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Prognostic role of SPRY4-IT1 in female breast carcinoma and malignant tumors of the reproductive system

A meta-analysis

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Abstract

Background: The prognostic value of SPRY4-Intronic transcript 1 (SPRY4-IT1) in women suffering from breast carcinoma and malignant tumors of the reproductive system remains to be ascertained. Therefore, this paper attempted to assess the relationship between SPRY4-IT1 with the clinicopathological indicators and survival analysis in women suffering from breast carcinoma and malignant tumors of their reproductive organs through meta-analysis.

Method: Related literature retrieved from Cochrane Library, Ovid, Embase, PubMed, the CNKI, and the Web of Science databases were reviewed. The latest article search was updated to September 1, 2021. The outcome indicators included as effective measures in the study were hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CI). The Stata 12.0 software was used to analyze the data.

Results: The elevated SPRY4-IT1 levels were indicative of poor overall survival (OS) [HR = 2.44, 95% CI = 1.35–4.43, $P < .05$], and were not related to Disease-Free Survival (DFS) [HR = 1.61, 95% CI = 0.50–5.18, $P = .43$] in female patients suffering from malignant tumors. In terms of lymph node metastasis (LNM) for the association between long noncoding RNA SPRY4-IT1(LncRNA SPRY4-IT1) and OS, elevated LncRNA SPRY4-IT1 implied poor OS with LNM [HR = 2.79, 95% CI: 1.81–4.28, $P < .001$]. Based on the aspect of the LNM for the association between LncRNA SPRY4-IT1 and DFS, SPRY4-IT1 was not correlated with DFS [HR = 0.97, 95% CI: 0.73–1.28, $P = .81$]. SPRY4-IT1 in the TNM stage was not related to OS [HR = 1.43, 95% CI: 0.55–3.70, $P = .46$]. In the TNM stage, SPRY4-IT1 was not related to DFS [HR = 1.68, 95% CI: 0.92–3.06, $P = .09$]. SPRY4-IT1 was found to be associated with lymph node metastasis (OR = 4.15, 95% CI: 2.75–6.25, $P = .000$) and TNM stage (OR = 2.89, 95% CI: 1.51–7.27 $P = .02$). No significant correlation was noted between SPRY4-IT1 and the age of the patients (OR = 0.89, 95% CI: 0.61–1.29 $P = .54$).

Conclusions: Thus, this study provides evidence-based medical evidence for the target treatment of female breast carcinoma and malignant tumors of the reproductive system. The elevated level of SPRY4-IT1 was associated with poor prognosis of female breast cancer patients and of those having malignant tumors in their reproductive organs. In addition, the SPRY4-IT1 expression was also associated with the disease progression and metastasis.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, LncRNA = long noncoding RNA, LNM = lymph node metastasis, OR = odds ratio, OS = overall survival, P_h = p values of Q test for heterogeneity testSPRY4-IT1 = SPRY4-Intronic transcript 1.

Keywords: breast carcinoma, long noncoding RNAs, prognosis, reproductive malignancies, SPRY4-Intronic transcript 1

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XQ and QY contributed equally to this work.

The ethics committees of Hebei General Hospital approved this study protocol. The data in the online databases were retrieved after obtaining written informed consent.

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Female breast carcinoma and malignant tumors of the reproductive system pose a serious threat to the health and lives of women across the world.[1–3] Although several treatment options are available in the form of surgery, endocrine therapy, radiotherapy, chemotherapy, and targeted therapy for treating such patients, much needs to be done in relation to prognosis for late patients and of those experiencing metastasis.[4] The reason for the high mortality of women with advanced breast cancer and reproductive system tumors is the lack of effective treatment options. In the future, experiments and clinical studies on effective prognostic biomarkers are expected to provide treatment solutions for them. The recent discovery of lncRNAs and the exploration of the associated mechanisms have resulted in great advances in the area of tumor biology. Effective prognostic biomarkers and therapeutic target guides have proven extremely useful to clinicians, helping them adopt effective treatment strategies.

Long noncoding RNA (LncRNA), which is more than 200 nucleotides long, cannot be translated into protein.[5] LncRNAs that form the basis of transcriptional and post-transcriptional regulation as well as dysregulation of LncRNAs can regulate the expression of downstream genes. LncRNAs contribute toward carcinoma development and metastasis.[6] SPRY4-intronic transcript 1 (SPRY4-IT1) is a type of LncRNA derived from an intron region within the *SPRY4-IT1* gene located at 5q31.3.[7,8] SPRY4-IT1 has been reported in melanoma cells. In addition, elevated SPRY4-IT1 level was associated with the location and stage of the carcinoma, indicating the need for determining the prognostic value in such cases.[9,10] At present, several studies are available that deal with the expression of SPRY4-IT1 in female patients suffering from breast carcinoma and malignant tumors in the reproductive system and their association with the prognosis of the disease. Shi et al[11] considered that the high expression of lncRNA was related to the size of the tumor and advanced stages of breast carcinoma, suggesting that SPRY4-IT1 may be a latent prognostic indicator for breast carcinoma. Zheng et al[12] believed that, in breast carcinoma patients, the SPRY4-IT1 expression is responsible for the suppression of the G1 phase arrest, apoptosis of breast cancer cells, and acceleration of the multiplication of cells by targeting ZNF703.[11] SPRY4-IT1 revealed high expression in female patients suffering from breast carcinoma. In addition, patients with higher SPRY4-IT1 expression showed poorer prognosis when compared to those with lower expression. Wang et al[13] suggested that SPRY4-IT1 acts as an independent prognostic indicator in clear-cell renal cell carcinoma, esophageal squamous cell carcinoma, and non-small cell lung cancer (NSCLC). Xiang et al[14] considered that, in comparison with the adjacent normal tissues, the SPRY4-IT1 expression showed remarkable upregulation of breast cancer cells. Wang et al[15] also shared a similar viewpoint. Cao et al[16] suggested that, in comparison with the adjacent normal tissues, the SPRY4-IT1 expression was higher in cervical carcinoma. The high expression of SPRY4-IT1 was associated with late clinical features, such as risk, relapse, progression, and reduced overall survival (OS). Li et al[17] suggested that the SPRY4-IT1 expression shows remarkable upregulation in ovarian tumor cell lines and carcinoma. In breast carcinoma, colorectal carcinoma, osteosarcoma, and glioma, the downregulation of SPRY4-IT1 inhibits cell apoptosis, proliferation, migration, and epithelial-mesenchymal transition.

This study investigated the prognostic role of lncRNA SPRY4-IT1 in female malignancies in China from the perspective of 2 survival indicators: OS and DFS. OS refers to the time from the start of randomization until death (due to any reason). DFS refers to the time from the start of randomization to the recurrence of the disease or death (due to any reason). Despite the availability of researches on carcinogenesis of SPRY4-IT1 in various carcinomas, less evidences are available on its prognostic value. The available data on prognosis of SPRY4-IT1 in several carcinomas rarely reflect their prognostic value. Although the diagnostic role of SPRY4-IT1 has been investigated in a single experiment in breast, ovarian, and cervical cancers, the prognostic role of SPRY4-IT1 in female malignant tumors needs to be analyzed. Currently, only a few studies are available on the role of SPRY4-IT1 in breast cancer and reproductive malignancies. The sample sizes in these studies were small. The findings from these studies were taken into consideration in order to outline the criteria for exploration and explanation of the connection between SPRY4-IT1 and its prognostic value in female patients. The present study was conducted to assess the prognostic value of SPRY4-IT1 expression in females suffering from malignancies of the reproductive systems.

2. Material and methods

2.1. Search strategy

The following databases were searched for the retrieval of relevant data: Cochrane Library, Ovid, Embase, PubMed, the CNKI, and the Web of Science. The latest update of the search was September 1, 2021. The key terms used in the searches included "LncRNAs" (e.g., "Long non-coding RNAs"); "SPRY4 Intronic Transcript 1" (e.g., "SPRY4-IT1"); "female malignant" (e.g., "female cancer"; "female carcinoma"; "breast cancer"; "breast carcinoma"; "ovarian cancer"; "ovarian carcinoma"; "cervical cancer"; and "cervical carcinoma").

2.2. Inclusion and exclusion criteria

The following points were kept in mind while selecting the sample patients.

The patients were pathologically verified for malignant tumors and

the connection of SPRY4-IT1 with OS and/or disease-free survival (DFS) was reported. The exclusion criteria included letters, abstracts, reviews, case reports or basic studies;

research reports of studies in languages other than Chinese and English;

studies lacking data on assessing hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CI);

study of nonmalignant tumors in females; and

studies had duplicated data or analysis.

2.3. Data extraction and quality assessment

Two investigators (Xiao-Ru Qin and Qi-Fan Yin) were involved in procuring the data. They independently procured the data from the available studies. In case where the retrieved studies could not be classified by title and abstract, the full text was reviewed. The 2 investigators consulted each other and reached at a consensus by seeking the opinion of a third investigator in case of any disagreement. During the data review process, details with respect to the following points were recorded: first author;

year of publication; nationality; type of cancer; blood or tissue; level of expression; experimental methods used; sample size; number of cases reported for SPRY4-IT1 expression; number of the SPRY4-IT1 expression level in age, LNM, TNM; P (age, LNM, and TNM); outcome indicators; follow-up (years); HRs with 95% CIs; statistical power; studies involving multivariate analysis and Newcastle–Ottawa Scale (NOS) score (population selection, comparability score, and results score) in Table 1. G* power software calculated the statistical power. The sample size, alpha value, and effect size that were calculated using sample size and alpha value by G * power software finally obtained statistical power. Each of the extracted studies was analyzed separately by 2 independent investigators for its quality using the NOS score. Five studies with scores 6 to 7 points were included for the purpose of analysis. A semi-quantitative evaluation of the selected studies was conducted independently by the 2 researchers considering the criteria for the selection of the study population; their comparability with other studies; and measurement of the exposure factor by employing the NOS12 quality review. The studies were categorized according to the scores, as: good quality (7–9); medium quality (6–7); and poor quality (≤ 5). The studies were reviewed and screened by the 2 investigators, keeping the unified quality standards in mind.

2.4. Statistical analysis

For the purpose of statistical analysis, STATA 12.0 (STATA, College Station, TX) which HR, OR, and CI was set at 95%. HR >1 demonstrated a poor prognosis of malignant tumor (breast carcinoma and malignant tumor in the reproductive organ). Cochran's Q-test and Higgins I^2 statistic were performed to quantify the degree of heterogeneity among the selected studies. Both fixed-effects model (Mantel–Haenszel method) and random effects (DerSimonian–Laird method) model were used for determining the pooled HRs, ORs, and 95% CIs. In the case of $P_{heterogeneity} < 0.10$ or $I^2 > 50\%$ that depicted significant heterogeneity and random-effect model were used. Otherwise, the fixed-effects model was applied. The assessment of publication bias was performed by using the Begg and Egge test. $P < .05$ was considered to be statistically significant.

3. Results

3.1. Identification of relevant studies

A total of 8 studies conducted between 2016 and 2021 were initially retrieved. After careful inspection of the available literatures, 63 articles were eliminated and 8 articles were selected for the purpose of meta-analyses. A total of 58 articles were eliminated mainly because they were letters, abstracts, reviews, cases reports, or basic studies and did not conform to the original data. Five of the 13 articles were culled out because the literature did not provide complete HR and 95% CI values. These dealt with 3 types of cancer and investigated a total of 670 patients. The findings in these 8 studies were based on the OS rate and the *P* value of multivariate analysis. The whole process involved in the search of literature has been depicted in the flow chart (Fig. 1).

3.2. Study characteristics

A total of 670 patients from China were selected for the purpose of meta-analysis.[12,14–20] The study conducted by Zheng et al[12]

Table 1

The basic characteristics of the enrolled papers in the study.

	Year	nationality	type of cancer	blood or tissue	Expression	Method	Sample size	SPRY4-IT1 High	SPRY4-IT1 low	Age ≤50 Low	Age ≤50 High	Age >50 Low	Age >50 High	LNM Negative	LNM positive	TNM I/II	TNM III/IV	P Age	P LNM	P TNM	outcome	Follow-up (Years)	OS HR	OS CI Lower	OS CI Upper	DFS HR	DFS CI Lower	DFS CI Upper	Statistical power	HR (Multivariate)	Population selection	Comparability score	Results score	NOS
Zheng [12]	2019	China	Breast cancer	tissue	up-regulation	qRT-PCR	60	41	19	9	24	10	17	9	3	10	38	NR	NR	2.704	0.002	NR	OS,DFS	6.7	1.45	0.39	5.31	1.31	0.35	4.91	0.48	NO	2	2	2	6
Xiang [14]	2019	China	Breast cancer	tissue	up-regulation	qRT-PCR	102	52	50	23	30	27	22	30	18	20	34	65	37	0.237	0.01	0.0008	OS,DFS	10	7.812	1.311	46.545	4.322	1.205	15.500	0.71	Yes	2	2	3	7
Wang [15]	2019	China	Breast cancer	tissue	up-regulation	qRT-PCR	99	48	51	24	17	27	31	46	31	5	17	70	29	0.240	<0.01	<0.01	OS,DFS	8	4.216	1.241	5.809	3.328	1.271	4.314	0.69	Yes	3	2	2	7
Mehdi.Mohebi[18]	2020	Iran	Breast cancer	tissue	up-regulation	qRT-PCR	69	43	27	15	23	12	20	NR	NR	NR	NR	40	20	0.86	NR	0.25	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	3	2	1	6
Song[19]	2019	China	Breast cancer	tissue	up-regulation	NR	101	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	OS	NR	1.6	1.17	2.19	NR	NR	NR	NR	NR	2	1	3	6
CaoY[16]	2016	China	Cervical cancer	tissue	up-regulation	qRT-PCR	100	54	46	NR	NR	NR	NR	45	19	9	27	110	NR	NR	<0.001	<0.001	OS	5	3.87	1.38	10.83	NR	NR	NR	0.74	Yes	3	2	2	7
Li H. [17]	2017	China	Ovarian cancer	tissue	up-regulation	qRT-PCR	124	62	62	25	29	37	33	45	30	17	32	48	76	0.469	0.006	<0.001	OS	5	5.283	1.209	8.138	NR	NR	NR	0.79	Yes	2	2	2	6
Jing [20]	2019	China	Ovarian cancer	tissue	down-regulation	qRT-PCR	15	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	OS,DFS	2	0.60	0.23	1.56	0.35	0.13	0.94	NR	NR	3	1	2	6

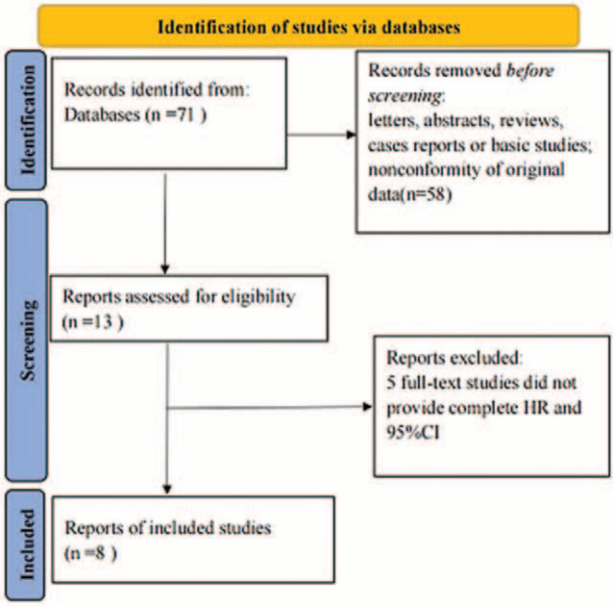

Figure 1. The entire process of literature search has been depicted in the flow diagram.

did not directly provide HR and 95% CI by *P* value of OS. The investigators calculated the HR and 95% CI by *P* value of OS and DFS using the method provided by Tierney et al.[13] Five studies provided data pertaining to the age of the patients. Five studies provided data on lymph node metastasis. Four studies provided data on the TNM stage of the carcinoma. The assessment of the SPRY4-IT1 expression in all the selected studies was performed by quantitative real time PCR (qRT-PCR) technique. Correlation between SPRY4-IT1 and the clinicopathological features as well as the relationship between SPRY4-IT1 and OS/DFS in the clinicopathological features are depicted in Table 2.

3.3. SPRY4-IT1 and OS in breast cancer and malignant tumors of the reproductive organs in women

Seven studies reported the elevated SPRY4-IT1 expression and OS in female breast cancer and malignant tumors of the reproductive system. For the purpose of analyzing the indicator of OS, 7 studies[12,14–17,8,19] were selected. Since the obvious heterogeneity was observed in the studies ($I^2 = 69.40\%$, $P_h = 0.003$), random effects model was adopted. The obtained results suggested that increased SPRY4-IT1 predicted poor OS in patients suffering from female breast cancer and malignant tumors of the reproductive organs with a combined HR of 2.44 (95% CI: 1.35–4.43; Fig. 2A).

3.4. SPRY4-IT1 and DFS in patients suffering from breast cancer and malignant tumors of the reproductive organs in women

Four studies provided data for determining the association between the elevated SPRY4-IT1 expression and DFS in women suffering from breast cancer and malignant tumors of the reproductive organs. Four studies were selected for analyzing the indicator of DFS.[12,14,15,19] Meta-analysis of the 4 studies suggested that high expression of SPRY4-IT1 was not associated with DFS (HR obtained from random-effects model: 1.61; 95% CI: 0.50–5.18; Fig. 2D) and with heterogeneity ($I^2 = 81.70\%$, $P_h = 0.001$).

3.5. Relationship between SPRY4-IT1 and OS/DFS in clinicopathological features

A meta-analysis was conducted between the SPRY4-IT1 and OS/DFS in clinicopathological features. The articles listed in Table 2 showed that increased SPRY4-IT1 expression was associated with poor OS in LNM[14–17] (HR = 2.79, 95% CI: 1.81–4.28, $P < .001$; Fig. 2B). However, the article demonstrated that the SPRY4-IT1 expression was not associated with DFS in LNM[14,15] (HR = 0.97, 95% CI: 0.73–1.28, $P = .812$ Fig. 2E). With reference to the TNM stage, the articles showed that the SPRY4-IT1 expression was not associated with OS[14,15] (HR = 1.43, 95% CI: 0.55–3.70, $P = .461$; Fig. 2C) and DFS[14,15] (HR = 1.68, 95% CI: 0.92–3.06, $P = .091$; Fig. 2F). In another word, increased SPRY4-IT1 expression was associated with poor OS in LNM.

3.6. SPRY4-IT1 and clinicopathological parameters

A meta-analysis was conducted to investigate the relationship between the expression level of SPRY4-IT1 and the clinicopathological features of female cancer patients. The relationship between the expression level of SPRY4-IT1 and the clinicopathological features of the patients has been depicted in Table 2, which shows that the level of SPRY4-IT1expression is

Table 2

Summary of the meta-analysis results of the included papers.

					Heterogenity							Heterogenity		
Clinicopathogical parameters	Studies N	Number of patients references	OR (95%CI)	*P* value	*I2* (%)	*Ph*	Model	studies N	Number of patients references	HR (95%CI)	*P* value	*I2* (%)	*Ph*	Model
Age	5	12,14,15,17,18	0.89 (0.61–1.29)	.54	0.00	0.47	Fixed-effect	NR	NR	NR	NR	NR	NR	NR
lymph node metastasis	5	12,14,15,16,17	4.15 (2.75–6.25)	.00	21.40	0.28	Fixed-effect	4*	14,15,16,17	2.79(1.81–4.28)	.00	24.7	0.26	Fixed-effect
								2†	14,15	0.97(0.73–1.28)	.81	0.00	0.81	Fixed-effect
TNM stage	4	14,15,17,18	3.04 (1.89–4.88)	.00	70.80	0.02	Fixed-effect	2*	14,15	1.43(0.55–3.70)	.46	75.2	0.045	Random-effect
	4	14,15,17,18	2.89 (1.51–7.27)	.02	70.80	0.02	Random-effect	2†	14,15	1.68 (0.92–3.06)	.09	53.9	0.14	Random-effect

DFS = disease-free survival, HR = hazard ratio, NR = not report in literature, OS = overall survival.
* stands for OS.
† stands for DFS.

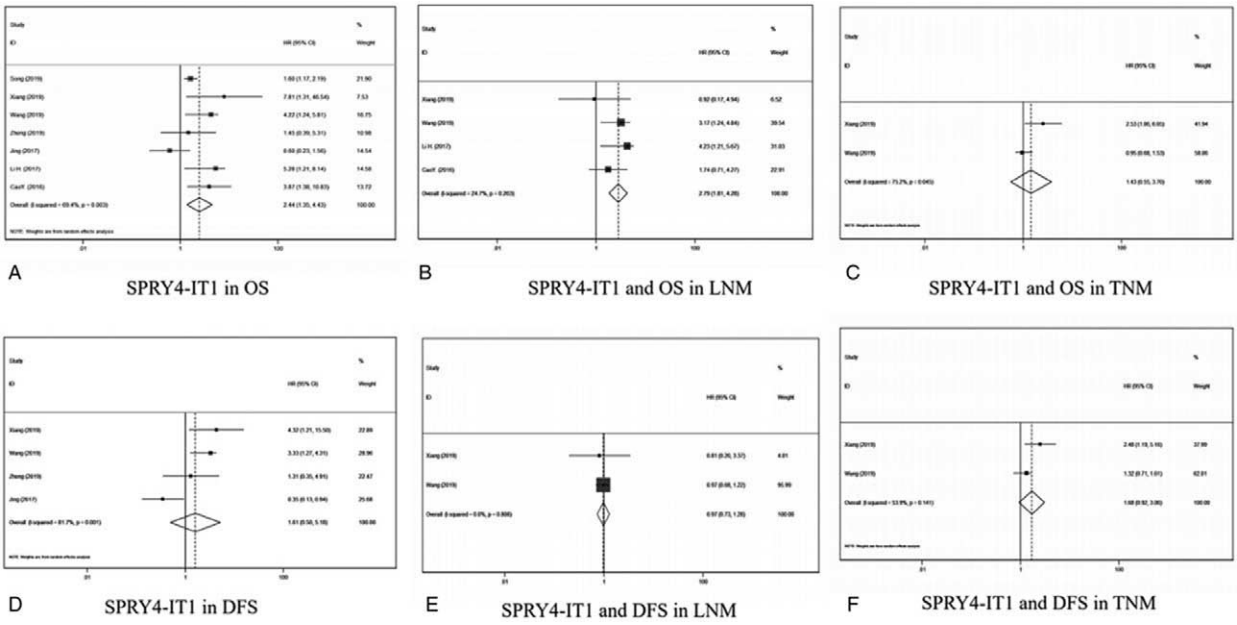

Figure 2. Relationship between SPRY4-IT1 and OS/DFS in female breast carcinoma and reproductive malignant tumors. (A) A total of 601 patients with breast carcinoma and reproductive malignant tumors were gathered from 7 papers. (B) Pooled OS from 4 papers, including 425 patients with female breast carcinoma and reproductive malignant tumors. (C) The data of 201 patients with breast carcinoma were collected from 2 studies. (D) Pooled DFS from 4 papers, including 276 patients with breast carcinoma. (E) Data from 201 patients with breast carcinoma were collected from 2 papers. (F) Data of 201 patients were collected from 2 papers to evaluate whether the expression of SPRY4-IT1 in breast carcinoma was associated with DFS in TNM.

not related to the age of the patients[12,14,15,17,18] (OR = 0.89, 95% CI: 0.61–1.29, $P = .54$, Fig. 3A). However, the studies suggested that high SPRY4-IT1 expression is obviously related to lymph node metastasis (LNM)[12,14–17] (OR = 4.15, 95% CI = 2.75–6.25, $P = .00$, Fig. 3B), TNM stage[14,15,17,18] (OR = 2.89, 95% CI = 1.51–7.27, $P = .02$; Fig. 3C). For determining the relationship between the increased expression of SPRY4-IT1 and TNM stage, a random effects model was applied, as the studies were found to be significantly heterogeneous ($I^2 = 70.80\%$, $P_h = 0.02$). The results of the fixed and random effects model were found to be similar, which suggested that the results (OR = 3.04, 95% CI = 1.89–4.88, $P = .00$) were stable. As data pertaining to other clinicopathological features (such as the depth of invasion; tumor differentiation; distant metastasis; and family history) was not available, the correlation between the expression level of SPRY4-IT1 and these clinicopathological features could not be ascertained.

3.7. Sensitivity analysis

Heterogeneity was observed ($I^2 = 69.4\%$; $P_h = 0.003$) when 7 studies on SPRY4-IT1 in OS. When a single study by Song was excluded, the heterogeneity was $I^2 = 67.4\%$; $P_h = 0.009$ (Supplementary Digital Content Figure S2, http://links.lww.com/MD2/A962). The sensitivity analysis revealed that the study by Song was not within the same CI value as the other 6 studies. We analyzed the heterogeneity in the remaining 6 articles in detail because the expression of SPRY4-IT1 in ovarian cancer as reported by Jing was contrary to that reported by Li H. After removing Song and Jing studies, a relatively stable result expression of SPRY4-IT1 was obtained in OS.

3.8. Publication bias

In order to estimate the publication bias, the Begg funnel plot and Egger linear regression test were applied. No publication bias was detected for OS in Begg test ($Pr > |z| = 0.764$; Fig. 4A) and Egger's test ($P > |t| = 0.328$; Fig. 4B).

4. Discussion

LncRNAs promote the cell proliferation, migration, differentiation, and cell death. The overexpression of SPRY4-IT1 has been observed in various types of tumor tissues and carcinoma cell lines. However, the exact mechanism remains unclear among carcinomas.[11,20] Sun et al[21] suggested that the downregulated expression of SPRY4-IT1 in NSCLC is related to bad prognosis. Shi et al[11] demonstrated that SPRY4-IT1 brings about the proliferation and apoptosis of carcinoma cells of the mammary glands in vitro by upregulating the expression of ZNF703. ZNF703, as a target of SPRY4-IT1, was downregulated by the knockdown of SPRY4-IT1. Zheng et al suggested that the expression of SPRY4-IT1 had a significant influence on the curative effect of neoadjuvant chemotherapy, which may possibly be related to the promotion of chemo-resistance of the cells to epirubicin by SPRY4-IT1. Zheng et al also assumed that the SPRY4-IT1 expression was strongly associated with elevated positive rates of LNM and recrudesce, which suggested that SPRY4-IT1 may be responsible for postoperative recurrence of tumors and metastasis in breast carcinoma. Besides, Xiang et al suggested that the elevated SPRY4-IT1 expression was positively related to tumor size and advanced clinical stage. The high expression of SPRY4-IT1 in female breast cancer patients was also associated with the TNM stage and LNM, indicating

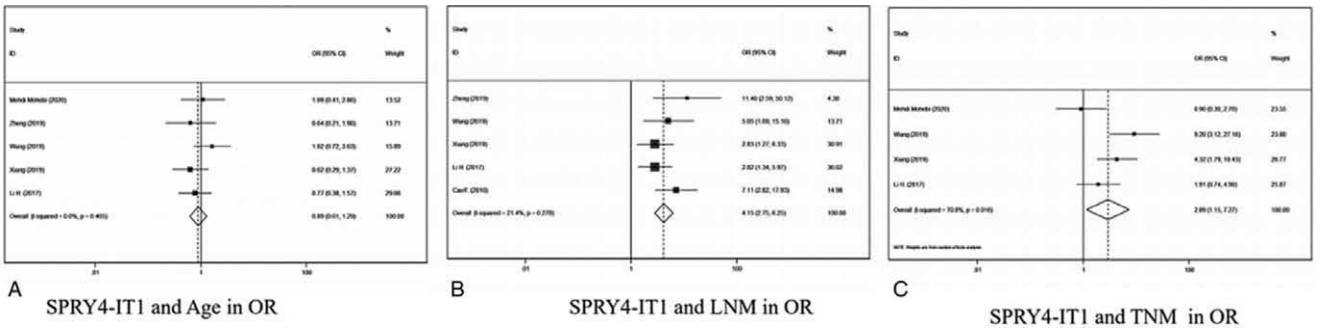

Figure 3. SPRY4-IT1 expression and clinicopathological parameters in female breast carcinoma and reproductive malignant tumors. (A) The data of 455 patients with breast carcinoma and reproductive malignant tumors were gathered from 5 papers. (B) The data of 485 patients with breast carcinoma and reproductive malignant tumors were collected from 5 papers. (C) Pooled OR from 4 papers, involving 343 patients with breast carcinoma and reproductive malignant tumors.

that SPRY4-IT1 might be involved in the process of recrudescence and metastasis of breast carcinoma. SPRY4-IT1 guides the curative treatment of patients, because of the interaction between the SPRY4-IT1 and the curative therapy. SPRY4-IT1 predicts patient survival significantly, irrespective of the treatment received, as aggressiveness of SPRY4-IT1 is strongly associated with the possibility of OS of the patient. Notably, the high expression of SPRY4-IT1 showed low OS and DFS. Cao et al believed that elevated SPRY4-IT1 expression was related to the tumor size, FIGO stage, and LNM in cervical carcinoma. Li et al suggested that the SPRY4-IT1 expression in ovarian malignant cell lines and carcinoma tissues were remarkably upregulated. The SPRY4-IT1 expression is high in breast cancer and female reproductive tumors, but, in Jing's study, the SPRY4-IT1 expression was low in ovarian cancer. In addition, the elevated SPRY4-IT1 expression was found to be associated with poor prognosis of carcinomas including colorectal cancer,[22] hepatocellular carcinoma,[23] Esophageal Squamous Cell Carcinoma,[24,25] gastric cancer,[26] glioma,[27] Renal Cell Carcinoma,[28] bladder cancer,[29] and melanoma.[10] However, only a few studies have been conducted to determine the prognostic value of SPRY4-IT1 in female carcinoma patients, and, if available, lack systematic analysis. Therefore, conducting meta-analysis is the most effective method, to gain an in-depth understanding of the prognostic impact of SPRY4-IT1 in female patients suffering from breast cancer and malignancies in the reproductive system.

For the purpose of meta-analysis, 670 female patients suffering from breast cancer and malignancies in the reproductive system, from 8 individual studies were selected for this study. Zheng, Xiang, Wang, Mehdi. Mohebi, Song, Cao, Li, and Jing[12,14–17,8,19] considered that the SPRY4-IT1 expression during multivariate analysis was an independent prognostic indicator for OS of women with breast carcinoma and malignancies in the reproductive system. Zheng, Xiang, Wang, and Jing[12,14,15,19] suggested that the SPRY4-IT1 expression during multivariate analysis is an independent prognostic indicator for DFS of patients suffering from the breast carcinoma and the ovarian cancer. Based on our results, the paper indicated that the elevated SPRY4-IT1 significantly predicted poor OS and

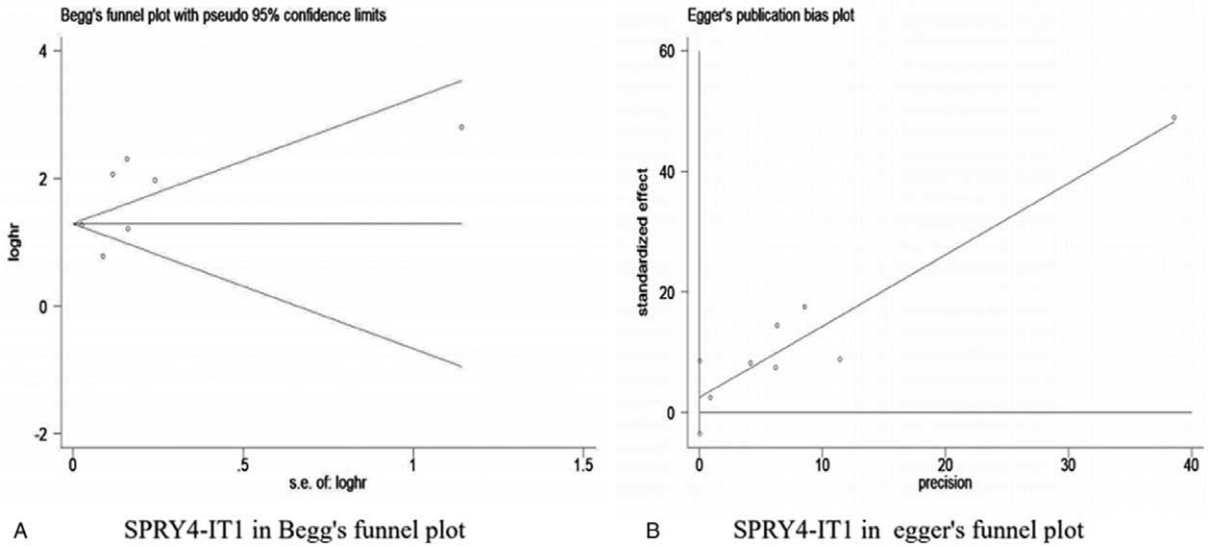

Figure 4. Begg funnel plot and Eegger funnel plot in the meta-analysis of female breast carcinoma and reproductive malignant tumors. (A) OS for SPRY4-IT1 in Begg funnel plot in the meta-analysis of breast carcinoma and reproductive malignant tumors. (B) OS for SPRY4-IT1 in Egger funnel plot in the meta-analysis of breast carcinoma and reproductive malignant tumors.

shorter DFS in female patients suffering from breast cancer (Supplementary Digital Content Figure S1A, C, http://links.lww.com/MD2/A961). SPRY4-IT1 was not associated with OS in women patients suffering from malignancies of the reproductive system [Supplementary Digital Content Figure S1B, http://links.lww.com/MD2/A961]. Most of the selected patients were from China and they did not differ from each other with regard to their ethnicity. The SPRY4-IT1 expression and clinicopathological features has also been reported in female breast cancer and reproductive malignancies population. In terms of the association between SPRY4-IT1 expression and clinicopathological features, the high expression of SPRY4-IT1 is indicative of a high risk of LNM and a more advanced clinical stage, which indicated that it might be responsible for post-operative metastasis and recurrence of carcinoma. The findings of the selected studies were consistent. Therefore, it can be concluded that, the expression of SPRY4-IT1 can be considered as an independent prognostic biomarker in patients suffering from breast carcinoma and malignant tumors in their reproductive organs.

Nevertheless, the meta-analysis has also posed some limitations that need to be mentioned. First, the study was retrospective in nature, which could easily lead to some bias. Second, most of these studies that were conducted or published in China, either in Chinese or English language were included for the purpose of analysis and so publication bias was almost inevitable. Third, only a limited number of documents were selected for the purpose of analysis. Further large-scale studies and randomized controlled trials need to be conducted in the future.

5. Conclusions

In summary, elevated expression of SPRY4-IT1 is indicative of poor prognosis of female breast cancer patients and those suffering from malignancies in the reproductive system. In the future, studies with long-term follow-up prospective, involving large-scale randomized control trials need to be conducted to provide further verification of the conclusion with respect to the association between the expression level of SPRY4-IT1 and prognosis of the diseases.

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