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Review

SIRT1 Expression Is a Promising Prognostic Biomarker in Esophageal Squamous Cell Carcinoma: A Systematic Review and Meta-analysis

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Abstract. *Background/Aim: Several articles have assessed the prognostic significance of the expression of sirtuin 1 (SIRT1) in esophageal squamous cell carcinoma (ESCC). However, evidence in this field is insufficient. Thus, we conducted a meta-analysis to investigate the prognostic and clinical impact of SIRT1 expression in ESCC. Materials and Methods: We searched the PubMed, Cochrane Library, and Web of Science databases for articles on the expression of SIRT1 and clinicopathological features in patients with ESCC. A meta-analysis was conducted. Results: Four studies with 429 patients were included. The meta-analysis revealed a significant relationship between the high expression of SIRT1 and higher T-stage (odds ratio=2.39. 95% confidence interval=1.12-5.13, p=0.02), more advanced TNM stage (odds ratio=2.35. 95% confidence interval=1.20-4.60, p=0.01), and a poor overall survival (hazard ratio=1.90, 95% confidence interval=1.45-2.47, p<0.00001). Conclusion: SIRT1 expression may be a promising prognostic biomarker for patients with ESCC.*

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Esophageal cancer is one of the most aggressive types of cancer and has a relatively poor prognosis among sufferers worldwide. The pathological classification of esophageal cancer can be broadly divided into two subtypes: esophageal squamous cell carcinoma (ESCC) and adenocarcinoma, with the former being the predominant histological type in East Asia (1).

With the improvement of diagnostic technology that has enabled early detection and the development of multidisciplinary treatment with surgery, chemotherapy, and radiation therapy, the prognosis of ESCC is improving; however, there is still room for improvement (2). Thus, the identification of specific molecular markers that can be used as prognostic and therapeutic targets is an important issue in relation to effective treatment and the improvement of the prognosis of ESCC.

In recent years, there has been growing public interest in aging and longevity, and attention to longevity-associated genes has been increasing (3). Sirtuin 1 (SIRT1) is a gene that is well known to be associated with cell senescence (4). SIRT1 is a nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylase that deacetylates various proteins that contribute to aging, DNA repair, metabolic regulation, apoptosis, and proliferation (5-7). While SIRT1 has been reported to be associated with longevity, previous reports showed that SIRT1 plays an important role in tumorigenesis and tumor progression in various types of cancer, including colorectal, gastric, liver, pancreatic, lung, prostate and breast cancer (8-14). On the other hand, several reports have revealed that SIRT1 has a tumor-suppressive function (15, 16). Hence, the role of SIRT1 in cancer is still controversial. In ESCC, several articles recently assessed the prognostic significance of the expression of SIRT1 (17-21). However, since ESCC is a relatively rare gastrointestinal malignancy, the size of these single-center studies is

relatively small and insufficient for evaluating the true value of SIRT1 in ESCC.

Thus, we conducted a meta-analysis to investigate the prognostic and clinical impact of the SIRT1 expression in ESCC.

Materials and Methods

Publication search strategy. The PubMed, Cochrane Library and Web of Science databases were searched to identify studies on the expression of SIRT1 and clinicopathological features in patients with esophageal cancer from inception until March 2021. The following search term was applied: "Sirtuin 1" or "Silent mating type information regulation 2 homolog 1" or "SIRT1" and "esophageal carcinoma" or "esophagus carcinoma" or "oesophageal carcinoma". The reference lists of all related articles were screened for other potential relevant studies. We performed this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (22).

Inclusion and exclusion criteria. The criteria for eligibility of reports included in this study were as follows: (i) The study included patients with ESCC; (ii) the expression of SIRT1 was measured by immunohistochemical (IHC) staining, western blotting or fluorescence in situ hybridization; (iii) clinicopathological features or overall survival rates were analyzed with the expression of SIRT1; and (iv) study written in English.

The following reports were excluded: (i) Studies without appropriate data; (ii) animal and laboratory research; (iii) studies including patients who had received any other preoperative treatments; and (iv) reports identified as letters, comments, correspondence, editorials, or reviews.

Data extraction. Full-text reviews were conducted according to the inclusion and exclusion criteria. The following information was extracted from each eligible study: First author, year of publication, patient source, research method, number of patients, age, sex, proportion with high expression of SIRT1, follow-up time, tumor differentiation, tumor depth, lymph node metastasis, TNM stage and overall survival (OS). TNM staging was defined based on the Union for International Cancer Control or the American Joint Committee on Cancer TNM classifications (23, 24). The quality of the included studies was evaluated according to the Newcastle–Ottawa Scale (25). Studies with a score of ≥6 were considered of high quality.

Statistical analyses. All statistics analyses were assessed using the Review Manager Version 5.3 software program (The Cochrane Collaboration, Oxford, UK). Analyses using fixed-effects and random-effects models were conducted. Heterogeneity was evaluated using the I^2 statistic, with a maximum value of 50% identifying significant heterogeneity. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were determined to evaluate the relationship between SIRT1 expression and clinicopathological characteristics (sex, tumor depth, lymph node metastasis, TNM stage and tumor differentiation). The association between the expression of SIRT1 and OS was evaluated according to pooled hazard ratios (HRs) and 95% CIs. The *p*-value of overall effect was assessed using the Z-test, with significance defined as $p<0.05$. Publication bias was evaluated by creating funnel plots.

Results

Description of studies. A flow diagram of the study is shown in Figure 1. A total of 48 studies were identified by the electronic search and 15 studies were excluded due to duplication. Based on the selection criteria, 26 articles were removed by title/abstract review. The remaining seven candidate articles were investigated by a full-text review; among these, two studies were removed due to the inclusion of patients with adenocarcinoma, and one study was excluded because it only examined cases negative for lymph node metastasis. Thus, four studies with 429 patients were finally included in the meta-analysis (18-21). The quality of the included studies was assessed using the Newcastle–Ottawa Scale, and all studies were graded as being of high quality. The number of cases ranged from 86 to 155 in all of the articles. All of the included studies assessed the clinicopathological and prognostic value of SIRT1 expression in ESCC using IHC staining. The details of the included studies are summarized in Table I.

Gender. All of the included studies described the gender ratio. The meta-analysis revealed no significant correlation between the expression of SIRT1 and sex (OR=1.31, 95% CI=0.71-2.41; $p=0.39$). There was no significant heterogeneity ($I^2=24\%$) (Figure 2).

Tumor depth. Tumor depth was reported in three studies (Table I). The meta-analysis of integrated data revealed a significant relationship between the high expression of SIRT1 and higher T-stage (OR=2.39, 95% CI=1.12-5.13; $p=0.02$), with significant heterogeneity ($I^2=57\%$) (Figure 2).

Lymph node metastasis. Three reports reported the relationship between SIRT1 expression and lymph node metastasis (Table I). The meta-analysis showed that a high SIRT1 expression tended to be related to lymph node metastasis; however, the association was not statistically significant (OR=2.15, 95% CI=1.01-4.56; $p=0.05$), with significant heterogeneity ($I^2=52\%$) (Figure 2).

TNM stage. All of the included articles reported the TNM stage (Table I). The meta-analysis revealed a significant relationship between high SIRT1 expression and more advanced TNM stage (OR=2.35, 95% CI=1.20-4.60; $p=0.01$), with significant heterogeneity ($I^2=51\%$) (Figure 2).

Tumor differentiation. Tumor differentiation was reported in all of the included studies (Table I). The meta-analysis revealed no significant correlation between the expression of SIRT1 and tumor differentiation (OR=1.13. 95% CI=0.69-1.83, $p=0.63$), with no heterogeneity ($I^2=0\%$) (Figure 2).

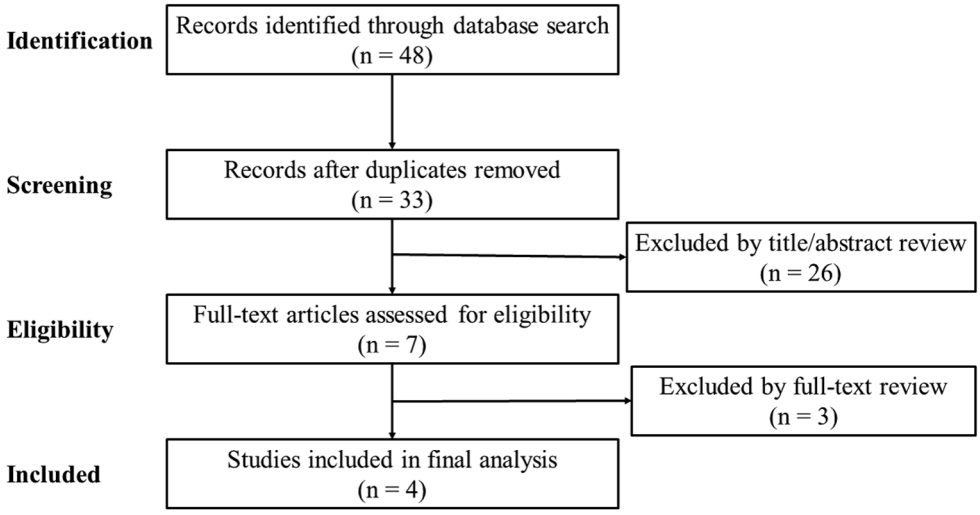

Figure 1. *Flow diagram of study selection for inclusion.*

Table I. *Main characteristics and results of the eligible studies.*

Author	Year	Country	Case, n	Method	Cut-off score	Gender Male/ female, n	Age ≤60/>60 years, n	T Category T1, 2/T3, 4, n	N Category N0/ N1-3, n	TNM stage I, II/III, IV, n	Differentiation G1, 2/ G3, n	Follow-up, months
He *et al*. (18)	2016	China	86	IHC	>3	H: 44/10 L: 20/12	NA	H: 19/35 L: 15/17	H: 20/34 L: 19/13	H: 30/24 L: 25/7	H: 41/13 L: 24/8	NA
Han *et al*. (19)	2018	China	95	IHC	≥6	H: 49/14 L: 25/7	H: 31/32 L: 13/19	NA	NA	H: 31/32 L: 24/8	H: 30/33 L: 14/18	60
Ma *et al*. (20)	2018	China	155	IHC	≥4	H: 75/2 L: 75/3	NA	H: 34/43 L: 45/33	H: 51/26 L: 55/23	H: 55/22 L: 57/21	H: 58/19 L: 66/12	65.8
Yan *et al*. (21)	2020	China	93	IHC	≥4	H: 66/9 L: 18/0	H: 24/51 L: 6/12	H: 12/63 L: 10/8	H: 32/43 L: 14/4	H: 32/43 L: 14/4	H: 70/5 L: 16/2	30

IHC: Immunohistochemistry; H: high expression; L: low expression; NA: not available.

Overall survival. The data extracted from all included studies were used to assess the correlation between SIRT1 and OS. The meta-analysis revealed that high expression of SIRT1 was significantly associated with poor OS (hazard ratio=1.90, 95% CI=1.45-2.47; $p<0.00001$). There was no significant heterogeneity ($I^2=0\%$) (Figure 3).

Publication bias. We conducted a funnel plot analysis to assess the possibility of publication bias. The funnel plot of OS revealed no obvious asymmetry, and therefore no bias (Figure 4).

Discussion

ESCC is a highly aggressive cancer type with a poor prognosis. Thus, the identification and assessment of prognostic biomarkers may be valuable for the management of patients with ESCC. SIRT1 plays important roles in life processes, and recently, several single-center reports have evaluated the prognostic value of the SIRT1 expression in patients with ESCC. However, since ESCC is a relatively rare gastrointestinal cancer, the scale of these studies is small, and there is great clinical value in integrating these data to assess the true value of SIRT1 in ESCC. Hence, we performed a meta-analysis to evaluate the prognostic and clinical impact of SIRT1 expression in ESCC.

The present results revealed a significant relationship between high expression of SIRT1 and a higher T-stage and more advanced TNM stage. Furthermore, the results of this meta-analysis revealed that high expression of SIRT1 was significantly correlated with a poor OS. These results suggest that SIRT1 is a promoter of tumor progression and that the

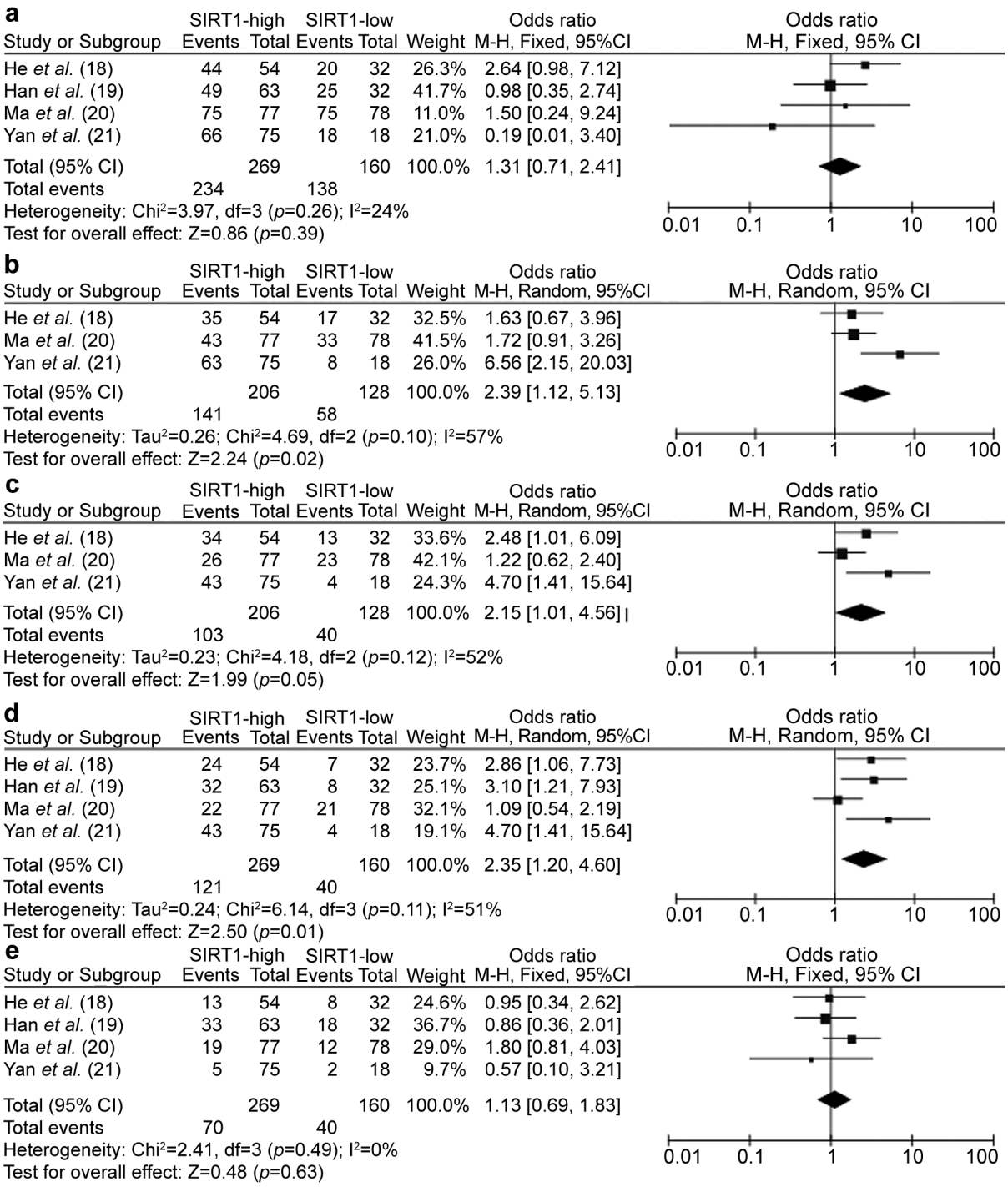

Figure 2. *Forest plots investigating the association between sirtuin 1 (SIRT1) expression and clinicopathological features in esophageal squamous cell carcinoma. A: Gender (male vs. female); B: tumor depth (T1+T2 vs. T3+T4); C: lymph node metastasis (negative vs. positive); D: TNM stage (I+II vs. III+IV); E: tumor differentiation (G1+G2 vs. G3). CI: Confidence interval.*

expression of SIRT1 may be a novel candidate prognostic biomarker for ESCC. To the best our current knowledge, this is the first meta-analysis to investigate the prognostic role of SIRT1 for ESCC.

SIRT1 has been considered to be a potential tumor promoter. Several potential mechanisms through which SIRT1 may be involved in tumor progression are as follows. SIRT1 can regulate tumor-suppressor genes, such as p53, forkhead

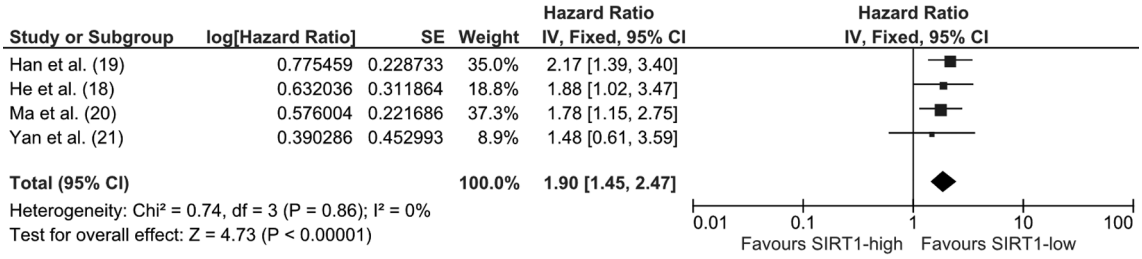

Figure 3. *Forest plot assessing the relationship between sirtuin 1 (SIRT1) expression and overall survival in esophageal squamous cell carcinoma. CI: Confidence interval.*

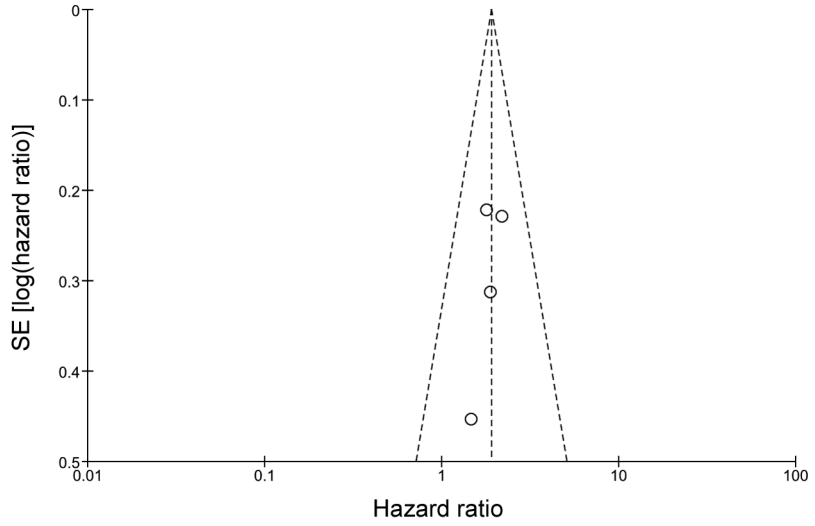

Figure 4. *Funnel plot of publication bias based on overall survival. CI: Confidence interval; SE: standard error.*

class O transcription factor family members, E2F transcription factor 1, and retinoblastoma (26, 27). Sirtinol, a SIRT1 inhibitor, attenuates RAS-mitogen-activated protein kinase signaling and induces senescence-like growth arrest in human cancer cells (28). SIRT1 can enhance prostate cancer cell migration and metastasis by inducing the epithelial–mesenchymal transition (29). Finally, SIRT1 can maintain silent chromatin by deacetylation of histone proteins and protect cells from apoptosis (26). In addition, it has been reported that a high expression of SIRT1 is associated with an advanced stage and poor prognosis in other cancer types, such as colorectal cancer (30), lung adenocarcinoma (31), and gastric cancer (32). The present results are consistent with these reported data and suggest that SIRT1 may be an important prognostic indicator for patients with ESCC.

Although there was no significant difference in lymph node metastasis in this study, there was a tendency for a high SIRT1 expression to be associated with positive lymph node metastasis. Two studies included in this meta-analysis reported that a high expression of SIRT1 was significantly associated with lymph node metastasis. A relationship between SIRT1 expression and lymph node metastasis has also been reported in breast cancer (33) and colorectal cancer (30), and SIRT1 expression is reportedly involved in cell migration in prostate cancer (29) and non-small-cell lung cancer (34). Therefore, we cannot deny the possibility that SIRT1 may play an important role in lymph node metastasis of ESCC.

There are reports that SIRT1 is involved in the regulation of cell differentiation and dedifferentiation (35, 36). Dedifferentiation and the associated epithelial-to-mesenchymal transition phenomenon play an essential role in early local and distant tumor spread. Observations linking the high expression of SIRT1 with poorly differentiated cancer have also been obtained by other researchers in cases of hepatocellular carcinoma (37), prostate cancer (8), and pancreatic ductal adenocarcinoma (14). However, the present results did not

show that a high expression of SIRT1 was associated with differentiation in ESCC. Whether or not this is a tumor-specific characteristic will be a very interesting issue to clarify.

In the present study, SIRT1 in ESCC was found to be a tumor-promoting factor, while SIRT1 has also been reported to act as a tumor suppressor. Firestein *et al*. reported that SIRT1 inhibited intestinal tumorigenesis and the growth of colon cancer by deacetylating β-catenin, and SIRT1 suppressed the ability of β-catenin to activate transcription and promote cell proliferation (15). In addition, Wang *et al*. reported that SIRT1 suppressed survivin, an inhibitor of apoptosis that is overexpressed in various cancers, including BRCA DNA repair-associated 1-related breast cancer (38). Thus, because of the seemingly contradictory results of many studies examining the effects of SIRT1 on cancer-related biological processes, further studies are needed to explore the relevance of SIRT1 to human cancer and tumorigenesis.

This meta-analysis was associated with some limitations. Firstly, the sample sizes of all of the included studies were relatively small; thus, there may have been some heterogeneity. Secondly, the studies enrolled in this study used IHC to investigate SIRT1 levels, and the cutoff values for the expression of SIRT1 differed in each study. Such inconsistent IHC assessment may have led to a potential bias in this meta-analysis. Thirdly, there may be some studies that have not been published due to negative or controversial results, which leads to an inevitable publication bias. Finally, the articles included in this meta-analysis were only conducted in China. Therefore, large multicenter studies conducted in other countries and regions would be desirable to confirm the results of this study.

Since sirtuins are involved in a wide range of diseases, various sirtuin activators and inhibitors are being developed for therapeutic purposes (39). Garcia-Peterson *et al*. reported that SIRT1 suppresses tumor development at the precancerous stage by promoting DNA repair, enhancing genomic stability, and suppressing inflammation; in addition, it enhances tumor growth, survival, and drug resistance at the stage of tumor progression, metastasis, and recurrence by anti-apoptosis effects, the promotion of tumor metabolism, and anti-inflammatory effects (inhibition of antitumor immunity) (40). Therefore, the development of both inhibitors and activators of SIRT1 will be important for cancer treatment. The present findings further suggest that SIRT1 may be a useful therapeutic target in ESCC at the stage of tumor progression.

In conclusion, we demonstrated that high expression of SIRT1 was correlated with poor OS, deeper tumor, and a more advanced TNM stage in patients with ESCC. These findings suggest that SIRT1 may be a promising novel prognostic biomarker and that the regulation of SIRT1 may become a significant target in the treatment ESCC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

Ryota Otsuka conceived and designed the study. Soichiro Hirasawa, Kazuya Kinoshita, Takuma Sasaki and Ryota Otsuka performed the literature search. Satoshi Endo, Toyozumi, Yasunori Matsumoto, Hiroshi Suito, Masahiko Takahashi, Nobufumi Sekino and Ryota Otsuka contributed to the data acquisition, analysis and interpretation. The article was prepared by Ryota Otsuka under the supervision of Haruhito Sakata, Kentaro Murakami, Masayuki Kano and Hisahiro Matsubara. All Authors read and approved the final article.

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