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ORIGINAL RESEARCH

Prognostic and clinicopathological value of SIRT3 expression in various cancers: a systematic review and meta-analysis

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Background: Several studies have explored the prognostic value of sirtuin 3 (SIRT3) in various cancers, but obtained inconsistent results. The current systematic review and meta-analysis was conducted to investigate the association between SIRT3 expression and prognosis in various cancers.

Methods: PubMed, Embase, Web of Science and the Cochrane Library were comprehensively retrieved by the end of September 29, 2017. All the relevant studies were checked and included in the meta-analysis if they met the inclusion criteria.

Results: A total of 17 studies involving 2,865 patients were included in the systematic review and meta-analysis. The results indicated that SIRT3 expression was not significantly associated with overall survival (OS) (hazard ratio [HR]=0.87, 95% CI=0.59–1.29, P=0.50) and disease-free survival (HR=0.87, 95% CI=0.57–1.31, P=0.50) in total various cancers. However, significant relationship between SIRT3 expression and OS in specific cancers was detected, including chronic lymphocytic leukemia (CLL) (HR=0.48, 95% CI=0.26–0.89, P=0.019), hepatocellular carcinoma (HCC) (HR=0.56, 95% CI=0.42–0.74, P<0.001), pancreatic carcinoma (PC) (HR=0.55, 95% CI=0.30–1.00, P=0.049), renal cell carcinoma (RCC) (HR=0.13, 95% CI=0.02–0.98, P=0.048), breast cancer (BC) (HR=2.53, 95% CI=1.83–3.67, P<0.001), colon cancer (CC) (HR=1.87, 95% CI=1.12–3.26, P=0.022) and non-small-cell lung cancer (NSCLC) (HR=2.20, 95% CI=1.38–3.50, P=0.001). Moreover, SIRT3 expression was obviously associated with tumor size (odds ratio [OR]=1.41, 95% CI=1.02–1.94, P=0.04), tumor differentiation (OR=1.52, 95% CI=1.08–2.16, P=0.02) and clinical stage (OR=2.07, 95% CI=1.23–3.46, P=0.01) in HCC.

Conclusion: SIRT3 was distinctly related to the OS in specific cancers. SIRT3 was an unfavorable prognostic factor in BC, CC and NSCLC; however, it was also a favorable prognostic factor in CLL, HCC, PC and RCC, especially in HCC.

Keywords: SIRT3, cancer, prognostic, clinicopathological, overall survival, meta-analysis

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Introduction

Cancer is a major public health problem and the second leading cause of death in the US. It is estimated that 1,688,780 Americans will be newly diagnosed with cancers and 600,920 Americans will die from cancers in 2017.[1] Despite enormous progress has been made in the diagnosis and therapy, the ending of most cancer patients remains disappointing. In consideration of the current situation, the prognostic factors, able to predict the clinical outcomes and guide the therapy, are drawing a majority of researcher's attention.[2–9]

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Sirtuins, a family of NAD^+-dependent deacetylases, regulate multiple signaling pathways' cellular biology including cellular proliferation, metabolism, stress reaction and oxidation resistance.[10–14] Seven isoforms of sirtuins (SIRT1–7) have been described in mammals. Among them, SIRT1 and SIRT2 are located preponderantly in the nucleus and cytosol, respectively. The remaining 3 sirtuins, SIRT3, SIRT4 and SIRT5, are located in the mitochondria.[15] Among this deacetylase family, SIRT3 is of particular interest. SIRT3 is synthesized as a 44 kDa peptide with an N-terminal sequence, which is the primary mitochondrial deacetylase and modulates the acetylation level of multiple mitochondrial proteins.[16] SIRT3 plays a critical role in various cellular activities, including cell proliferation, apoptosis and stress reaction.[15,17] Owing to the important role of SIRT3 in cellular pathways, previous studies have testified that SIRT3 participated in the development of various diseases, such as diabetes[18] and myocardial injury.[19] In recent years, SIRT3 attracted researchers' attention on account of its dual role in tumorigenesis.[10,17,20,21] A great number of studies have been conducted to investigate the association between SIRT3 and tumorigenesis of various cancers, including hepatocellular carcinoma (HCC),[22] lung cancer,[23] gastric cancer (GC)[24] and breast cancer (BC).[25] However, the results were controversial. Zhang et al[22] collected 248 primary HCC specimens and found the patients with high SIRT3 expression tended to have longer overall survival (OS) compared to patients with low SIRT3 expression (hazard ratio [HR]=0.56, 95% CI=0.34–0.90, P=0.016). Similarly, Jeh et al[26] validated that renal cell carcinoma (RCC) patients with high SIRT3 expression had longer OS (HR=0.13, 95% CI=0.02–0.94, P=0.047). However, different observations were made in other studies. He et al[27] performed a study comprising 308 patients with BC to explore the correlation between SIRT3 expression and prognosis and unexpectedly found that BC patients with high SIRT3 expression possessed shorter OS compared to patients with low SIRT3 expression, which indicated that SIRT3 might reduce OS and be a unfavorable prognostic biomarker (HR=2.53, 95% CI=1.83–3.67, $P<0.001$). Coincidentally, the results of Yang et al[39] study reaffirmed the conclusion that SIRT3 might be a tumor promoter and could reduce the prognosis of cancer patients (HR=2.20, 95% CI=1.38–3.50, P=0.001). In view of the abovementioned controversial results, the dispute on the prognostic value of SIRT3 in various cancers spontaneously arises.

In view of the discrepancy, the current systematic review and meta-analysis was conducted to investigate the association between SIRT3 expression and prognosis in various cancers.

Materials and methods

Literature search strategy

PubMed, Embase, Web of Science and the Cochrane Library were comprehensively searched by the end of September 29, 2017. The search terms were as follows: "SIRT3", "silent mating type information regulation 2 homolog 3", "SIR2L3" OR "sirtuin 3" combining with "tumor", "carcinoma" OR "cancer". The references of the retrieved articles were also checked to avoid missing relevant studies.

Inclusion and exclusion criteria

The study would be included in this systematic review and meta-analysis if it met all the following criteria: 1) observational studies with cohorts; 2) investigating the relationship between SIRT3 expression and prognosis in various cancers; 3) covering treatment-free survival (TFS), recurrence-free survival (RFS), OS, disease-free survival (DFS), time to recurrence (TTR), cancer-specific survival (CSS) or clinicopathological parameters and 4) with full text. The exclusion criteria were as follows: duplicate publications, reviews, case reports, animal experiments, cell experiments and inefficient data.

Data extraction and quality assessment

An extraction template was designed in advance, and then 2 reviewers extracted the following data independently: the family name of the first author, publication year, country, ethnicity, sample size, the percentage of the male, the percentage of the patients with high SIRT3 expression level, cutoff value, clinical outcomes, cancer type and analysis model and information needed to evaluate the quality of each study. Any discrepancies during study selection and data extraction were resolved by discussion with the third reviewer. The HRs along with 95% CI obtained directly from published articles were integrated in the meta-analysis according to the study conducted by Tierney et al.[28] Two reviewers evaluated all the included studies independently after reading the full text of each study. The Newcastle–Ottawa scale (NOS) was utilized to assess the quality of the included studies.[29]

Statistical analysis

All pooled analyses were conducted using Review Manager 5.3 (Cochrane Collaboration; UK) and STATA 12.0 software (StataCorp LP, College Station, TX, USA). For prognostic index, eg, OS, HR and corresponding 95% CI were used as the summary measure. For clinical parameters, dichotomous, the odds ratio (OR) and corresponding 95% CI were used to analyze the results. Chi-square test and I^2 statistic were

utilized to evaluate the interstudy heterogeneity. I^2 equal to or less than 50% indicated that the heterogeneity was not statistically obvious, and the fixed-effect model was employed. If not, the random-effect model was applied. Begg's test and Egger's test conducted by STATA 12.0 were applied to assess the publication bias among the included studies. Sensitivity analysis performed by STATA 12.0 was applied to confirm the robustness of the results.

Results

Selection and characteristics of the included studies

This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for reporting systemic review and meta-analysis.[30] The process of literature search is shown in Figure 1. In total, 798 papers were initially retrieved. Then, 578 papers remained when 220 duplicates were removed. Regarding the remaining 578 papers, titles or abstracts of them were screened and 532 were directly excluded for not concerning this topic. The full text of the remaining 46 papers was carefully read, and 29 papers were abandoned for the following reasons: 22 papers not focusing on this topic and 7 papers for inefficient data. Ultimately, 17 studies involving 2,865 patients were included into this systematic review and meta-analysis.[22–27,31–41]

The characteristics of included studies are presented in Table 1. Throughout these studies, 15 and 2 studies were carried out in Asian people[22–24,26,27,31–34,36–41] and Caucasian people,[25,35] respectively. Additionally, the sample size varied a lot among the included studies, from 30 to 350. In total, 15 studies reported the percentage of male, from 0% to 88.71%.[22–27,32–34,36–41] Moreover, 15 studies illustrated the percentage of patients with high SIRT3 expression, varying from 25.81% to 60.00%.[22–27,31–34,36–40] With respect to prognostic outcomes, 14 studies reported clinicopathological parameters,[22,23,25–27,31–34,36–40] 11 studies covered OS,[22,24,27,31–33,35–37,39,41] 1 covered CSS,[26] 2 reported DFS,[24,27] 1 covered RFS,[22] 1 reported TFS and 1 covered TTR.[36] Furthermore, as for cancer type, 9 cancers were investigated, including chronic lymphocytic leukemia (CLL),[35] HCC,[22,40] esophageal cancer (EC),[37,41] GC,[31,38] BC,[25,27] colon cancer (CC),[33] pancreatic carcinoma (PC),[32] RCC[26] and non-small-cell lung cancer (NSCLC).[23,39] In terms of analysis model, OS was analyzed using multivariate analysis in 10 studies[22,26,27,31–33,36,37,39,41] and using univariate analysis in 2 studies.[24,35] NOS used for evaluating quality of included studies varied from 5 to 8.

Meta-analysis of OS

A total of 11 studies covered the OS and 1 study presented CSS; hence, 12 studies containing 2,352 patients were

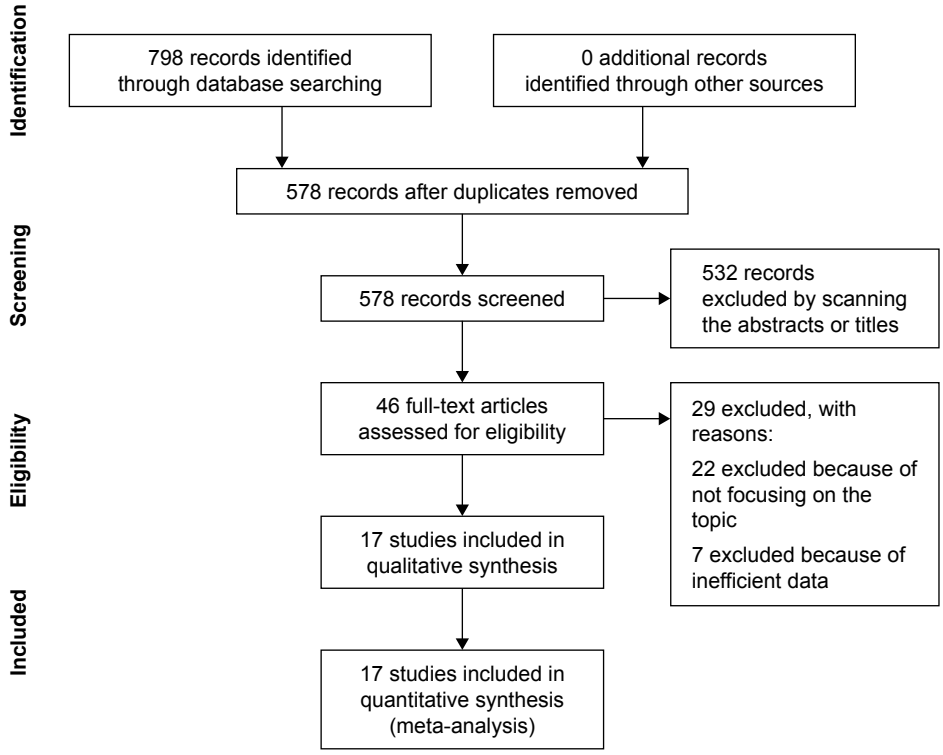

Figure 1 Flow diagram of study selection process.

Table 1 Characteristics of the included studies

Study	Country	Ethnicity	Sample size (n)	Male (%)	High SIRT3 (%)	Cutoff value	Outcome	Cancer type	Analysis	NOS
Van Damme et al[35]	Belgium	Caucasian	200	NA	NA	NA	TFS, OS	CLL	U	5
Zhang et al[22]	China	Asian	248	220 (88.71)	81 (32.66)	ROC ≥2.5	RFS, OS, CP	HCC	M	7
Zhang et al[40]	China	Asian	30	21 (70.00)	18 (60.00)	1+	CP	HCC	NA	6
Zhao et al[41]	China	Asian	94	66 (70.21)	NA	NA	OS	EC	M	5
Huang et al[31]	Taiwan	Asian	221	NA	129 (58.37)	1+	OS, CP	GC	M	7
Desouki et al[25]	USA	Caucasian	186	0 (0.00)	48 (25.81)	≥1%	CP	BC	NA	6
He et al[27]	China	Asian	308	0 (0.00)	160 (51.95)	IRS >6	DFS, OS, CP	BC	M	7
Liu et al[33]	China	Asian	127	50 (39.37)	71 (55.91)	IRS >6	OS, CP	CC	M	8
Yan et al[37]	China	Asian	252	182 (72.22)	132 (52.38)	IRS >6	OS, CP	EC	M	7
Yang et al[38]	China	Asian	65	52 (80.00)	21 (32.31)	HS >10%	CP	GC	NA	6
Wang et al[36]	China	Asian	342	290 (84.80)	194 (56.73)	≥5%	TTR, OS, CP	HCC	M	8
Hur et al[24]	Korea	Asian	350	240 (68.57)	142 (40.57)	IHC score ≤6	DFS, OS	GC	U	6
Song et al[34]	China	Asian	60	50 (83.33)	16 (26.67)	NA	CP	HCC	NA	6
Huang et al[32]	China	Asian	79	54 (68.35)	31 (39.24)	Negative/ positive	OS, CP	PC	M	7
Jeh et al[26]	Korea	Asian	102	74 (72.50)	54 (52.94)	Score ≥4	CSS, CP	RCC	M	7
Xiong et al[23]	China	Asian	70	61 (87.14)	42 (60.00)	NA	CP	NSCLC	NA	6
Yang et al[39]	China	Asian	131	73 (55.72)	77 (58.78)	Score ≥4	OS, CP	NSCLC	M	6

Abbreviations: BC, breast cancer; CC, colon cancer; CLL, chronic lymphocytic leukemia; CP, clinical parameters; CSS, cancer-specific survival; DFS, disease-free survival; EC, esophageal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; IRS, immunoreactivity scores; M, multivariate analysis; NA, not available; NOS, Newcastle–Ottawa Scale; NSCLC, non-small-cell lung cancer; OS, overall survival; PC, pancreatic carcinoma; RCC, renal cell carcinoma; RFS, recurrence-free survival; ROC, receiver-operator characteristic; SIRT3, sirtuin 3; TFS, treatment-free survival; TTR, time to recurrence; U, univariate analysis.

involved in the meta-analysis of OS. As shown in Figure 2, random-effect model was used for the evident heterogeneity (I^2=89%). The results indicated that the SIRT3 expression was not significantly associated with OS (HR=0.87, 95% CI=0.59–1.29, P=0.50). The sensitivity analysis conducted by STATA 12.0 confirmed the robustness of the results (Figure 3). Moreover, as shown in Figure 4, no obvious publication bias was detected among included studies based on the results of Begg's test (P=0.945) and Egger's test (P=0.344).

In view of the distinct heterogeneity of OS, the subgroup analysis was conducted to further explore the relationship between SIRT3 expression and various cancers. As shown in Table 2, the subgroup analyses were implemented based on analysis model, ethnicity, sample size and cancer type. Regarding analysis model, no statistically evident correlation was detected between SIRT3 expression neither when using multivariate analysis model (P=0.657) nor when using univariate analysis model (P=0.404). Similarly, there was no obvious relationship between SIRT3 expression and OS in cancer patients whether the sample size was greater (P=0.526) or less than 200 (P=0.698). Regarding the ethnicity, the results presented that patients with high SIRT3 expression might have obviously longer OS compared to patients with low SIRT3 expression in Caucasian (P=0.019); however, no relationship between SIRT3 expression and OS was observed in Asian (P=0.685). Furthermore, the subgroup analyses classified by cancer type validated that high SIRT3 expression was a favorable prognostic factor in patients with CLL (P=0.019), HCC (P<0.001), PC (P=0.049) and RCC (P=0.048). Nevertheless, the results also indicated that high SIRT3 expression was also an unfavorable prognostic factor in BC (P<0.001), CC (P=0.022) and NSCLC (P=0.001). In addition, there was no significant association between SIRT3 expression and OS in patients with EC (P=0.806) and GC (P=0.347).

Meta-analysis of DFS

Among the 17 studies, 2 reported DFS, 1 covered RFS, 1 reported TFS and 1 covered TTR, and all these 5 studies

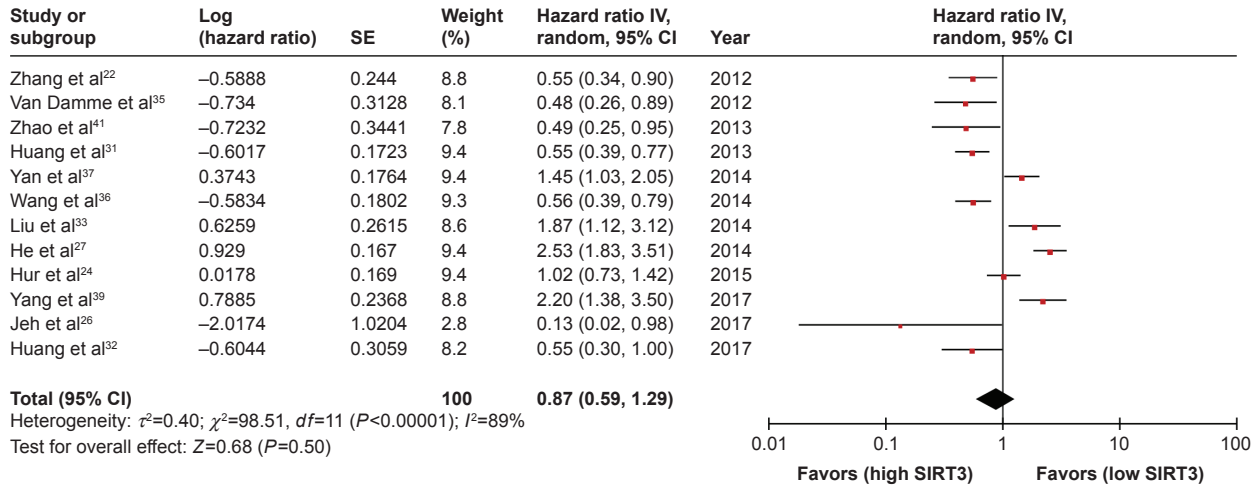

Figure 2 Meta-analysis of OS.
Abbreviations: OS, overall survival; SE, standard error; SIRT3, sirtuin 3.

were integrated into the meta-analysis of DFS. As shown in Figure 5, the random-effect model was used for the distinct heterogeneity (I^2=83%). The results demonstrated that there was no relationship between SIRT3 expression and DFS in patients with various cancers (HR=0.87, 95% CI=0.57–1.31, *P*=0.50). The sensitivity analysis tested the robustness of the results (Figure 6). As shown in Figure 7, there was no obvious publication bias among included studies based on the results of Begg's test (*P*=1.000) and Egger's test (*P*=0.901).

Meta-analysis of clinicopathological parameters

Among the included studies, 14 studies reported data about the relationship between SIRT3 expression and clinicopathological parameters, and the main clinicopathological

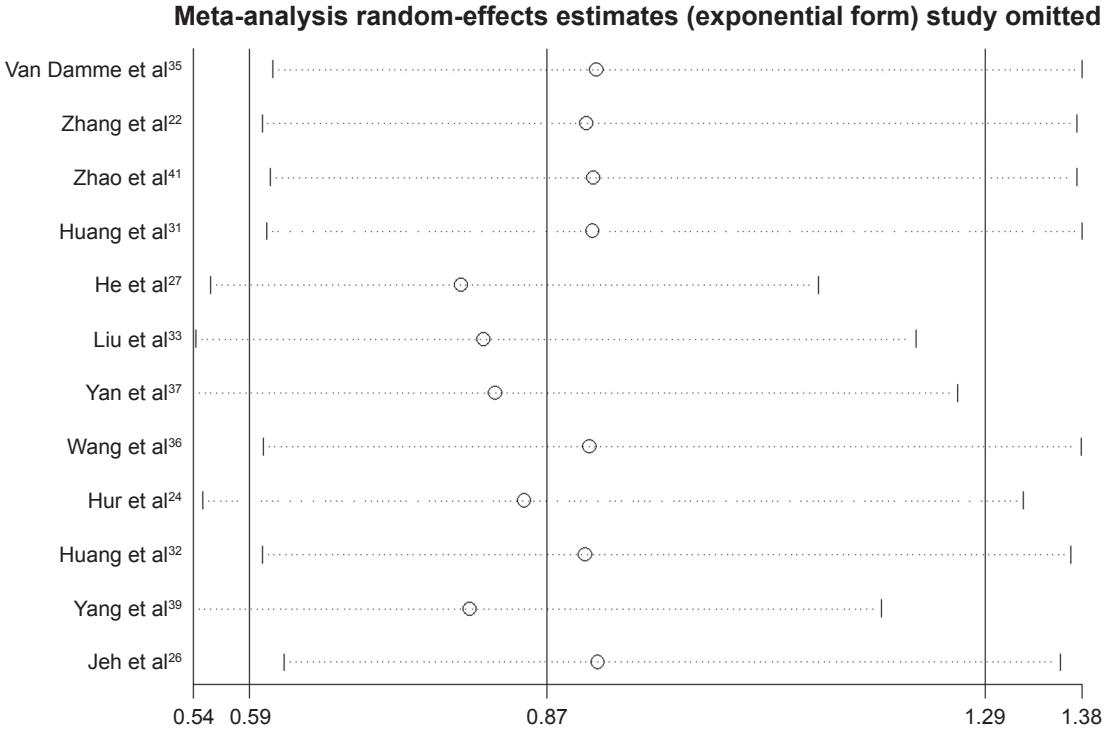

Figure 3 Influence analysis of OS.
Abbreviation: OS, overall survival.

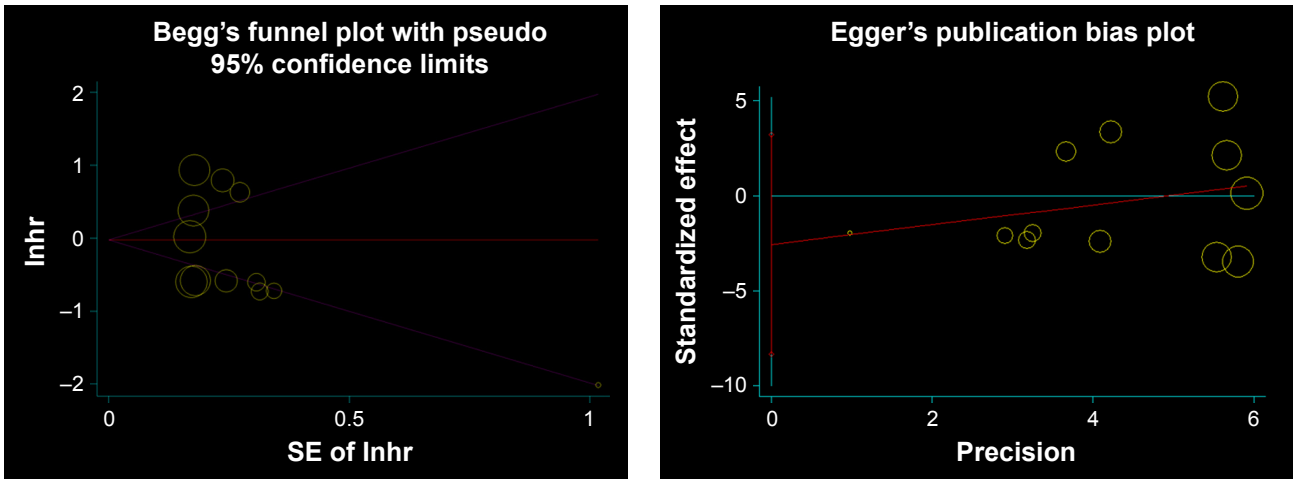

Figure 4 Publication bias of OS based on Begg's test and Egger's test.
Abbreviations: OS, overall survival; SE, standard error; hr, hazard ratio.

parameters in this meta-analysis included age, sex, tumor size, tumor differentiation, clinical stage, vascular invasion, cirrhosis, alpha fetal protein (AFP) and hepatitis B virus (HBV) infection. As listed in Table 3, the results indicated that there was no significant relationship between SIRT3 expression and all abovementioned clinicopathological parameters. Now that significant association between SIRT3 expression and OS was observed in HCC patients, a subgroup analysis of clinicopathological parameters focusing on HCC patients was performed. The results demonstrated that HCC patients with high SIRT3 expression tended to be associated with smaller tumor size (OR=1.41, 95% CI=1.02–1.94, P=0.04; I^2=46%), better tumor differentiation (OR=1.52, 95% CI=1.08–2.16, P=0.02; I^2=50%) and earlier clinical stage (OR=2.07, 95% CI=1.23–3.46, P=0.01; I^2=0%). However, no relationship was detected between SIRT3 expression and cirrhosis (P=0.71), and similar result was found in terms of AFP (P=0.48) and HBV infection (P=0.14) in HCC.

Table 2 Subgroup analyses of OS

Variables	Included studies	HR (95% CI)	*P*-value	I^2 (%)	Model
Analysis model					
Multivariate	10	0.90 (0.57, 1.43)	0.657	89.90	Random
Univariate	2	0.73 (0.35, 1.52)	0.404	77.50	Random
Ethnicity					
Caucasian	1	0.48 (0.26, 0.89)	0.019*	0	Fixed
Asian	11	0.92 (0.61, 1.38)	0.685	88.70	Random
Sample size					
<200	5	0.86 (0.39, 1.87)	0.698	85.40	Random
≥200	7	0.86 (0.53, 1.38)	0.526	90.70	Random
Cancer type					
CLL	1	0.48 (0.26, 0.89)	0.019*	0	Fixed
HCC	2	0.56 (0.42, 0.74)	<0.001*	0	Fixed
EC	2	0.87 (0.30, 2.55)	0.806	87.60	Random
GC	2	0.75 (0.41, 1.37)	0.347	84.80	Random
BC	1	2.53 (1.83, 3.67)	<0.001*	0	Fixed
CC	1	1.87 (1.12, 3.26)	0.022*	0	Fixed
PC	1	0.55 (0.30, 1.00)	0.049*	0	Fixed
NSCLC	1	2.20 (1.38, 3.50)	0.001*	0	Fixed
RCC	1	0.13 (0.02, 0.98)	0.048*	0	Fixed

Note: *P<0.05, the difference was statistically significant.
Abbreviations: BC, breast cancer; CC, colon cancer; CLL, chronic lymphocytic leukemia; EC, esophageal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PC, pancreatic carcinoma; RCC, renal cell carcinoma.

Discussion

SIRT3, an arresting member of the sirtuins family located in mitochondria, plays a critical role in multiple cellular activities such as energy metabolism, cell proliferation and cell apoptosis.[11–13,15–17] Recently, SIRT3 is gaining attention from more and more researchers due to its dual role in tumorigenesis.[22–24,26,33–41]

In the current study, we validated that SIRT3 expression might not be related to the prognosis in various cancers, which was in accordance with the previous meta-analysis.[42] Regarding the subgroup analyses of OS, we found the high SIRT3 expression might be a favorable factor in Caucasian. However, it should be noted that only 1 study focusing on CLL was included into these subgroups; therefore, the conclusion was not quite unconvincing. It is worth mentioning that we noticed significant correlation between SIRT3 expression and prognosis in several specific cancers. The results manifested that SIRT3 might be a tumor suppressor in CLL, HCC, PC and RCC. Conversely, the results also indicated that SIRT3 might promote the cancer development and decrease

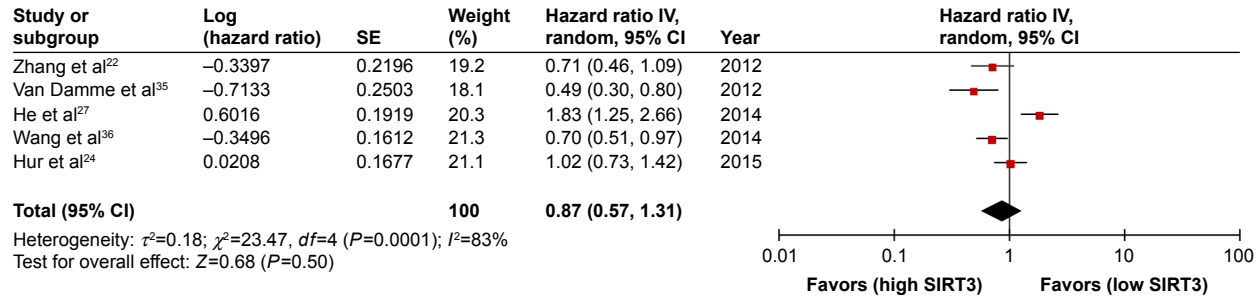

Figure 5 Meta-analysis of DFS.
Abbreviations: DFS, disease-free survival; SE, standard error; SIRT3, sirtuin 3.

the OS in patients with BC, CC or NSCLC. Meanwhile, no obvious relationship between SIRT3 expression and clinicopathological parameters in total various cancers was detected in the current study.

Yu et al[42] previously performed a meta-analysis involving 15 studies to explore the prognostic value of SIRT3 in various cancers and found no distinct relationship between SIRT3 expression and OS. Despite similar results, there were several differences between the current study and the previous meta-analysis.[42] First, in the previous meta-analysis, although the authors declared that 15 studies were included in the previous study, only 7 studies were analyzed in the meta-analysis of OS. The small population certainly reduced the convincing of the conclusion and restricted its clinical application. However, in the current study, 12 studies comprising 2,352 patients were involved in the meta-analysis of OS, and the results were clear and convincing. Second, Chinese databases such as China National Knowledge Infrastructure and Wanfang Data were searched in the previous studies, which might increase the selection bias in the previous meta-analysis. More importantly, 2 dissertations without peer-reviewed process were included into the previous meta-analysis, which decreases the persuasion of the conclusion to a great extent. Third, the quality assessment by NOS, the meta-analysis of DFS and the publication bias based on Begg's test and Egger's test were performed in the current meta-analysis, which was not reported in the previous meta-analysis. Hence, the methodology of the current study

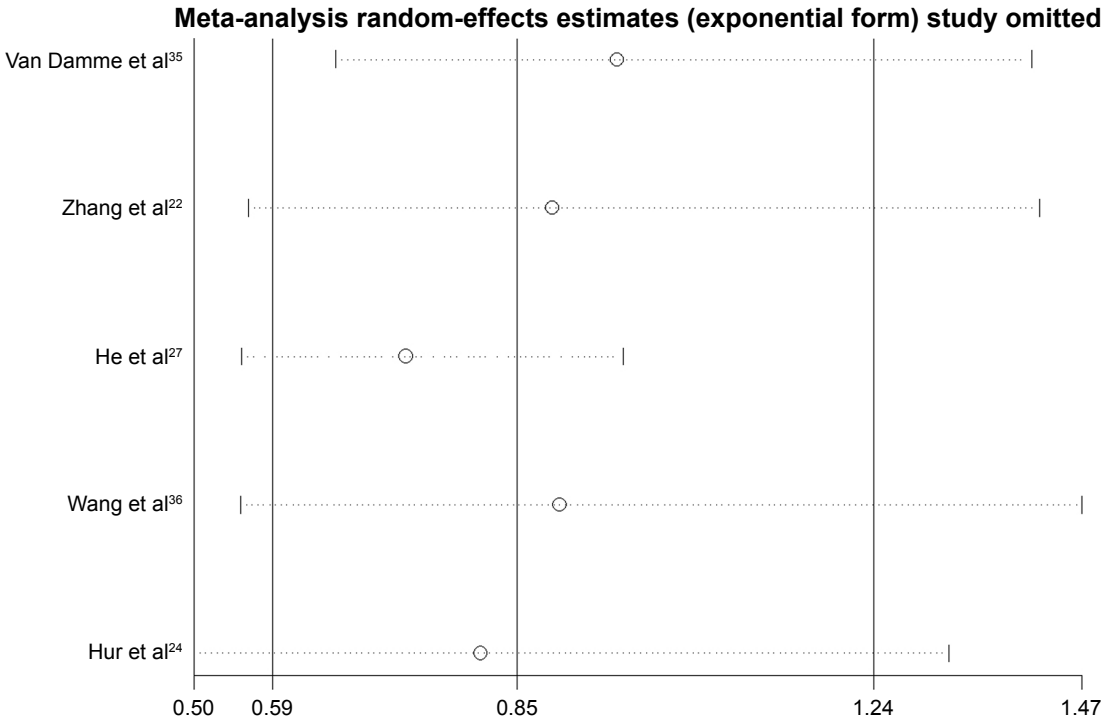

Figure 6 Influence analysis of DFS.
Abbreviation: DFS, disease-free survival.

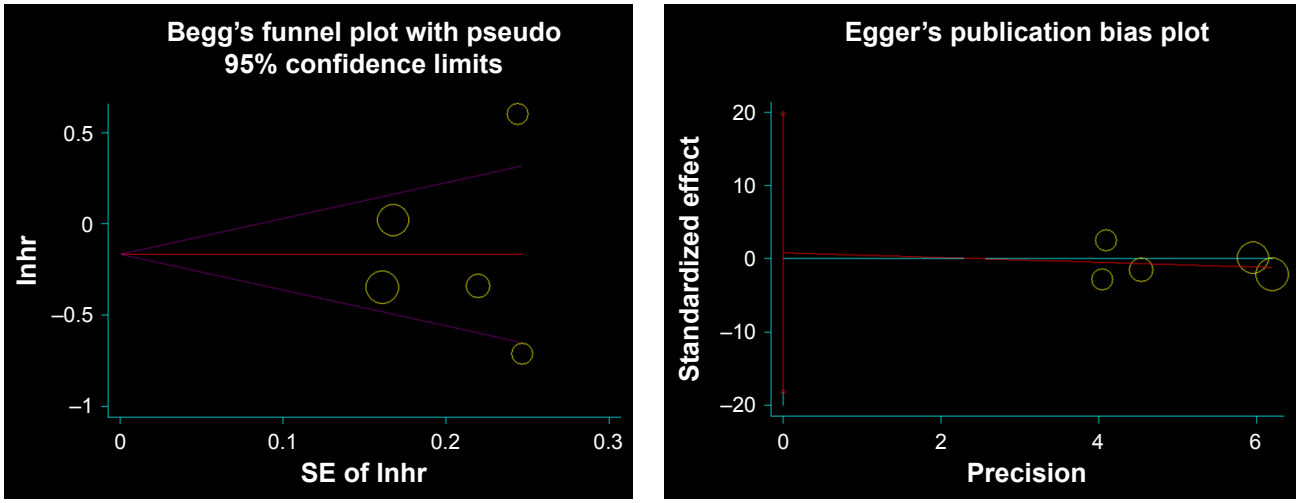

Figure 7 Publication bias of DFS based on Begg's test and Egger's test.
Abbreviation: DFS, disease-free survival; SE, standard error; hr, hazard ratio.

was more normative, and the conclusion could be drawn for enough credibility.

In spite of the numerous relative studies focusing on the prognostic role of SIRT3 in cancers, the underlying mechanism remains unclear. The complex mechanism might be on account of multiple biological roles of SIRT3 in cellular pathways, including cell proliferation, apoptosis and metabolism.[12,17,18,43] In the current study, we discovered that SIRT3 functioned as a tumor suppressor or a tumor promoter in specific cancers, which indicated that SIRT3 might be involved with different signaling pathways in specific cancers. Regarding BC, Wei et al[44] focused on the association between cell metabolism and cancers, and they discovered that SIRT3 played a vital role in the BC cell proliferation, and the results indicated that oroxylin A inhibits glycolysis-dependent proliferation of BC cells through the suppression of HIF1α stabilization via SIRT3 activation. In addition, SIRT3 is absolutely necessary in the regulation of

Table 3 Association between the SIRT3 expression level and clinicopathological parameters

Variables	Included studies	Patients (n)	OR (95% CI)	*P*-value	I^2 (%)	Model
Age (old vs young)	11	1,838	0.96 (0.80, 1.16)	0.68	23	Fixed
HCC	2	620	0.99 (0.71, 1.37)	0.94	33	Fixed
Other cancers	9	1,218	0.95 (0.75, 1.19)	0.65	29	Fixed
Sex (male vs female)	10	1,404	1.05 (0.81, 1.37)	0.69	80	Random
HCC	4	680	1.28 (0.81, 2.00)	0.29	0	Fixed
Other cancers	6	724	0.95 (0.69, 1.32)	0.77	32	Fixed
Tumor size (large vs small)	10	1,616	0.97 (0.65, 1.41)	0.89	68	Random
HCC	4	680	1.41 (1.02, 1.94)	0.04*	46	Fixed
Other cancers	6	936	0.69 (0.46, 1.05)	0.09	51	Random
Tumor differentiation (well/ moderate vs poor)	12	1,916	1.43 (0.82, 2.50)	0.20	83	Random
HCC	4	680	1.52 (1.08, 2.16)	0.02*	50	Fixed
Other cancers	8	1,236	1.29 (0.59, 2.84)	0.52	87	Random
Clinical stage (I/II vs III/IV)	10	1,355	1.40 (0.91, 2.15)	0.12	64	Random
HCC	2	308	2.07 (1.23, 3.46)	0.01*	0	Fixed
Other cancers	8	1,047	1.31 (0.79, 2.18)	0.29	69	Random
Vascular invasion (yes vs no)	4	656	0.77 (0.54, 1.08)	0.13	0	Fixed
HCC	2	308	0.79 (0.46, 1.35)	0.40	0	Fixed
Other cancers	2	348	0.75 (0.48, 1.17)	0.20	0	Fixed
Cirrhosis (yes vs no)	3	650	0.92 (0.61, 1.40)	0.71	0	Fixed
AFP	3	620	0.72 (0.29, 1.78)	0.48	80	Random
HBV infection	2	590	1.36 (0.90, 2.05)	0.14	0	Fixed

Note: *$P<0.05$, the difference was statistically significant.
Abbreviations: AFP, alpha fetal protein; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OR, odds ratio; SIRT3, sirtuin 3.

reactive oxygen species (ROS) production. Torrens-Mas et al[45] discovered that SIRT3 could be a therapeutic target for BC and improve the effectiveness of cisplatin (CDDP) and tamoxifen (TAM) treatments based on the ROS production. With regard to HCC, the study conducted by Liu et al found that the expression of SIRT3 was lower in HCC tissue than in non-HCC tissue, which manifested that SIRT3 was involved in the development of HCC and that SIRT3 acted as a tumor suppressor in HCC. Further in vitro experiments indicated that SIRT3 could inhibit the growth and proliferation of HepG2 cells and induce cell apoptosis,[46] which was consistent with our results. Similarly, Song et al[34] analyzed 60 HCC specimens and discovered that high SIRT3 expression was an unfavorable factor, and their further research validated that SIRT3 inhibited cell growth through the glycogen synthase kinase-3β/BCL2-associated X protein-dependent apoptotic pathway, which was in accordance with the viewpoint that the prognostic value of SIRT3 in specific cancers might be associated with the regulation of metabolism. In the current study, we also detected that HCC patients with high SIRT3 expression had longer OS, smaller tumor size, better tumor differentiation and earlier clinical stage compared to those with low SIRT3 expression. In view of the limited population, more studies should be carried out to ascertain the prognostic value of SIRT3 in HCC. Furthermore, other researchers testified that SIRT3 also acted as a tumor suppressor in RCC by regulating glutamine-derived mitochondrial respiration.[26,47] Conversely, Liu et al[33] analyzed 127 patients with CC and discovered that patients with high SIRT3 expression had a better OS, which suggested that high SIRT3 expression was an unfavorable factor in CC, and similar result was observed in a study by Yan et al,[37] which found that high SIRT3 expression was associated with worse prognosis in EC. Taken together, despite the discrepancy, extensive studies have demonstrated that SIRT3 expression was significantly related to OS in specific cancers.

There are some highlights in the current study. First, a total of 2,865 patients were finally included into the meta-analysis and the conclusion was convincing enough. Second, comprehensive subgroup analyses of OS and clinicopathological parameters were performed to elucidate this issue, which increased clinical application value of the conclusion. Nevertheless, the current study was not without drawbacks. The cutoff values of SIRT3 expression varied a lot in some included studies. Hence, the clinical applicability of the conclusion was affected. In addition, the sample size of some subgroup analyses was relatively small, which might lower the influence of the results. Last but not least, the previous report did not show the detailed characteristics of various cancers, which might affect the reliability of the conclusion. Despite the abovementioned shortcomings, the current meta-analysis still gave more convincing evidence on the prognostic role of SIRT3 in various cancers and could help researchers to catch the important development in this filed.

Conclusion

There was no evident relationship between the SIRT3 expression and prognosis in total cancers. However, SIRT3 expression might be a critical prognostic factor in specific cancers, including CLL, HCC, BC, CC, PC, NSCLC and RCC, especially in HCC. More clinical cohort studies with large population size and strict methodology should be carried out to clarify the issues in future.

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Disclosure

The authors report no conflicts of interest in this work.

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