Original Article

The Prognostic and Clinicopathological Roles of Sirtuin-6 in Various Cancers: A Meta-Analysis

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Abstract

Background: SIRT6, a chromatin-associated nuclear protein, exhibits beneficial and pivotal functions in longevity, cardiovascular diseases, and cancer. However, the significant and controversial clinical value of SIRT6 in cancers has not been fully defined. In this manuscript, we performed an updated and comprehensive meta-analysis of all relevant clinical data in order to gain an exhaustive summary of the clinicopathological roles of SIRT6 in various human cancers. **Materials and Methods:** A systematic literature searching was performed in PubMed, Web of Science, Embase, and CNKI up to April 2019. Studies enrolled in our quantitative meta-analysis were selected according to inclusion and exclusion criteria. Our meta-analysis was performed using total effect analyses and subgroup analyses to evaluate the relationship between SIRT6 expression and overall survival, clinicopathological parameters of multiple types in cancer patients including cancer/noncancer tissues, lymph node metastasis, metastasis, distant metastasis, differentiation, tumor stage and tumor node metastasis (TNM) stage, tumor size, gender, estrogen receptor, and progesterone receptor. The hazard ratios (HRs) or odds ratios (ORs) of the 95% confidence intervals (CIs) were calculated to reveal the risk or hazard association. All analyses were conducted using the Cochrane Collaboration Review Manager 5.3 software. **Results:** A total of twenty studies comprising 2700 patients from five countries who represented nine cancer types were included to assess the association between SIRT6 immunohistochemical expression and overall survival or clinicopathological characteristics. Cancer type subgroup analysis showed that high SIRT6 expression was associated with worse OS in hepatocellular carcinoma (HR: 1.49, 95% CI: [1.22, 1.81], $P < 0.0001$, $I^2 = 0\%$), osteosarcoma (HR: 2.05, 95% CI: [1.28, 3.30], $P = 0.003$, $I^2 = 0\%$), and non-small cell lung cancer (NSCLC) (HR: 1.88, 95% CI: [1.02, 3.47], $P = 0.004$, $I^2 = 73\%$). In addition, our results demonstrated that SIRT6 expression was statistically significant in noncancer tissues higher than in cancer tissues (OR = 0.32, 95% CI = 0.13–0.79, $P = 0.01$, random-effects model). Furthermore, it has been shown that SIRT6 expression was well correlated with lymph node metastasis in patients with breast carcinoma (OR = 1.76, 95% CI = 1.17–2.66, $P = 0.007$, fixed-effects model), the stages of pathological differentiation in cancer patients (OR = 1.53, 95% CI = 1.08–2.18, $P = 0.02$, fixed-effects model), tumor stages (I–IV) in NSCLC patients (OR = 0.40, 95% CI = 0.20–0.80, $P = 0.01$, fixed-effects model), and TNM stages in colon cancer patients (OR = 2.41, 95% CI = 1.38–4.20, $P = 0.002$, fixed-effects model). Nevertheless, there was no detectable correlation between SIRT6 expression and other clinicopathological parameters in total or subgroup analyses. **Conclusion:** Our current meta-analysis indicates that the expression level of SIRT6 is highly associated with overall survival and clinical features in specific cancers.

Keywords: Cancers, clinical features, overall survival, sirtuin-6, sirtuins

Introduction

The (NAD) +-dependent histone deacetylase, the sirtuin family (SIRT1-7), is highly conserved from lower organisms to humans and is linked to the regulation of diverse biological processes, including cellular apoptosis, differentiation, senescence, survival, aging, metabolism, inflammation, and cancer.[1] SIRTs have been proposed to play a key role in the development of inflammation and cardiovascular diseases in our previous findings.[2-4]

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Quick Response Code:

Website: https://journals.lww.com/mtsm

DOI: 10.4103/MTSM.MTSM_5_19

SIRT6, a chromatin-associated nuclear protein, exhibits both deacetylase and mono-ADP-ribosylase activities by modifying acetyl groups from histone 3 lysine 9 (H3K9) and

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How to cite this article: Jing T, Yang XF, He YH. The prognostic and clinicopathological roles of sirtuin-6 in various cancers: A meta-analysis. Matrix Sci Med 2023;7:95-103.

Received: 04-06-2019, **Revised:** 03-02-2020,
Accepted: 06-05-2020, **Published:** 20-11-2023

histone 3lysine 56 (H3K56) among seven types of SIRTs.[1] Research on SIRT6 has focused on its beneficial and pivotal functions in longevity, cardiovascular diseases, and cancer.[5] In 2016, Li *et al*. reported the association of SIRT6 gene polymorphisms with human longevity.[6] SIRT6 also has been shown to protect against atherosclerosis by reducing foam cell formation through an autophagy-dependent pathway,[7] which is in accordance with our previous research results.

Owing to its significance and controversial role in multiple types of cancer, the clinical relevance of SIRT6 expression to clinicopathological features, prognosis, and cancer progression was noticed by the research community.[8] Downregulation of SIRT6 by miR-34c-5p promotes colon cancer proliferation through inhibiting apoptosis via the JAK2/STAT3 signaling pathway.[9] Other groups have also demonstrated that SIRT6 inhibits colon cancer progression by modulating PTEN/AKT signaling.[10] Moreover, degradation of SIRT6 phosphorylated by AKT1 accelerated tumorigenesis in breast cancer.[11] Moreover, Kugel *et al*. implied that SIRT6 suppresses pancreatic cancer through the control of Lin28b.[12] In addition, it has been shown SIRT6 silencing results in poor prognosis in patients with non-small cell lung cancer (NSCLC)[13-16] and hepatocellular carcinoma (HCC). The latest research showed that SIRT6 inhibited proliferation and invasion in osteosarcoma cells, given that N-cadherinb was a direct target inhibited by SIRT6.[17] For the above reasons, SIRT6 has been regarded as a tumor suppressor gene. Contrarily, an increasing number of studies confirmed that the expression of SIRT6 functions as a powerful oncogene in colon cancer, colon cancer, breast cancer, osteosarcoma, liver cancer, renal cell carcinoma, and HCC. Notably, higher expression of SIRT6 was reported to be significantly correlated with poor prognosis and worse overall survivals.[18] Accumulating evidence suggested that high nuclear SIRT6 expression was associated with poor outcome in breast cancer patients.[19,20] In addition, SIRT6 contributed to migration and invasion of osteosarcoma cells via the ERK1/2/MMP9 pathway.[21] Recently, reports suggested a carcinogenic function of SIRT6 in liver carcinogenesis via BCL2-associated X protein-dependent apoptotic pathway[22,23] and renal cell carcinoma.[24] Therefore, the functional role of SIRT6 in cancer is complicated, with some studies supporting a tumor suppressive role, and others a cancer-promoting role.

Comprehensively, the clinical value of SIRT6 in cancers is complex and requires further investigation. However, up to date, there are still no systematic meta-analyses discussing the role and clinical significance of SIRT6 in cancers. In this manuscript, we performed an updated and more comprehensive meta-analysis of all relevant clinical data in order to gain a complete, exhaustive summary of the prognostic and clinicopathological roles of SIRT6 in various human cancers.

Materials and Methods

Search strategy

PubMed, Web of Science, Embase, and CNKI (China National Knowledge Infrastructure) were systematically searched in March 2019 using the following search terms: "SIRT6" OR "SIRT 6" OR "SIRT6" OR "sirtuin6" OR "sirtuin6" OR "sirtuin-6" OR "SIR2L3" OR "silent mating type information regulation 2 homolog 3" AND "cancer" OR "tumor" OR "neoplasm" OR "carcinoma," combined with "survival" or "prognosis" or "outcome."

Inclusion and exclusion criteria

Studies were eligible and enrolled in our quantitative meta-analysis if they satisfied the following requirements: (1) human studies and patients diagnosed with cancer; (2) the expression of SIRT6 was reported; and (3) detected by immunohistochemistry (IHC). The exclusion criteria included: (1) reviews, letters, conference abstracts, and single case reports; (2) animal or laboratory studies; (3) lack of methodological description; (4) studies without SIRT6 expression data or the IHC results were only presented in figures; (5) the hazard ratio (HRs) and 95% confidence intervals (CIs) of survival indicator related to SIRT6 expression were not available or could not be calculated or extracted indirectly from tables or Kaplan–Meier curves; and (6) duplicate publications or data, or overlapping populations, except for latest research.

Data extraction

Two authors independently searched the databases, excluded the irrelevant studies with double check, and discrepancies were resolved by mutual discussions. The major items of each eligible study included the following: first author, year of publication, study sites, cancer type, number of cases, methods, cutoff definition, information about OS (HR value and follow-up duration), and clinicopathological parameters (cancer/noncancer, differentiation, metastasis, pathological differentiation, tumor node metastasis [TNM], etc.)

Statistical methods

All analyses were conducted using the Cochrane Collaboration Review Manager 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). HRs and the corresponding 95% CIs were combined to evaluate the association between SIRT6 and overall survival (OS). The HRs were indirectly extracted based on Kaplan–Meier curves as previously described by Tierney *et al*.[25] using Engauge Digitizer version 4.1 for survival studies that did not provide the numerical data. Pooled HRs <1 and their 95% CIs did not overlap the invalid line in the forest plot, which suggested a good OS in patients with high expression of SIRT6. For dichotomous data, odds ratios (ORs) and 95% CIs were used to assess the relation between SIRT6 expression and clinical features including lymph node metastasis, pathological differentiation, TNM, tumor stage, tumor size, and gender. Heterogeneity among studies was calculated using both the I^2 test and Q-test, Random-effects model was selected for use when I^2 >50% or $P < 0.10$, otherwise the fixed-effects model was employed. Additionally, the significance of the pooled HR or OR was assessed by the Z test. The potential publication bias was evaluated by creating funnel plots, and was estimated by

Egger's and Begg's tests. $P < 0.05$ was suggested statistically significant and all P values were two tailed.

Results

Eligible studies and characteristics

A search strategy for the included studies was described in Figure 1. A total of 643 articles were found during the initial search. A total of 598 irrelevant record data were eliminated which did not meet the selection criteria by screening the titles and abstracts. Subsequently, we assessed the reserved full-text 43 articles and then ruled out 25 articles for the following criteria: (1) laboratory or cell assay only ($n = 12$); (2) abstract and review ($n = 1$); (3) lack of clinical data or statistical analysis ($n = 6$); (4) SIRT6 was not detected by IHC ($n = 5$); and (5) overlapped data ($n = 1$). Finally, twenty articles were eligible and included in the current meta-analysis.

As summarized in Table 1, the twenty eligible studies were published in between 2014 and 2019, and included a total of 2700 patients from five countries who represented nine cancer types. All the studies used IHC technology to measure the expression level of SIRT6 and 16 studies reported osteosarcoma patients data.

SIRT6 expression and OS in patients with cancers

To investigate the relationship between SIRT6 expression level and OS of 16 studies included 2117 patients, a random-effects model was recommended for calculating the pooled HR with the corresponding 95% CI due to apparent heterogeneity ($I^2 = 83.0\%$). Unfortunately, our meta-analysis failed to conclude a detectable relation between SIRT6 expression and OS in nine types of cancer, with the pooled HR of 1.39 (95% CI = 1.02–2.16, $P = 0.89$) [Figure 2a]. And then, it is necessary to perform the relationship between SIRT6 expression and OS by cancer types to explore the between-study heterogeneity. Cancer type subgroup analysis showed that high SIRT6 expression was associated with worse OS in HCC (HR: 1.49, 95% CI: [1.22, 1.81], $P < 0.0001$, $I^2 = 0\%$), osteosarcoma (HR: 2.05, 95% CI: [1.28, 3.30], $P = 0.003$, $I^2 = 0\%$), and NSCLC (HR: 1.88, 95% CI: [1.02, 3.47], $P = 0.004$, $I^2 = 73\%$). Depending on the data provided in Figure 2b, it was correlated with a better OS in the pooled group of patients with colon cancer (HR: 0.87, 95% CI: [0.04, 1.83], $P = 0.71$, $I^2 = 80\%$) and breast carcinoma (HR: 2.08, 95% CI: [0.76, 5.70], $P = 0.16$, $I^2 = 82\%$).

Correlation of SIRT6 expression with clinicopathological parameters

The impact of SIRT6 expression on clinicopathological parameters of multiple types in cancer patients was assessed by total effect analyses and subgroup analyses according to each pathological feature [Table 2]. We performed an analysis of eight studies contained SIRT6 expression data in cancer/noncancer tissues. The results showed that SIRT6 expression was statistically significantly in noncancer tissues higher than that in cancer tissues (OR = 0.32, 95% CI = 0.13–0.79, $P = 0.01$, random-effects model). Subgroup analyses were also done based on cancer types, and there was a statistically significant difference between SIRT6 positivity/high expression and cancer/noncancer tissues in patients with colon cancer (OR = 0.16, 95% CI = 0.04–0.62, $P = 0.01$, random-effects model) or NSCLC (OR = 0.24, 95% CI = 0.16–0.38, $P < 0.00001$, fixed-effects model), which indicated that the expression of SIRT6 was downregulated in colon cancer and NSCLC tissues as compared with noncancerous tissues.

We then analyzed the correlation between SIRT6 expression and other clinicopathologic features. However, no association was found between SIRT6 expression and lymph node metastasis in cancer patients (OR = 1.24, 95% CI = 0.97–1.59, $P = 0.09$, random-effects model), a further subgroup

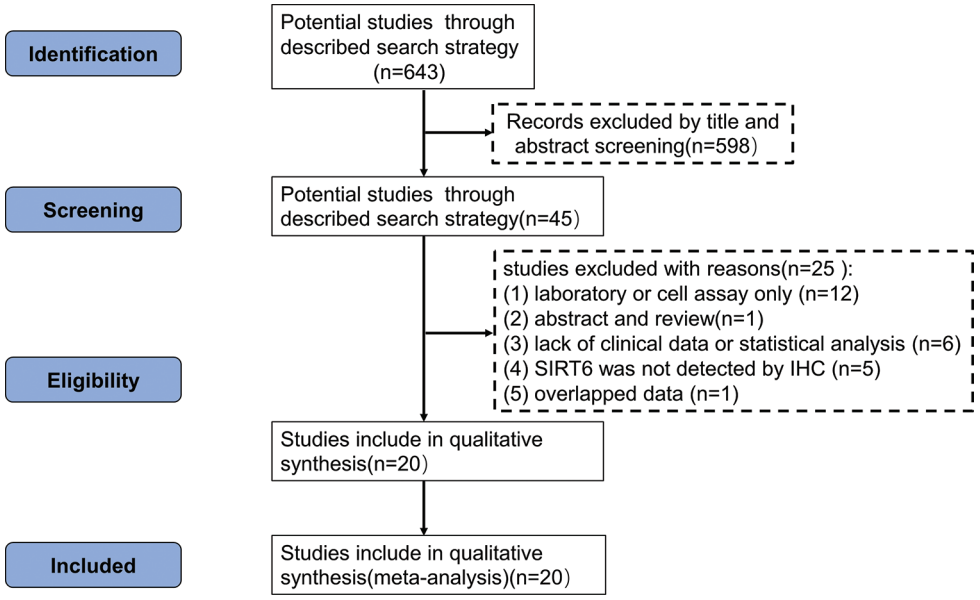

Figure 1: Flow diagram of the identification and selection process for eligible studies

Table 1: Main characteristics of the eligible studies in this meta-analysis

Study[ref.no.]	Year	Country/region	Race	Cancer type	No. of cases	Detection method	Cut off	Outcome
JIA QI *et al*.[8]	2018	China	Asian	Colon cancer	113	IHC	≥3	NA
NING LI *et al*.[9]	2018	China	Asian	Colon cancer	100	IHC	≥6	OS
Chang hui Geng *et al*.[18]	2017	China	Asian	Colon cancer	196	IHC	1+	NA
Junhong Tian *et al*.[10]	2018	China	Asian	Colon cancer	90	IHC	>0	OS
Angela Rizzo *et al*.[26]	2017	Italy	latium	Colon cancer	185	IHC	2+	NA
Jun Sang Bae *et al*.[19]	2016	Korea	Asian	Breast cancer	142	IHC	≥6	OS
Mattaka Khongkow *et al*.[20]	2013	British	Caucasian	Breast cancer	118	IHC	>0	OS
Umadevi Thirumurthi *et al*.[11]	2014	USA	Caucasian	Breast cancer	312	IHC	3+	OS
Bojin Zhu *et al*.[13]	2018	China	Asian	NSCLC	86	IHC	3+	OS
TAO CHEN *et al*.[14]	2016	China	Asian	NSCLC	122	IHC	3+	OS
YOKO AZUMA, MD *et al*.[15]	2015	Japan	Asian	NSCLC	98	IHC	≥20%	OS
Lihong Bai *et al*.[16]	2015	China	Asian	NSCLC	174	IHC	> 6	OS
Hang Lin *et al*.[21]	2017	China	Asian	Osteosarcoma	60	IHC	1+	OS
YI GAO *et al*.[17]	2019	China	Asian	Osteosarcoma	112	IHC	3+	OS
Seong Uk Jeh *et al*.[24]	2017	Korea	Asian	Renal cell carcinoma	119	IHC	≥4	OS
Nan Huang *et al*.[28]	2017	China	Asian	Esophageal cancer	89	IHC	2+	NA
Sita Kugel *et al*.[12]	2016	USA	Caucasian	Pancreatic cancer	120	IHC	2+	OS
Long-Kuan Ran *et al*.[22]	2016	China	Asian	Hepatocellular Carcinoma	53	IHC	3+	OS
Shi Song *et al*.[23]	2018	China	Asian	Hepatocellular Carcinoma	343	IHC	1+	OS
JIANMEI ZHOU *et al*.[27]	2017	China	Asian	Gastric cancer	68	IHC	3+	OS

analysis according to cancer type showed that elevated SIRT6 expression predicted a statistically significantly lymph node metastasis in patients with breast carcinoma (OR = 1.76, 95% CI = 1.17–2.66, $P = 0.007$, fixed-effects model), but not correlated with the colon cancer (OR = 0.13, 95% CI = 0.73–1.74, $P = 0.58$, random-effects model). Next, when we restricted the analysis to three cancer studies related to metastasis and SIRT6 expression, no association of SIRT6 expression with metastasis was evident, which resulted in an OR of 0.86 with a 95% CI of 0.17–4.36 used a random-effects model. In addition, we applied a random-effects model ($I^2 = 69\%$, $P = 0.004$) to analyze the associations between SIRT6 expression and distant metastasis of another nine included studies, yielding a result without statistical significant difference (OR = 1.88, 95% CI = 0.55–6.45, $P = 0.32$).

Moreover, SIRT6 expression is closely related to the pathological differentiation stage of cancer patients, indicating that compared with those with negative SIRT6 expression, patients with positive SIRT6 expression have a weaker degree of cancer differentiation (OR = 1.53, 95% CI = 1.08–2.18, $P = 0.02$, fixed-effects model). However, no correlation was found in the subgroup analysis of colon cancer (OR = 1.37, 95% CI = 0.86–2.19, $P = 0.18$, fixed-effects model). The combined analysis of the studies that covered all tumor stages (I–IV) showed no correlation of high SIRT6 expression with tumor stages (OR = 2.36, 95% CI = 1.70–3.28, $P = 0.59$, random-effects model), whereas a contrary result was observed in the subgroup analyses of NSCLC patients (OR = 0.40, 95% CI = 0.20–0.80, $P = 0.01$, fixed-effects model), which suggested high SIRT6 expression had stronger efficacy in III/IV tumor stages than I/II tumor stages.

As to TNM, high SIRT6 expression was distinct associated with TNM in colon cancer patients (OR = 2.41, 95% CI = 1.38–4.20, $P = 0.002$, fixed-effects model).

Besides the above clinicopathological parameters mentioned, there was no statistically significant correlation between SIRT6 expression and tumor size (OR = 1.44, 95% CI = 0.60–3.43, $P = 0.42$, random-effects model), gender (OR = 0.99, 95% CI = 0.78–1.27, $P = 0.9$, fixed-effects model), estrogen receptor (ER) (OR = 1.41, 95% CI = 0.95–2.10, $P = 0.09$, random-effects model), and progesterone receptor (PR) (OR = 0.71, 95% CI = 0.29–1.69, $P = 0.95$, random-effects model) in total or subgroup analyses.

Publication bias

Begg's funnel plot was performed to evaluate the publication bias of the literature [Figure 3]. The funnel plot did not reveal obvious evidence of publication bias in the overall meta-analysis of all articles.

Discussion

The SIRT family comprises seven members in mammals, and was widely involved in several biological processes. As a nuclear protein like SIRT1, it has been generally accepted that SIRT6 served versatile roles in human cancer-associated

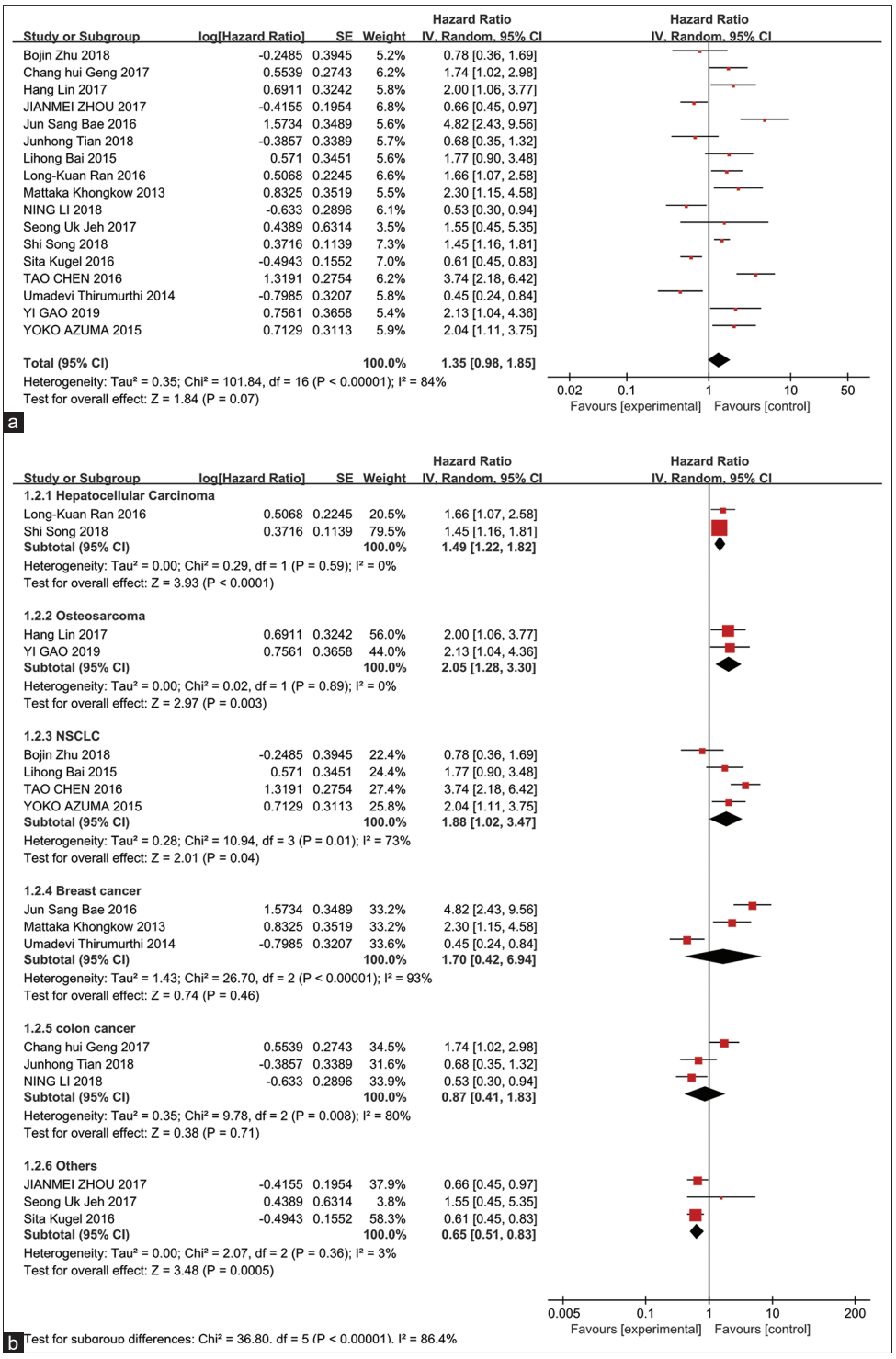

Figure 2: (a and b) Forest plot for the association between SIRT6 expression and overall survival of patients with cancer

functions, including transcription, DNA repair,[26] and gene transcription repression. But, what's striking and inconclusive is that whether SIRT6 is a tumor suppressor[27] or an oncogenic.[28] Therefore, we conducted a meta-analysis focused on the relationship between SIRT6 expression and OS of cancers, patient clinicopathological outcomes including OS of cancer patients, cancer/noncancer tissues, lymph node metastasis, TNM stage, lymph node metastasis, distant metastasis, differentiation, tumor stage, tumor size, and gender.

The current systematic results of our overall analysis pooled the survival data of 16 studies that randomly assigned 2117 patients with varying degrees and types of cancer and found no correlation between SIRT6 overexpression and OS in various cancer patients (HR = 1.05, 95% CI = 0.51–

Table 2: Correlations of clinicopathological parameters with SIRT6 expression

Parameters	Total effect or subgroup analyses	Studies [ref. no.]	Heterogeneity		Model	Outcomes	
			I2%	*P* value		OR (95% CI)	*P* value
Cancer/non-cancer tissues	Total	[8,9,10,13,14, 18,22,24]	93	<0.00001	Random	0.32[0.13,0.79]	0.01
	colon cancer	[8,9,10]	88	0.002	Random	0.16[0.04,0.62]	0.008
	NSCLC	[13,14]	0	0.77	Fixed	0.24[0.16,0.38]	<0.00001
	Others	[22,24,28]	95	<0.00001	Random	0.74[0.14,4.02]	0.73
Lymph node Metastasis	Total	[8,10,13,15,18, 19,20,28,27]	77	<0.0001	Random	1.24[0.97,1.59]	0.09
	colon cancer	[8,10,18]	91	<0.0001	Random	0.13[0.73,1.74]	0.58
	Breast Carcinoma	[19,20]	0	0.58	Fixed	1.76[1.17,2.66]	0.007
	NSCLC	[13,14]	86	0.007	Random	0.80[0.14,4.65]	0.81
	Others	[23,28]	0	0.91	Fixed	0.83[0.42,1.68]	0.61
(metastasis+ vs. metastasis-)	Total	[17,21,24]	89	<0.0001	Random	0.86 [0.17,4.36]	0.86
Distant metastasis (Yes vs. No)	Total	[8,19,27]	69	0.04	Random	1.88[0.55,6.45]	0.32
Differentiation (poorly vs. moderate/well differentiated)	Total	[8,10,16,18, 28,27]	41	0.13	Fixed	1.53[1.08,2.18]	0.02
	colon cancer	[8,10,18]	47	0.15	Fixed	1.37[0.86,2.19]	0.18
	Others	[16,27,28]	55	0.11	Fixed	1.76[1.03,3.01]	0.04
Tumor stage (I/II vs. III/IV)	Total	[9,15,16,19,20, 24]	93	<0.00001	Random	2.36[1.70,3.28]	0.59
	Breast Carcinoma	[19,20]	95	<0.00001	Random	4.21[0.12,148.78]	0.43
	NSCLC	[15,16]	0	0.95	Fixed	0.40[0.20,0.80]	0.01
	Others	[9,24]	68	0.08	Random	2.37[0.17,32.99]	0.52
TNM (I/II vs. III/IV)	Total	[8,9,10,13,19, 27,28]	67	0.006	Random	1.84[0.93,3.60]	0.08
	colon cancer	[8,9,10]	0	0.5	Fixed	2.41[1.38,4.20]	0.002
	Others	[13,19,27,28]	79	0.003	Random	1.27[0.78,2.05]	0.34
Tumor size (≥3cm vs. <3cm)	Total	[8,18,22]	72	0.03	Random	1.44[0.60,3.43]	0.42
Gender (male vs. female)	Total	[8,9,18,10,13,15, 16,17,21,22,27,28]	10	0.34	Fixed	0.99[0.78,1.27]	0.9
	colon cancer	[8,9,10,18]	0	0.74	Fixed	0.81[0.56,1.18]	0.27
	NSCLC	[13,15,16]	0	0.57	Fixed	1.23[0.76,1.98]	0.40
	Osteosarcoma	[17,21]	0	0.82	Fixed	1.62[0.86,3.02]	0.14
	Others	[22,27,28]	61	0.08	Random	0.64[0.21,1.98]	0.44
ER (positive vs. negative)	Total	[19,20]	95	<0.0001	Random	1.41[0.95,2.10]	0.09
PR (positive vs. negative)	Total	[19,20]	76	0.04	Random	0.71[0.29,1.69]	0.43

OR: Odds ratio, CI: Confidence interval, ER: Estrogen receptor, PR: Progesterone receptor

2.16, $P = 0.89$). Then, we have attempted a subgroup analysis grouped by cancer types, which indicated that overexpression of SIRT6 was closely associated with poor overall survival in HCC (HR = 0.56, 95% CI = 0.42–0.74, $P < 0.0001$), osteosarcoma (HR = 0.62, 95% CI = 0.43–0.89, $P < 0.0001$), and NSCLC patients, indicating a tumorigenesis role of SIRT6 in HCC, osteosarcoma, and NSCLC. Previously, decreased expression of SIRT6 was closely related to poor prognosis and unfavorable clinical features of GC patients.[27] Moreover, the up-regulation of SIRT6 is related to the clinicopathological characteristics and poor prognosis of patients with osteosarcoma. The possible reason is that SIRT6 negatively regulates (matrix metallopeptidase 9) MMP9 levels and ERK1/2 phosphorylation.[29] Additionally, as Song *et al*. reported,[23] the patients with high levels of SIRT6 induced by miR-125b had poor 5-year overall survival rate in human HCC. It has also been reported that SIRT6 was upregulated and promoted cancer aggressiveness of papillary thyroid cancer, cellular senescence in HCC, and HCC via numerous mechanisms.[30-32] Notably, it is indicated that patients with high expression of SIRT6 had more aggressive cancer and shorter overall survival, and the author also revealed that the reason was that SIRT6 was mainly distributed in the cytoplasm of NSCLC. These association analyses further strengthened the meta-analysis results in our present study that high elevated SIRT6 expression predicted worse OS in HCC, osteosarcoma, and NSCLC. On the other hand, it should be noted that there were many opposite clinical outcomes regarding the relationship between SIRT6 and survival in cancer patients. For instance, Bai *et al*. showed that the cumulative survival

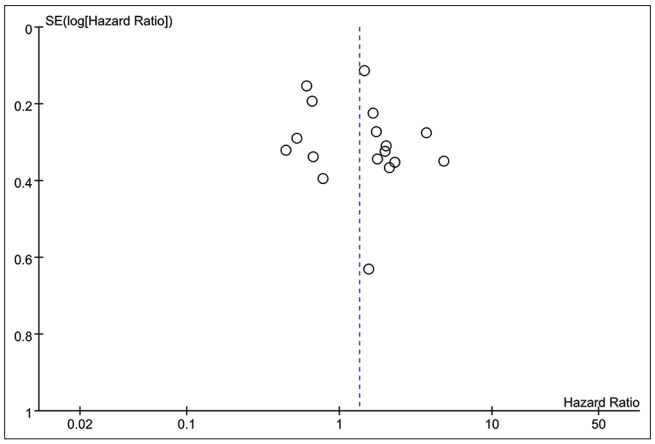

Figure 3: Funnel plot for the 17 studies included in this meta-analysis regarding SIRT6 expression and overall survival

rate of NSCLC patients with high SIRT6-expressing was lower than that with SIRT6-expressing patients.[16] Several preliminary studies have also provided that the survival time of SIRT6-positive patients with NSCLC was significantly longer than that of SIRT6-negative patients, and the mechanism is possibly by promoting apoptosis or autophagy,[13,15] which coincided with our previous research on the relationship between SIRT6 and autophagy. Moreover, decreased expression of SIRT6 contributed to tumor cell growth and was intimately correlated with the poor prognosis of ovarian cancer, gastric cancer, and glioma.[33,34] Here, regarding the opposite results of studies, we concluded that SIRT6 accelerated cancer progression and function as an oncogene with poor overall survival rate in HCC, osteosarcoma, and NSCLC. Unfortunately, the present meta-analysis failed to validate the association between SIRT6 and overall survival rate in breast carcinoma or colon cancer, suggesting that the function of SIRT6 may be diverse depending on the cell type or tumor type. However, it has been preliminary and widely confirmed that aberrant expression of SIRT6 is a novel biomarker affecting tumor survival rates in several cancers.[13,14]

We further revealed that SIRT6 expression was remarkably decreased in cancer tissues as compared with adjacent tissues ($P = 0.01$), suggesting that the expression of SIRT6 in tissues may possibly account as potential diagnostic biomarker for cancers. A subgroup analysis also showed that SIRT6 expression was statistically significantly increased in colon cancer or NSCLC ($P < 0.05$), which was supported by numerous studies *in vitro* and *in vivo* on animals and human cells. For example, Lin *et al*.[29] validated reduced protein expression SIRT6 in colon cancer tissues as compared with that in adjacent normal tissues, and Rizzo and Junhong Tian *et al*. confirmed this point. Therefore, previous studies combined[22,34-36] with our results suggest that aberrant expression of SIRT6 play a fateful role in the process of various types of cancers.

Next, according to the results of Zhu *et al*.,[13] the rate of positive SIRT6 samples was significantly correlated with the degree of differentiation, TNM stage, and lymph node metastasis. We concluded SIRT6 expression and clinicopathological parameters in cancer patients and found that SIRT6 overexpression was associated with lymph node metastasis, differentiation, tumor stage, and TNM stage. Yet, no correlation was obtained between SIRT6 expression and metastasis, distant metastasis, tumor size, depth of tumor invasion, gender, ER, or PR. We found that high SIRT6 expression was associated with poor differentiation of cancer patients in total effect analyses ($P = 0.02$). At the same time, subgroup analysis results showed a statistically significant association between SIRT6 expression and lymph node metastasis in breast carcinoma (OR = 1.76, 95% CI = 1.17–2.66, $P = 0.007$). For the tumor stage and TNM stage, we then further demonstrated that overexpressed SIRT6 was specifically associated with a higher tumor stage in NSCLC (OR = 0.40, 95% CI = 0.20–0.80, $P = 0.01$) and TNM stage in colon cancers (OR = 2.41, 95% CI = 1.38–4.20 $P = 0.002$), supported by the subgroup analysis. Consistently, Zhou *et al*. reported that decreased SIRT6 was significantly associated with adverse clinical parameters such as tumor size, differentiation, TNM stage, and rate of overall survival.[27] Moreover, studies on cancer showed SIRT6 exerted a positive correlation with the differentiation status due to SIRT6-repressed cell migration and invasion, suggesting that the potential mechanism may be related to the regulation of SIRT6 in apoptosis.[9] In addition, results from NSCLC-related research[11,12] revealed that SIRT6 mRNA and protein levels were shown to be gradually decreased with tumor stage mainly affected by proliferation and apoptosis in patients. It is noteworthy that previous studies demonstrated SIRT6 overexpression-induced apoptosis in tumor cells.[36,37] Nevertheless, besides clinical characteristics, no statistically significant correlation was obtained between SIRT6 expression and metastasis (OR = 0.86, 95% CI = 0.17–4.36, $P = 0.86$) or distant metastasis (OR = 1.88, 95% CI = 0.55–6.45, $P = 0.32$). The above observation together with the present study results revealed that SIRT6 can serve as a potential therapeutic target and prognostic biomarker to predict the prognosis of cancer patients.

However, the multiple function of SIRT6 in cancer was still under battle. Under most of the circumstances, SIRT6 acted as a tumor suppressor in pancreatic cancer, teratocarcinomas, breast cancer, and SIRT6 depletion, which markedly promoted tumor cell growth of ovarian cancer, gastric cancer, and glioma. The present study demonstrated that SIRT6 plays a role as a tumor suppressor gene in pancreatic cancer by controlling lin-28 homologous protein B[12] and promoted the production and migration of pancreatic cancer cytokines by regulating the Ca^{2+} response. In addition, the studies of Kugel S and Sebastián C revealed that SIRT6, as a tumor suppressor gene, is based on its regulation of aerobic glycolysis and cancer-related point mutations in tumor cells. More research found that SIRT6 significantly inhibited the proliferation of NSCLC by acting on Twist1.[38,39] Inversely, some researchers recently have found opposite findings. Cancer progression in lung cancer, prostate cancer, and skin cancer also need SIRT6 for survival,

proliferation of invasion, and repairing disastrous genomic events, suggesting that SIRT6 genes may exacerbate cancer progression and drive the cancer cells to more advanced stages. A recent study has demonstrated that SIRT6 is upregulated and contributed to the progression of thyroid papillary carcinoma and HCC through multiple mechanisms. Furthermore, it has been reported that SIRT6 remarkably suppresses HCC cell proliferation via ERK signaling pathway. Comprehensively, these studies combined our results contributed to revealing of the prevention and diagnosis significance of SIRT6 in many types of human cancer, and large-scale and high-quality studies are needed to confirm the effect of SIRT6 on cancer progression.

It should be noted that several limitations remained in our meta-analysis. First, except Asian patients, there are only three studies focused on Caucasian patients and one research with Latium patients, which inevitably made it difficult to come to a definite conclusion on the clinical value of SIRT6 for Caucasian, Latium, or other ethnic cancer patients; second, HR values of some studies are obtained from Kaplan–Meier survival curve rather than given data, which may lead to inaccurate results; third, the amount of studies in the subgroup analysis maybe too small to yield effective results about the association between SIRT6 and clinicopathological characteristics in some types of cancer, and more pathological samples are needed to confirm these conclusions further; fourth, other clinicopathology and individual condition that may contribute to the integrity and comprehensiveness of our analysis, such as tumor infiltration, therapeutic regimen, pathological grading, recurrence, body mass index, and mean age. We barely succeed in analyzing the relationship between SIRT6 expression and these pathological indicators due to the lack of enough data; and fifth, although S6 is defined as a nucleoprotein, it may still be present in the cytoplasm. Some included studies performed localization analysis of SIRT6 expression, while others did not, which may reduce the credibility of our study.

Conclusion

This is the first meta-analysis study with pragmatic value that revealed the correlation between SIRT6 and clinical values in different types of cancer such as OS or clinicopathological parameters. Our meta-analysis showed that high SIRT6 expression was clearly associated with worse OS in various cancer patients, including HCC, osteosarcoma, and NSCLC. Moreover, we indicated that SIRT6 expression was remarkably decreased in cancer tissues as compared with adjacent tissues. Besides, elevated expression of SIRT6 predicts higher lymph node metastasis, differentiation, tumor stage, and TNM stage in certain type of cancers, but not metastasis, distant metastasis, tumor size, depth of tumor invasion, gender, ER, or PR. Our study indicates that SIRT6 gene expression might serve as a potential therapeutic target and prognostic marker in various cancers.

Acknowledgments

This work was supported by the major provincial scientific research projects in Guangdong universities (No. 2018KQNCX367).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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