender, tumor size, pathological grade, depth of tumor invasion, lymph node status and the American Cancer Federation (AJCC, 7th edition) cancer staging information of the patient. Seven patients had no T stage information. Five patients had no AJCC stage information. The major clinico-pathological parameters are shown in **Table 1**.

Tissue gene array chips were obtained commercially (Superchip Inc., Shanghai, China). Among the 93 cases providing samples, 87 cases contained ESCC and a corresponding adjacent non-neoplastic tissue specimen, and another 6 cases only provided ESCC tissue. Thus, there were 180 points on one tissue microarray. The diameter of tissue pieces on the tissue microarray was 1.5 mm, and all points were overlaid with paraffin wax.

*Immunohistochemistry*

The tissue microarray was prepared by baking in a hot oven incubator for 2 hrs and then incubated twice in xylene for 5 min per incubation to deparaffinize the specimen. The tissue microarray was then transferred to 100%, 100%, 95%, 80%, and 70% successive ethanol washes every 5 min to rehydrate the specimen. Antigen retrieval was performed in a pressure cooker with citrate buffer (10 mM citrate and 0.05% Tween 20, pH 6.0). The tissue microarray was incubated in 0.3% $H_2O_2$ in TBS for 15 min to suppress endogenous peroxidase and then incubated with an affinity-isolated polyclonal rabbit antibody against SIRT7 (AP6246a, 1:1000, Abgent, Suzhou, China) at 4°C overnight. Secondary antibody was applied using the GTVision Kit (Gene Tech Inc., Shanghai, China). The tissue microarray was stained with diaminobenzidine (DAB), counterstained with hematoxylin, dehydrated, and sealed with coverslips according to standard procedures. Tissues treated with antibody dilution solution alone served as a negative control.

SIRT7 immunostaining intensity was evaluated by two pathologists blinded to the patient information under a light microscope. Each tissue point was multiplied by a score based on the staining intensity and the area of the stain [9]. The staining intensity was scored using the following criteria: 0 = no staining; 1 = weak staining; 2 = moderate staining; and 3= strong staining. Staining area assessment was as follows: 0 = 5% or none of the cells was stained; 1 = 5-25% of the cells were stained positive; 2 = 26-50% of the cells were stained positive; 3 = 51-75% of the cells were stained positive; and 4

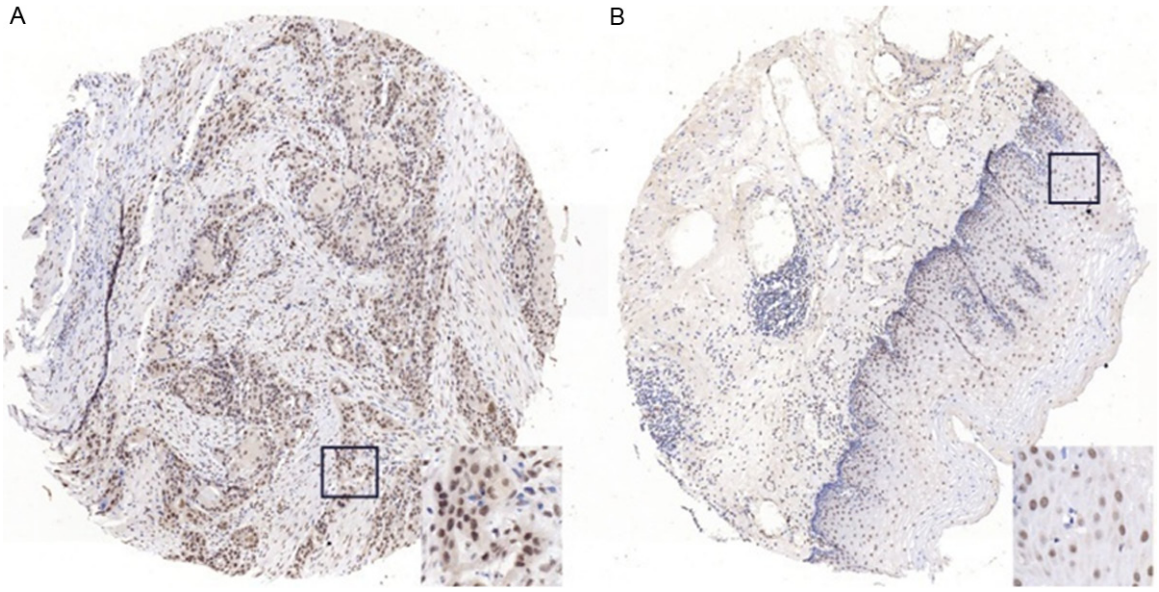


**Figure 1.** Representative immunohistochemical staining of SIRT7. SIRT7 was mainly located in the nuclei and was more highly expressed in tumor tissues compared with adjacent non-neoplastic esophageal tissues. A. The micrographs show strong staining of SIRT7 in the ESCC tissues. B. Relevant expression of SIRT7 in corresponding adjacent non-neoplastic esophageal tissues. (Magnification: 100× and 400×).

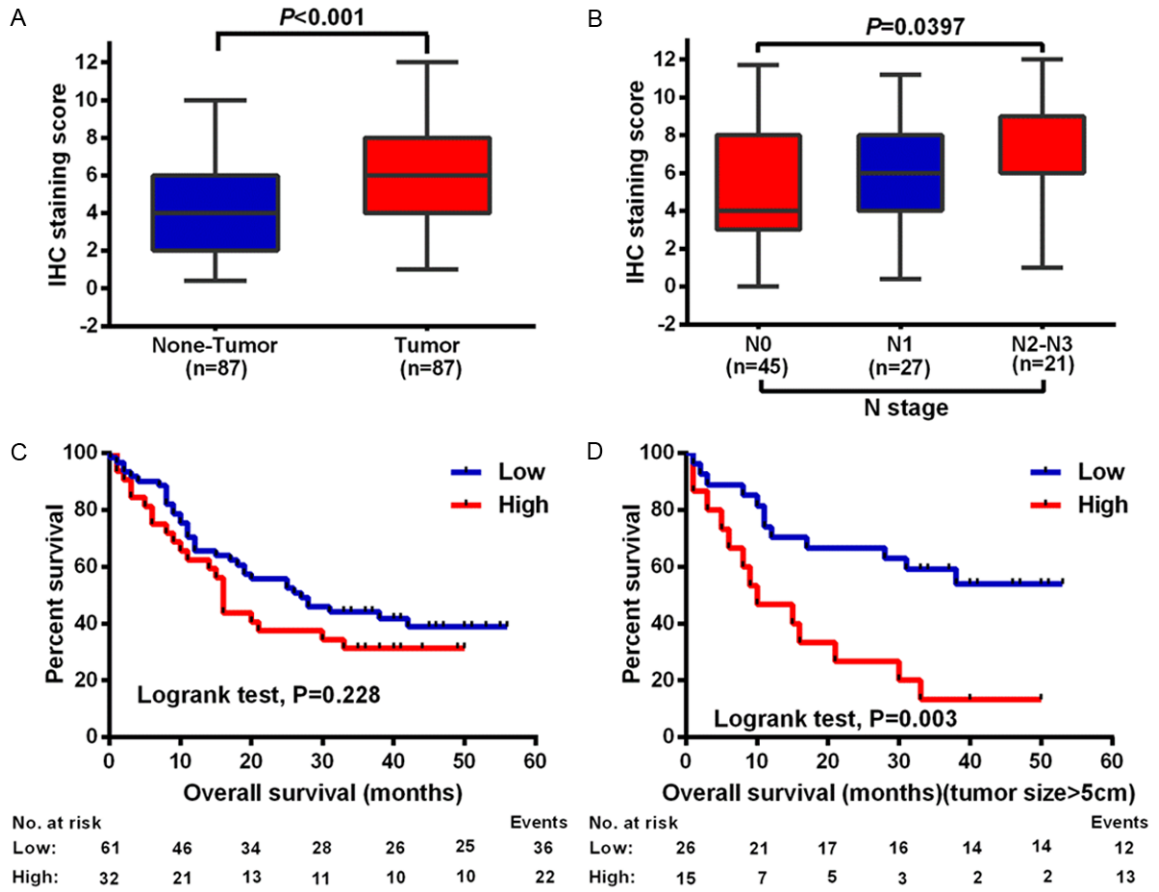


**Figure 2.** A. SIRT7 protein levels measured in 93 esophageal carcinoma tissues and paired adjacent normal esophageal tissues by tissue microarray. SIRT7 protein levels were higher in tumor tissues compared with adjacent non-

neoplastic esophageal tissues (P<0.001). The boxes represent the interquartile range; whiskers represent the 5th-95th percentile range; and bars represent the median. B. SIRT7 is more likely to be highly expressed at a higher N stage. The boxes represent the interquartile range; whiskers represent the 5th-95th percentile range; and bars represent the median. C. The average survival time of patients of ESCC with high SIRT7 levels was lower than that of patients with low SIRT7 levels. D. The average survival time of ESCC patients (tumor size > 5 cm) with high SIRT7 levels was significantly lower than that of patients with low SIRT7 levels (P = 0.003).

**Table 2.** Univariate analysis of SIRT7 expression and clinicopathologic variables in 93 patients with ESCC

| Variable | All cases | Overall survival (months) | | *P*-value[a] |
|---|---|---|---|---|
| | | Mean | Median | |
| Age (years) | | | | 0.834 |
| ≤60 | 27 | 30.0 | 27.0 | |
| >60 | 66 | 28.1 | 20.0 | |
| Gender | | | | 0.190 |
| Male | 77 | 34.1 | 20.0 | |
| Female | 16 | 28.1 | 21.0 | |
| Tumor size (cm) | | | | 0.726 |
| ≤5 | 51 | 28.7 | 20.0 | |
| >5 | 42 | 29.2 | 28.0 | |
| Differentiation | | | | 0.955 |
| I-II | 74 | 29.5 | 21.0 | |
| III-IV | 19 | 27.4 | 17.0 | |
| T stage | | | | **0.030** |
| T1-T2 | 22 | 38.0 | NR | |
| T3-T4 | 27 | 25.7 | 17.0 | |
| N stage | | | | **0.016** |
| N0 | 45 | 35.2 | 42.0 | |
| N1-N3 | 49 | 23.2 | 15.0 | |
| AJCC stage | | | | **0.002** |
| I-II | 48 | 35.5 | 42.0 | |
| III-IV | 40 | 20.0 | 14.0 | |
| SIRT7 expression | | | | 0.228 |
| Low | 61 | 31.7 | 27.0 | |
| High | 32 | 23.8 | 16.0 | |

Bold values are statistically significant (*P*<0.05). NR, not reached. [a]log-rank test.

= greater than 75% of the cells were stained positive. The degree of staining was divided into two grades: 0-6, low expression; 7-12, high expression. When the evaluations of the staining pattern did not agree, a consensus opinion was arrived at by both pathologists.

*Statistical analysis*

Statistical analysis was performed using the SPSS software package version 20.0 (SPSS, Inc., IBM, USA). A paired Student's t-test was used to analyze the final score of the tumor and non-tumor tissues. Chi-squared analysis was used to analyze the relationships between SIRT7 expression and the clinico-pathological parameters. The Kaplan-Meier method (the log-rank test) was used for single-factor analysis. The Cox proportional hazards regression model was used to identify the independent prognostic factors. *P* values less than 0.05 (two tailed) were considered statistically significant.

## Results

*SIRT7 expression in ESCC and adjacent non-neoplastic tissues*

SIRT7 was predominantly expressed in the nuclei of esophageal squamous cell carcinoma and non-neoplastic esophageal tissues (**Figure 1**). Importantly, the staining intensity of SIRT7 was stronger in ESCC compared to adjacent non-neoplastic esophageal tissues (**Figure 2A**).

*Relationship between SIRT7 levels and clinicopathological parameters in patients with ESCC*

Associations between SIRT7 levels and clinicopathological features were evaluated by immunohistochemistry (**Table 1**). We found significant associations between SIRT7 levels and AJCC staging (P = 0.049). We did not find any significant associations between SIRT7 levels and other parameters including age, gender, pathological grade, and tumor invasion (T) and lymph node metastasis (N) staging (P > 0.05). However, we found that an increase in the number of lymph node metastasis was associated with increased levels of SIRT7 staining (**Figure 2B**).

*Association between SIRT7 levels and total survival time of patients with ESCC after operation*

Kaplan-Meier analysis and the log-rank test were used to investigate the prognostic value of SIRT7 expression and classic clinico-pathologic characteristics on patient survival. In univariate analysis, we found that depth of T, N

**Table 3.** Cox multivariate analyses of prognostic factors on overall survival

| Variables | HR | 95%CI | *P*-value[a] |
|---|---|---|---|
| T stage (T1-T2 versus T3-T4) | | | n.s. |
| N stage (N0 versus N1-N3) | | | n.s. |
| AJCC stage (I-II versus III-IV) | 2.247 | 1.306-3.865 | **0.003** |
| SIRT7 expression (Low versus High) | | | n.s. |

Bold values are statistically significant ($P<0.05$). HR, hazard ratio; CI, confidence interval; n.s., no significance. [a]Forward: LR method.

and AJCC stage were associated with overall survival (P = 0.030, P = 0.016, P = 0.002, respectively, **Table 2**) in patients with ESCC. In addition, we did not find a correlation between the expression of SIRT7 and the total survival time of patients with ESCC (P = 0.228). Although not statistically significant, the average survival time of patients with high SIRT7 levels in ESCC tissues was lower than that of patients with low levels (mean survival time: SIRT7 High = 23.8 months compared with SIRT7 Low = 31.7 months) (**Figure 2C**). However, to our surprise, for ESCC patients with a tumor size greater than 5 cm, the overall survival time was significantly lower in patients with high SIRT7 expression compared with patients with low SIRT7 levels (**Figure 2D**).

Next, we used COX regression analysis to analyze the independent prognostic factors for the overall survival time of patients with ESCC. After adjusting the prognostic factors in univariate analysis, we found that there was a significant correlation between AJCC stage and total survival time of patients with ESCC (P = 0.003, hazard ratio = 2.247; **Table 3**).

## Discussion

The present study observed that multiple SIRT family members play different roles in different tumors, which may depend on the specific tissue and tumor type [10]. For example, SIRT1 is expressed in stomach [11], colon [12], prostate [13] and skin [14] tumors amongst others, suggesting it has a role in promoting the formation of tumors in these tissues. However, other studies reported that SIRT1 expression is reduced in breast cancer [15], and that its expression in $APC^{min/+}$ mice inhibited the formation of intestinal tumors [16]. This is similar to SIRT2, which is downregulated in breast cancer [17], glioma [18] and skin cancer [19]; however, SIRT2 expression was enhanced in acute myeloid leukemia [20] and prostate cancer [21]. Thus, we cannot easily extrapolate the observations for one tumor type and the conclusions drawn from them to the study of another tumor type.

The expression of SIRT7 is upregulated in most tumors. Kim et al. [22] found that SIRT7 was upregulated in human HCC tissues, and the knockdown of SIRT7 inhibited the growth of HCC cells *in vitro* and *in vivo* by affecting cell cycle and autophagy related proteins. Yu et al. [23] found that the expression of SIRT7 in colon cancer was upregulated and that SIRT7 affected the proliferation and migration of colon cancer cells by regulating the MAPK signaling pathway and epithelial-mesenchymal transition. Geng et al. [24] reported the expression of SIRT7 was associated with a bad prognosis of breast cancer and Ashraf et al. [25] found that the expression of SIRT7 was upregulated in breast cancer. In addition, SIRT7 was also found to be upregulated in gastric cancer and ovarian cancer cells [26, 27]. However, McGlynn et al. [28] found that the expression of SIRT7 in pancreatic cancer was decreased and the expression of pancreatic cancer with high SIRT7 expression had a longer survival time. These results suggest that SIRT7 may function as an oncogene and tumor suppressor gene.

To date, no study has reported the relationship between SIRT7 expression and the clinicopathological parameters of patients with ESCC. In the present study, we analyzed the SIRT7 protein levels in ESCC and the relationship between SIRT7 levels and the clinico-pathological parameters of patients with ESCC. Our results showed that SIRT7 levels were higher in esophagus tumor tissues compared with adjacent non-neoplastic tissues. Furthermore, patients with higher SIRT7 levels were more likely to have a later AJCC stage. Moreover, an increase in the number of lymph node metastasis was associated with increased SIRT7 staining levels. Furthermore, the average survival time of patients with high SIRT7 expression in esophageal cancer tissues was lower than that of patients with low SIRT7 expression, especially in patients with a tumor size larger than 5 cm. These observations suggest that SIRT7 may participant in the development of ESCC, and may function as an oncogene.

To the best of our knowledge, this is the first study of the relationship between SIRT7 expression level and clinico-pathological parameters in human esophageal squamous cell cancer specimens. Although the average survival time of esophageal cancer patients with high expression of SIRT7 was significantly lower than that of patients with low expression, the difference was not statistically significant. Therefore, our future studies will use a larger sample and use more tumor types to verify the relationship between SIRT7 levels and the prognosis of esophageal cancer patients. We will also study the effect of SIRT7 on the biological behavior of esophageal cancer cells.

In summary, our results suggest that SIRT7 may participant in the development of ESCC and may be a promising target for the diagnosis and treatment of esophageal cancer.

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## Disclosure of conflict of interest

None.

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