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Review Article

Long non-coding RNA SPRY4-IT1 as a common molecular marker for clinicopathological features and prognosis: a meta-analysis

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Abstract: Long non-coding RNA (lncRNA) SPRY4-IT1 has been reported to be aberrantly expressed in various cancers and correlated with progression. We conducted a meta-analysis to further investigate its prognostic potential in malignant tumors. Relevant literature was searched in several electronic databases using combinations of keywords relating to SPRY4-IT1 and cancer. The pooled hazard ratios (HRs) or odds ratios (OR) with a 95% confidence interval (95% CI) were used to evaluate its prognostic value. Quality assessment of the included studies was performed by the Newcastle-Ottawa Scale. 12 studies with a total of 1261 participants were included in the current meta-analysis. The results revealed a significant association between elevated SPRY4-IT1 expression with poor overall survival (OS) in 10 types of cancers (HR=2.26, 95% CI=1.44-3.54, P=0.0004). Additionally, elevated SPRY4-IT1 expression was also correlated with lymph node metastasis (LNM) (OR=2.57, 95% CI=1.18-5.64, P=0.02) and tumor-node-metastasis (TNM) stage (OR=2.61, 95% CI=1.15-5.89, P=0.02). In the subgroup analysis, we found that increased SPRY4-IT1 expression was an unfavorable prognostic factor for patient OS indigestive system cancers (OR=1.92, 95% CI=1.12-3.30, *P*=0.02). This meta-analysis indicated that elevated SPRY4-IT1 expression may serve as a potential novel biomarker for LNM, TNM stage and OS in different types of cancer.

Keywords: Long non-coding RNA, SPRY4-IT1, lymph node metastasis, TNM stage, overall survival

Introduction

Tumors are a serious threat to human health because tumor cells proliferate at an abnormal rate [1] and readily metastasize [2, 3]. A total of 14.1 million cancer cases and 8.2 million cancer deaths were reported to occur in 2012, and the burden of cancer has gradually transferred to economically developing countries [4]. Although several treatments are available for tumor therapy, including surgery, chemotherapy and radiation therapy, patient prognosis is still not ideal, especially for those with advanced stage cancers [5-7]. Therefore, to diagnose tumors earlier, more effective molecular markers related to the development and metastases of tumors are needed.

Long non-coding RNAs (lncRNAs; >200 nucleotides in length) are RNA molecules with a non-protein coding capacity that are transcribed by RNA polymerase II [8, 9]. Okazakib [10] identified the first known lncRNA as a mouse DNA transcription product. lncRNAs have a wide range of biological functions, including cancer progression and metastasis, transcriptional and post-transcriptional regulation, regulation of subcellular localization, and production of endogenous small interfering RNA [11-13].

LncRNA SPRY4 intronic transcript 1 (SPRY4-IT1) was first reported as highly expressed in melanoma [14] and has extensive regulatory functions. Altering the expression of SPRY4-IT1 *in vitro* had a significant impact on tumor cell proliferation, metastasis, and apoptosis [15-17]. However, most studies examining the implications of SPRY4-IT1 expression were limited by their small sample size. Therefore, we conducted this quantitative meta-analysis to explore the prognostic value of lncRNA SPRY4-IT1 in different types of cancer.

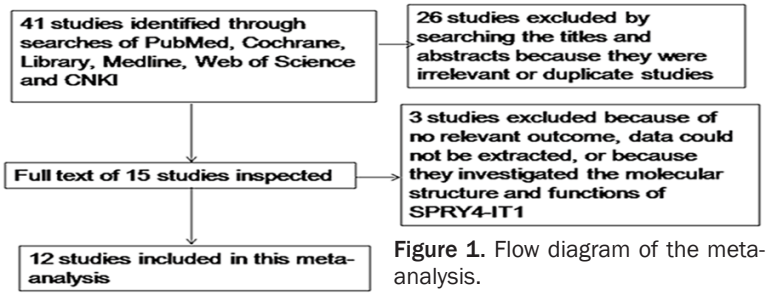

Figure 1. Flow diagram of the meta-analysis.

Materials and methods

Search strategy

Eligible studies were identified in PubMed, Cochrane Library, Medline, Web of Science, and CNKI databases from 2011 to 2017. The search strategy was ("sprouty RTK signaling antagonist 4 intronic transcript 1" or "SPRY4-IT1" or "SPRY4 intronic transcript 1") and ("outcome" or "prognos*" or "surviv*" or "clinicopathologic feature" or "os"). Reference lists of retrieved articles were searched manually to increase the sensitivity of the search strategy.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) studies investigating the expression levels of SPRY4-IT1 in human cancers; (2) patients grouped according to SPRY4-IT1 expression level; (3) correlations reported between SPRY4-IT1 expression and clinicopathological feature or prognosis; and (4) availability of a hazard ratio (HR), odds ratio (OR) and 95% confidence interval (CI), or data that could be used to calculate these values. Exclusion criteria were as follows: (1) reviews, comments, letters, case reports, and editorials; (2) lack of usable data for further analysis; and (3) non-human research, non-English papers, and duplicate publications.

Data extraction and quality control

Two authors independently extracted the critical data from eligible papers according to the inclusion and exclusion criteria. The following information was recorded for each eligible study: first author name, publication year, country, tumor type, sample size, tumor-node-metastasis (TNM) stage, number of high SPRY4-IT1 expression and low expression groups, number of patients with lymph node metastasis (LNM) in each group, method of SPRY4-IT1 testing, Newcastle-Ottawa Scale (NOS) score, HR, OR, 95% CI, and outcome. Some HRs were obtained directly from the papers, but others had to be collected from Kaplan-Meier survival curves by Engauge Digitizer version 4.1, as previously described [18]. If the data had been analyzed by both univariate and multivariate methods, the latter was preferred. All eligible literature was assessed by NOS for quality control [19]. Any disagreement was resolved by discussion with a third author.

Statistical analysis

All extracted data were analyzed using Review Manager Version 5.3 (Revman, the Cochrane Collaboration, Oxford, UK) and Stata 12.0 Software. The chi-square Q test and I^2 statistic were used to assess the heterogeneity of pooled HRs. Pooled HRs and 95% CIs were used to evaluate the effect of SPRY4-IT1 expression levels on clinical prognosis. A HR of >1 indicated a worse prognosis in patients with evaluated SPRY4-IT1 expression. Statistical significance was considered when the 95% CI did not include 1 and $P<0.05$. ORs were used to clarify a link between evaluated SPRY4-IT1 expression and clinicopathological features. The random-effects model was applied to calculate the pooled HR and 95% CI when heterogeneity was significant ($P<0.1$ and $I^2>50$), otherwise, the fixed-effects model was used. A funnel plot based on the Begg's test was conducted to estimate the potential publication bias [20]. A sensitivity analysis was conducted to test whether the removal of a single study influenced the overall outcome.

Results

The electronic search retrieved a total of 41 references, of which 26 were excluded after careful screening of the titles and abstracts for irrelevant and duplicate studies. A further 3 studies did not comply with the inclusion criteria after a more detailed inspection. Therefore, 12 published articles were enrolled in the current meta-analysis [14, 21-31] (**Figure 1**) with an accrual period between 2014 and 2017, and a

Table 1. Characteristics of studies in this meta-analysis

First Author	Year	Country	Tumor type	Sample size (n)	SPRY4-IT1 expression					TNM stage (I-II) VS (III-IV)			Outcome	NOS	Detection method
					High expression	High with LNM	High with DM	Low expression	Low with LNM	Low with DM	High expression	Low expression			
Sun	2014	China	NSCLC	121	60	23	NR	61	40	NR	47/13	30/31	OS	8	qPT-PCR
Liu	2016	China	Melanoma	70	32	NR	NR	38	NR	NR	4/28	28/10	OS	7	qPT-PCR
Zhang	2014	China	ccRCC	98	52	13	14	46	1	2	26/26	37/9	OS	8	qPT-PCR
Zhao	2015	China	UCB	68	38	18	NR	30	1	NR	NR	NR	OS	9	qPT-PCR
Liu	2017	China	UCB	60	45	18	7	15	4	1	NR	NR	NR	9	qPT-PCR
Xie	2014	China	ESCC	92	46	29	NR	46	16	NR	NR	NR	OS	8	qPT-PCR
Zhou	2016	China	Glioma	163	81	NR	NR	82	NR	NR	28/53	45/37	OS	9	qPT-PCR
Peng	2015	China	GC	175	98	51	66	77	44	68	40/58	55/22	OS	8	qPT-PCR
Cao1	2016	China	CRC	84	36	NR	NR	48	NR	NR	13/23	28/20	OS	8	qPT-PCR
Tan	2017	China	CRC	106	58	34	36	48	17	18	25/33	32/16	OS	9	qPT-PCR
Cao2	2016	China	CC	100	46	27	NR	54	9	NR	NR	NR	OS	7	qPT-PCR
Li	2017	China	OC	124	62	32	NR	62	17	NR	NR	NR	OS	7	qPT-PCR

NSCLC non-samll cell lung cancer, ccRCC clear cell renal cell carcinoma, UCB urothelial carcinoma of the bladder, ESCC esophageal squamous cell carcinoma, GC Gastric cancer, CRC colorectal cancer, CC cervical cancer, OC ovarian cancer, NR not reported, TNM tumor-node-metastasis, NOS Newcastle-Ottawa Scale, qRT-PCR quantitative real-time PCR.

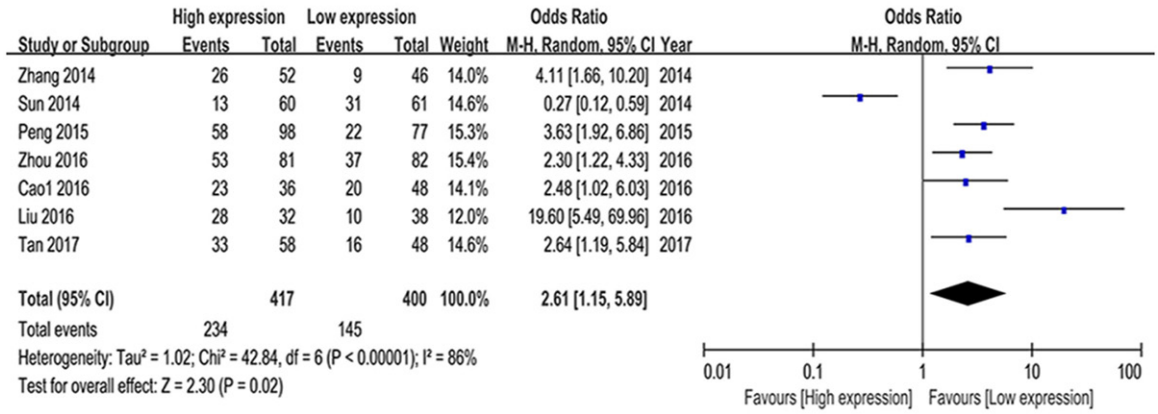

Figure 2. Association of SPRY4-IT1 expression with tumor-node-metastasis stage.

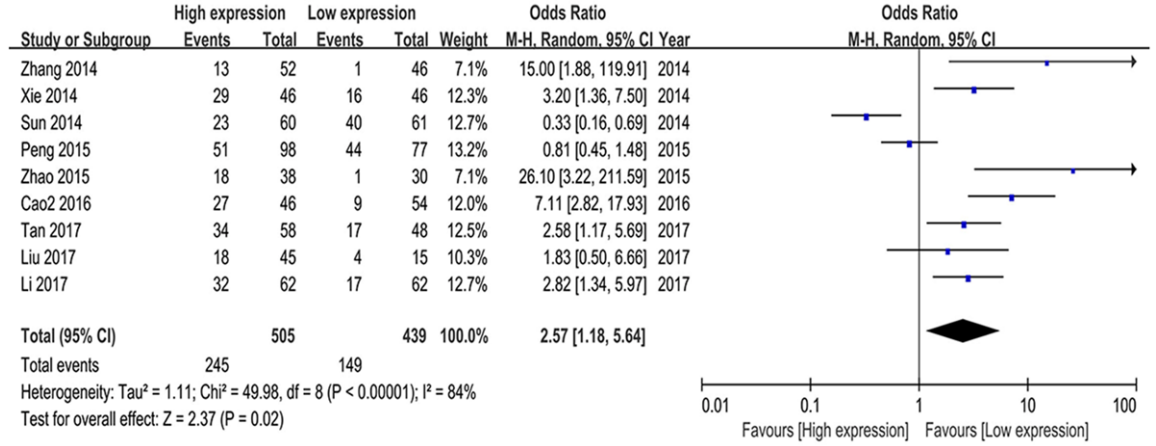

Figure 3. Forest plots of odds ratios for the association between SPRY4-IT1 expression and lymph node metastasis.

range of sample sizes of 60-175 (mean, 105). All included studies came from China and were assessed to be of high quality by the NOS. A total of seven different types of cancers were evaluated in this meta-analysis, including 1 non-small cell lung cancer (NSCLC), 1 melanoma, 1 clear cell renal cell carcinoma (ccRCC), 2 urothelial carcinoma of the bladder (UCB), 1 esophageal squamous cell carcinoma (ESCC), 1 glioma, and 1 gastric cancer (GC), 2 colorectal cancer (CRC), 1 cervical cancer (CC) and 1 ovarian cancer (OC). Based on the different expression levels of SPRY4-IT1 in each study, all participants were divided into two groups: high and low expression. All cancerous specimens had been well preserved before RNA extraction, and all diagnoses of clinicopathological features were based on pathology. The expression levels of SPRY4-IT1 had all been measured by quantitative real-time PCR. The main characteristics of the included studies are shown in **Table 1**.

Association of SPRY4-IT1 expression with TNM stage

A total of 7 studies including 817 patients reported the relationship between SPRY4-IT1 expression levels and TNM stage. The random-effects model was adopted because of the significant heterogeneity (I^2=86%, *P*<0.00001). The result showed that elevated SPRY4-IT1 expression was associated with higher TNM stage with a pooled OR of 2.61 (95% CI=1.15-5.89, P=0.02) (**Figure 2**). Therefore, compared with the low SPRY4-IT1 expression group, the high SPRY4-IT1 expression group was at higher risk of developing to an advanced tumor stage.

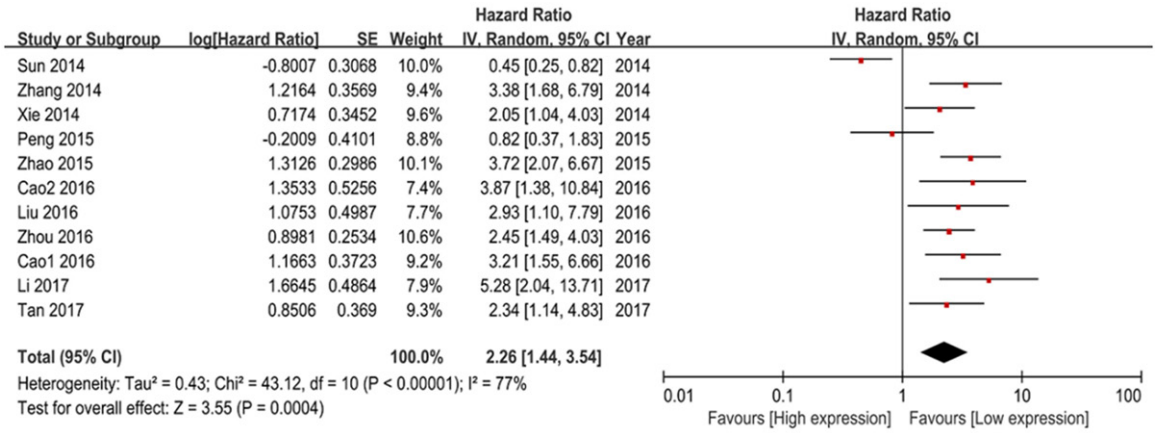

Figure 4. Forest plot for the correlation between SPRY4-IT1 expression and overall survival of patients with human cancers.

Association of SPRY4-IT1 expression with LNM

Nine studies including a total of 944 patients reported patients with LNM based on different SPRY4-IT1 expression levels. Significant heterogeneity was observed (I^2=84%, P<0.00001), so the random-effects model was adopted. The odds ratios, expressed as high SPRY4-IT1 expression group versus low SPRY4-IT1 expression group, was 2.57 (95% CI 1.18-5.64, P=0.02) (**Figure 3**). The high SPRY4-IT1 expression group had a significantly elevated LNM rate. This revealed that patients with high SPRY4-IT1 expression were more likely to develop LNM.

Association of SPRY4-IT1 expression with OS

Eleven studies including 1201 patients assessed the effect of up-regulated expression of SPRY4-IT1 on OS. The result revealed that increased SPRY4-IT1 expression predicted a poor outcome for OS in seven types of cancer (HR=2.26, 95% CI=1.44-3.54, P=0.0004) with significant heterogeneity (I^2=77%, *P*<0.00001) (**Figure 4**). Additionally, subgroup analysis was also conducted based on cancer type (digestive system cancers or others). A significant relevance was found between elevated SPRY4-IT1 expression and poor OS in digestive system cancers (HR=1.92, 95% CI=1.12-3.30, *P*=0.02) (**Figure 5**). Therefore, patients with elevated SPRY4-IT1 expression were more prone to poor OS in different kinds of cancer.

Publication bias and sensitivity analysis

To assess publication bias in this meta-analysis, the included studies were conducted using funnel plots and Begg's test. As shown in **Figure 6**, the shape of the funnel plot exhibited no significant asymmetry for OS. Meanwhile, a sensitivity analysis was also conducted to determine whether the removal of a single study influenced the overall outcome. The result suggested that the pooled HR for deregulated SPRY4-IT1 associated with OS was not significantly affected by the exclusion of any of the studies and indicated that our analysis was relatively stable and reliable (**Figure 7**).

Discussion

Early studies indicated that lncRNAs were considered to be simply transcriptional 'noise' or cloning artifacts [32]. However, increasing evidence suggested that lncRNAs have a vital role in tumor progression and development [33] and can be considered as biomarkers and prognosis factors [34]. For example, HOX transcript antisense RNA (HOTAIR) and metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1) have already been used to predict prognosis in different types of cancer [35, 36].

LncRNA SPRY4-IT1 (GenBank Accession ID AK024556) was initially identified in adipose tissue and transcribed from the second intron of SPRY4 gene, which is a 703-bp molecule that maps to chromosome 5q31.3. Khaitan *et al*. [37] found that, compared with melanocytes, SPRY4-IT1 is overexpressed in melanoma cells and SPRY4-IT1 transcripts are processed in the nucleus prior to transport to the cytoplasm. Liu *et al.* [14] also observed that SPRY4-IT1 was increased in the plasma of melanoma patients compared with that in healthy controls, which

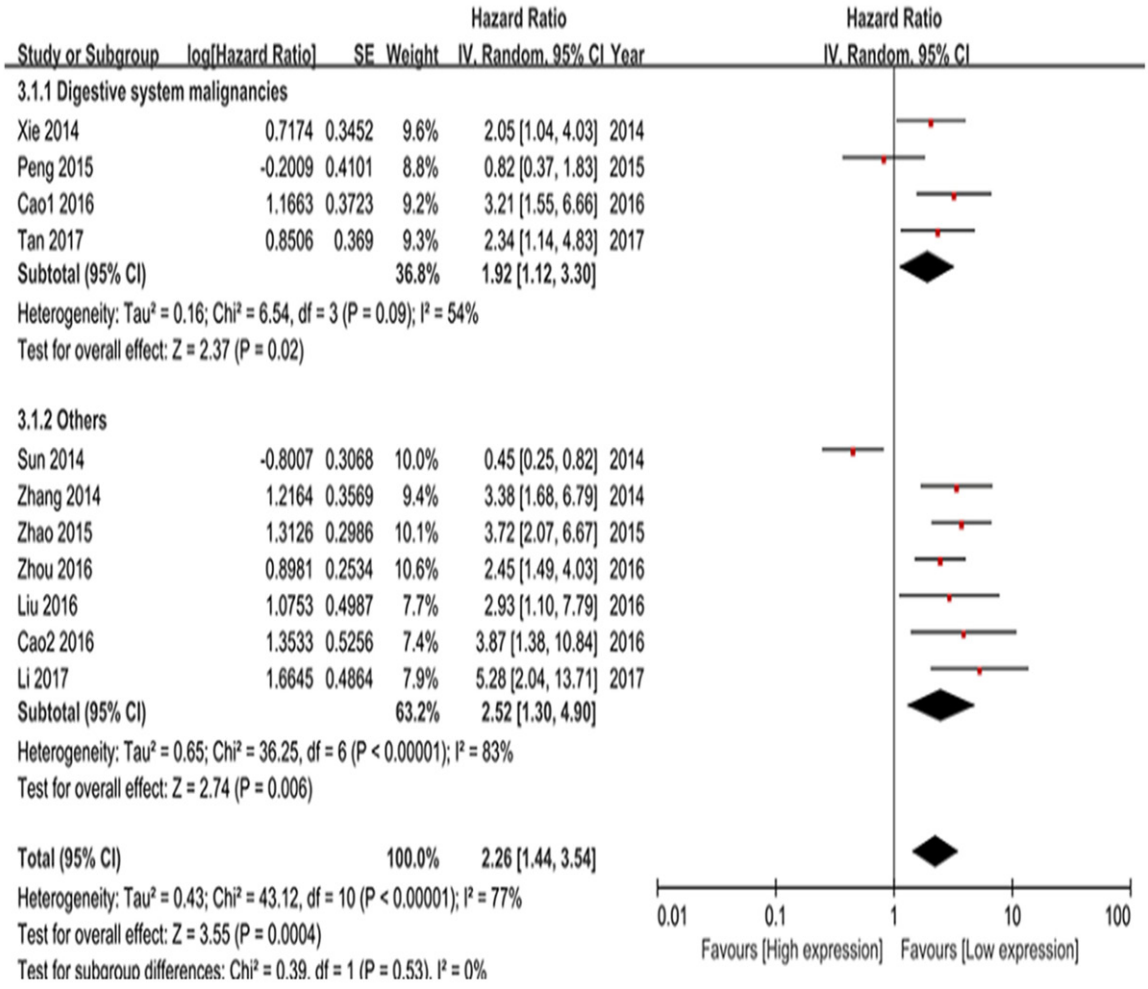

Figure 5. Forest plot showing association between overall survival and elevated SPRY4-IT1 expression in the different types of cancer.

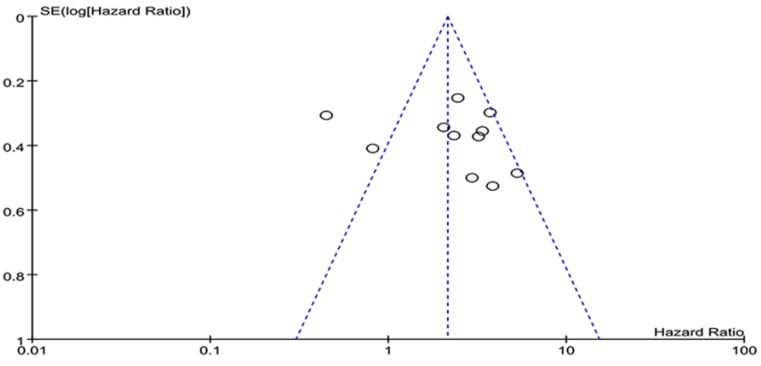

Figure 6. Begg's funnel plot for the evaluation of potential publication bias for overall survival estimation.

was used as an independent prognosis factor in melanoma, as well as esophageal squamous cell carcinoma [38-40]. The dysregulated expression of SPRY4-IT1 affected cell proliferation, metastasis, invasion, and apoptosis by various mechanisms in different kinds of cancer including gallbladder cancer, hepatocellular carcinoma, osteosarcoma, prostate cancer and melanoma, and so on [15, 41-44]. Mazar *et al.* [44] found that on one hand, the loss of lipin 2 most likely led to destabilize SPRY4-IT1 expression in human melanoma cells. On the other hand, knockdown of the SPRY4-IT1 gene increased both lipin 2 mRNA and protein expression. But interestingly, the transcriptional and functional independence of SPRY4-IT1

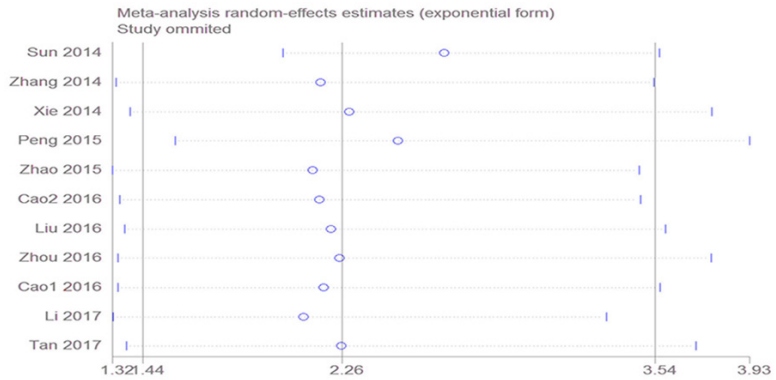

Figure 7. Sensitivity analysis of the pooled HRs of SPRY4-IT1 expression for overall survival for the included studies.

and its host gene SPRY4, and the expression of neither SPRY4-IT1 nor lipin 2 was influenced when they pulled down the SPRY4 gene. Sun *et al.* [21] indicated that EZH2-mediated epigenetic suppression of SPRY4-IT1 promotes NSCLC cell proliferation and metastasis by affecting the epithelial-mesenchymal transition. Shi *et al.* [45] found that ZNF703 showed the most substantial expression change in response to SPRY4-IT1 knockdown in breast cancer cells. In addition, the MDA-MB-231 and MDA-MB-435S cell lines showed high SPRY4-IT1 expression, whereas the MCF-7 cell line showed low SPRY4-IT1 expression compared with normal breast epithelial cells (MCF-10A), which was also apparent in prostate cancer [43]. Thus, we needed more studies to explore the mechanism of SPRY4-IT1 in tumors.

Some limitations should be taken into consideration in our study. First, we only included twelve eligible articles, which might lead to publication bias. Additional eligible studies should therefore be included. Second, all patients were from China, which might have generated selection bias and limit the broader applicability of our results. Third, the cut-off value used to distinguish high and low SPRY4-IT1 expression varied in different studies and potentially introduced further bias. Fourth, most of the included articles reported positive results because articles with negative findings are not typically published. Fifth, several HRs were calculated by reconstructing survival curves because some articles did not include available HRs. Sixth, two studies used risk ratio (RR) as index for OS, which were also included in analysis of the pooled HR for OS. Compared with HR, RR only considered the differences of the end point events, but ignored the time to the end point events and censored data. Finally, our results were likely to overstate the predictive value of SPRY4-IT1 in the prognosis of patients with cancer.

This meta-analysis of twelve studies representing a total of 1261 patients identified a significant association between SPRY4-IT1 expression levels and LNM, TNM stage, and OS in different types of cancer. These results indicate that elevated SPRY4-IT1 expression is closely linked to LNM, TNM stage and poor OS. Therefore, lncRNA SPRY4-IT1 has the potential to be used as a novel, reliable biomarker to predict the clinical outcome of cancer patients.

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Disclosure of conflict of interest

None.

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