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ORIGINAL ARTICLE

Long Non-Coding RNA SPRY4-IT1 Can Predict Poor Prognosis in Digestive System Malignancies: a Meta-Analysis

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Abstract Recent studies have reported that long non-coding RNA SPRY4 intron transcript 1 (SPRY4-IT1) is abnormally expressed in malignant digestive tumors and associated with prognosis. But its clinical relevance is unclear. Here, we performed a meta-analysis aims to evaluate the prognostic value of SPRY4-IT1 in digestive system malignancies. We systematic search the PubMed, Web of Science, ScienceDirect and Wiley Online Library database to eligible studies. The pooled hazard ratios (HRs) with a 95% confidence interval (95% CI) were calculated to explored the association of lncRNA SPRY4-IT1 with prognosis. Five studies were eligible for analysis, a total of 518 patients were included. Meta-analysis indicated that overexpression of SPRY4-IT1 was associated with poor over survival (OS) (HR = 1.24, 95%CI:0.49–1.98; random-effects model). The clinicopathological parameters analysis further showed that increased expression level of SPRY4-IT1 was positively correlated with lymph node metastasis (HR = 1.45, 95% CI =0.88–2.02; fixed-effects model), TNM stage (HR = 1.24,95% CI = 0.78–1.70; fixed-effects model), and invasion depth (HR = 1.25,95% CI = 0.63–1.88; fixed-effects model). lncRNA SPRY4-IT1 may serve as a potential prognostic marker in malignant digestive tumors.

Keywords lncRNA · SPRY4-IT1 · Prognosis · Metastasis · Meta-analysis

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Introduction

Colorectal cancer, gastric cancer, esophageal cancer is the most common malignant digestive tumors with high incidence, high mortality and hidden symptoms. Early diagnosis is one of the major strategies to reduce mortality and improve patient quality of life. Tumor markers play an important role in the monitoring and diagnosis of malignant digestive tumors. Therefore, the search for new early diagnostic biomarkers has become the key to clinical work [1–3].

Recently, numbers of studies have found that long noncoding RNAs (lncRNAs),which refer to a class of RNA transcripts of greater than 200 nucleotides without protein-coding function [4], are play a role in tumor suppressing or cancer-promoting. With the deepening research of lncRNA function, the study revealed that there are a large number of abnormal expression of lncRNAs in digestive system malignancies [5–8], which play an important role in the development and progression of digestive system tumors. SPRY4 Intronic transcript 1 (SPRY4-IT1) is a 708-nucleotide-long lncRNA, which found that abnormally expression in digestive system tumors, including colorectal cancer (CRC) [9, 10], gastric cancer(GC) [11, 12], esophageal squamous cell carcinoma(ESCC) [13].

Besides, some studies reported aberrant expression of SPRY4-IT1 has association with prognosis, but this studies exploring the implication of SPRY4-IT1 are limited by small sample size, and there is no systematic meta-analysis of the association of SPRY4-IT1 with the prognosis of digestive system cancer patients, thus, It is necessary to conduct meta-analysis to explore SPRY4-IT1 expression was associated with prognosis in digestive system cancers patients, and discuss whether SPRY4-IT1 can be used as a potential prognositic biomarker in digestive system malignancies.

Evidence Acquisition

Literature Search

Collecting potential qualifying studies through searching in the following databases: PubMed, Web of Science, ScienceDirect, Wiley Online Library and the deadline for February 24, 2017, for the related studies in Chinese or English. The literature search strategy involved a combination keywords included: "SPRY4 intronic transcript 1", "SPRY4-IT1", "long non-coding RNA SPRY4-IT1", "lncRNASPRY4-IT1", "cancer", "tumor", "carcinoma", "neoplasm".

Inclusion and Exclusion Criteria

The collected studies were considered eligible if they met the following criteria: (1) articles study was to investigate the role of SPRY4-IT1 in digestive system cancer; (2) associations of SPRY4-IT1 expression levels with prognosis; (3) patients were grouped according to the expression levels of SPRY4-IT1; (4) articles study containing sufficient data for the computation of hazard ratios (HRs) and corresponding 95% confidence intervals (CI) for overall survival, lymph node metastasis, advanced TNM stage and invasion depth. Exclusion criteria were as follows: (1) studies without usable data; (2) duplicated publications; (3) studies only investigated the molecular structure and functions of SPRY4-IT1; (4) letters, reviews, case reports and expert opinions.

Data Extraction and Quality Assessment

All study and usable data were screened and extracted by two independent investigators (Cheng, Sun and Yangyang, Ding), according to the inclusion and exclusion criteria. Data extraction of literature was as follows: first author, year, country, ethnicity, tumor type, sample size, number of patients in high and low SPRY4-IT1, HR, NOS, cutoff value and Method. The quality of each studies were evaluated by using Newcastle-Ottawa Scale(NOS) standard, which included selection, comparability, and outcome with a score range of 0–9. Two investigators (Cheng, Sun and Yangyang, Ding) assess the quality of each study independently.

Statistical Methods

Statistical analyses of HRs for OS, LNM, TNM stage and invasion depth were calculated by Stata12 (Stata Corp, College Station, Texas). All p values were 2-sided, and $p < 0.01$ was considered as statistically significant. Statistical heterogeneity among the studies was tested by Cochran Q test and I^2 statistic. If heterogeneity was significant (Cochran Q test: p value < 0.10 or $I^2 > 50\%$), the random-effects model was used to estimate the pooled HR, and if not, the fixed effects model was implemented. The publication bias was assessed by Begg's funnel plot, and the p value <0.05 was considered as the presence of publication bias.

Evidence Synthesis

Characteristics of Included Studies

Literature search and screening process is presented in Fig. 1. Based on the inclusion criteria, five studies involving a total of 518 patients met the inclusion criteria, and the patient sample size ranges from 61 to 175 with a median sample size value of 92. All studies were come from China, 3 types of human cancer were included in this analysis with 2 colorectal cancer(CRC), 2 gastric cancer(GC) and 1 esophageal squamous cell carcinoma(ESCC). The levels of SPRY4-IT1 expression were detected by reverse transcription quantitative polymerase chain reaction (qRT-PCR), and all included studies consisted of two groups: high and low expression of SPRY4-IT1. Main information of the included studies were shown in Table 1.

Association between SPRY4-IT1 Expression Levels and OS in Malignant Digestive Tumors

Five studies involving a total of 518 patients were included in the analysis. Pooled hazard ratios (HRs) and the respective 95% confidence interval (CI) to estimate the association bewteen SPRY4-IT1 expression and OS. The result of analysis showed that the pooled HR for OS was 1.24(95%CI:0.49–1.98, $P < 0.01$) (Fig. 2) with heterogeneity ($I^2 = 62.2\%$, $P_h = 0.032$). Due to the heterogeneity, we also performed a sensitivity analysis, after excluding the Xie study [12], the observed heterogeneity disappeared and the results did not change. This result shown that SPRY4-IT1 overexpression predicted poor OS in malignant digestive tumors.

Association between SPRY4-IT1 Expression Levels and Clinicopathological Parameters in Malignant Digestive Tumors

Lymph Node Metastasis

A total of four studies reported the association between lncRNA SPRY4-IT1 expression and lymph node metastasis. The result of analysis showed that the pooled HR for LNM was 1.45(95% CI: 0.88–2.02, $P < 0.01$) (Fig. 3) without heterogeneity ($I^2 = 17.0\%$, $P_h = 0.306$). This result shown that overexpression of SPRY4-IT1 predicted a higher incidence of lymph node metastasis in malignant digestive tumors.

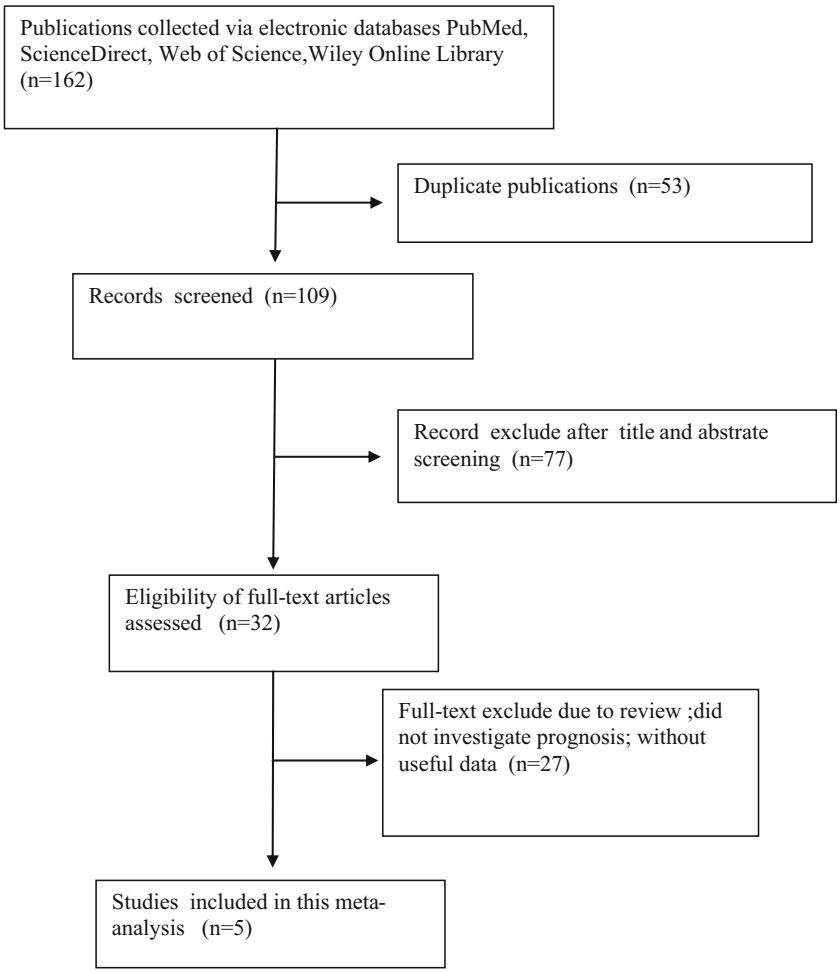

Fig. 1 Literature search and screening process

TNM Stage

A total of three studies reported the association between lncRNA SPRY4-IT1 expression and TNM stage. The result of analysis showed that the pooled HR for TNM stage was 1.24(95%CI:0.78–1.70, $P < 0.01$) (Fig. 4) without heterogeneity ($I^2 = 0.00\%$,$P_h = 0.378$). This result shown that overexpression of SPRY4-IT1 predicted advanced TNM stage in malignant digestive tumors.

Invasion Depth

A total of three studies reported the association between lncRNA SPRY4-IT1 expression and TNM stage. The result of analysis showed that the pooled HR for TNM stage was 1.25(95% CI:0.63–1.88, $P < 0.01$) (Fig. 5) without heterogeneity ($I^2 = 0.00\%$,$P_h = 0.976$). This result shown that overexpression of SPRY4-IT1 predicted a higher risk of deep tumor invasion in malignant digestive tumors.

Table 1 Characteristics of patients in malignant digestive tumors

Study	Year	Region	Tumor type	Sample size	SPRY4-IT1 expression		HR (95% CI)	NOS	Cutoff value	Method
					High expression	Low expression				
Cao [9]	2016	China	CRC	84	36	48	3.21(1.55–6.67)	7	2.87	qRT-PCR
Peng [11]	2015	China	GC	175	98	77	0.818(0.314–1.567)	8	0.778	qRT-PCR
Xie [13]	2014	China	ESCC	92	46	46	2.049(1.042–4.032)	8	4.52	qRT-PCR
Xie [12]	2015	China	GC	61	30	31	0.5(0.23–1.10)	6	0.535	qRT-PCR
Tan [10]	2017	China	CRC	106	58	48	2.341(1.136–4.826)	8	mean	qRT-PCR

Abbreviations: *HR*, Hazard ratios; *OS*, Overall survival; *CRC,* Colorectal cancer; *ESCC*, Esophageal squamous cell carcinoma; *GC*, Gastric cancer; *qRT-PCR*, Reverse transcription quantitative polymerase chain reaction

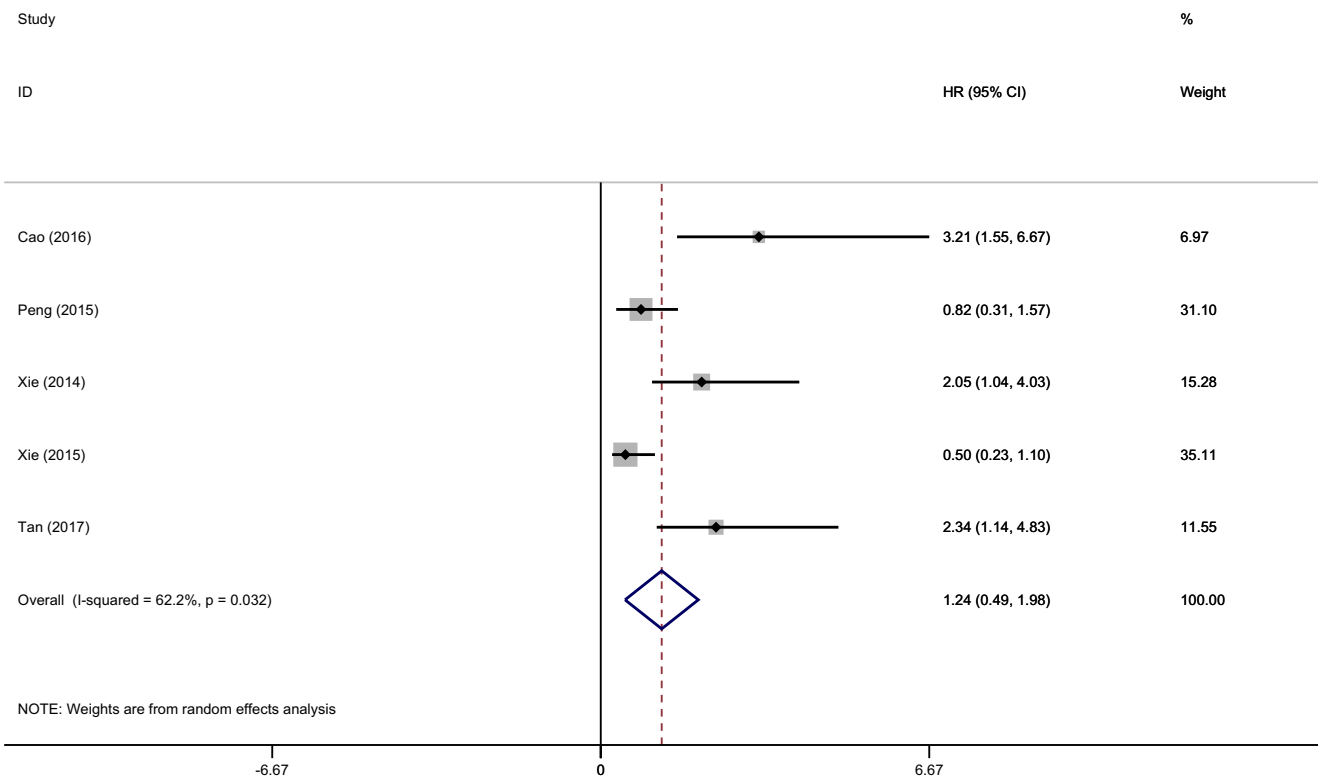

Fig. 2 Forest plot of HRs for the association between high SPRY4-IT1 expression and overall survival (OS) in digestive system malignancy patients

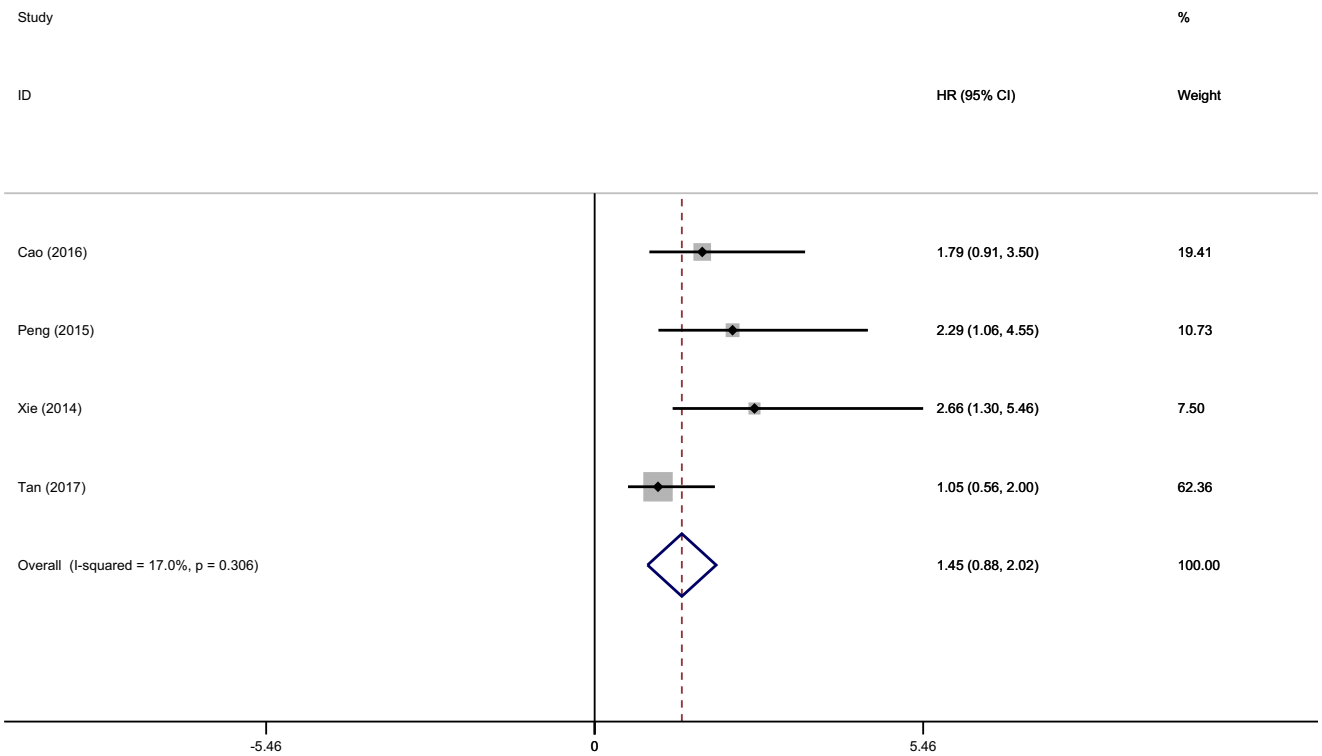

Fig. 3 Forest plot of HRs for the association between high SPRY4-IT1 expression and lymph node metastasis in digestive system malignancy patients

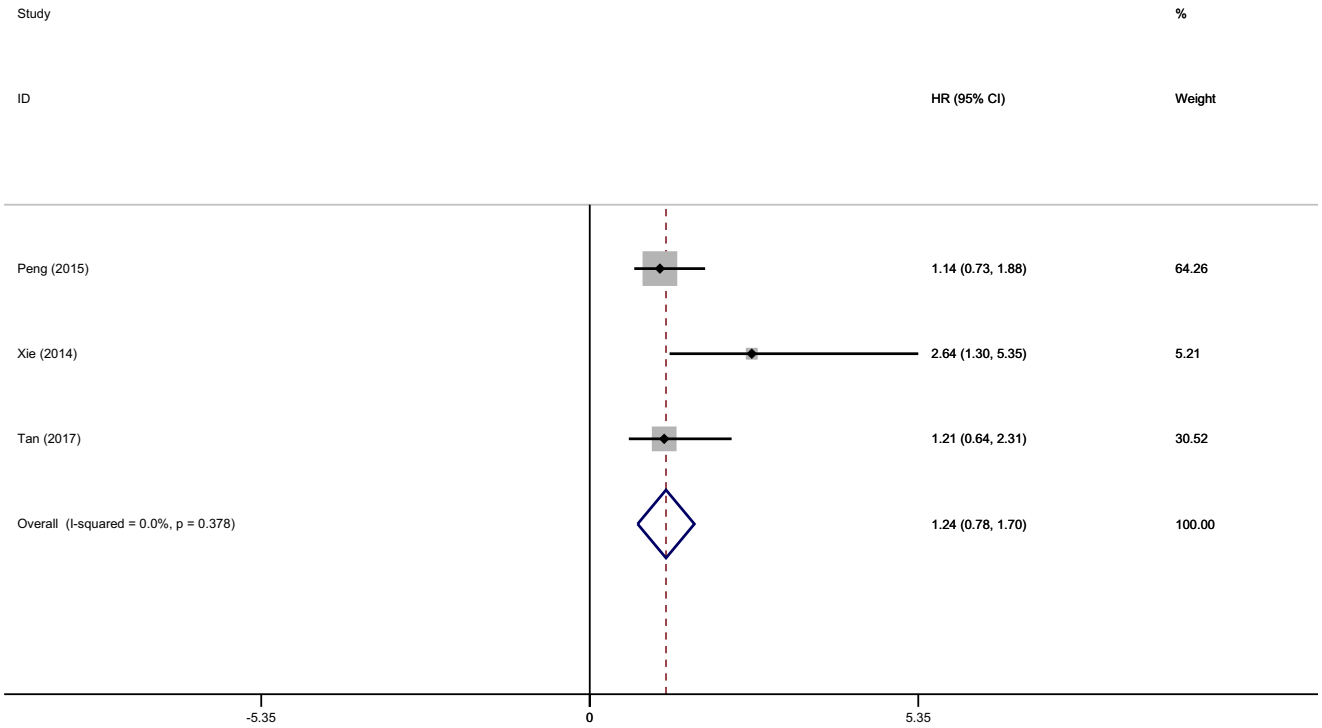

Fig. 4 Forest plot of HRs for the association between high SPRY4-IT1 expression and TNM stage in digestive system malignancy patients

Publication Bias and Sensitivity Analysis

In order to assess whether publication bias, we used funnel plot and Begg's test to assess this meta-analysis. Begg's test showed that there was no publication bias in analysis of OS (P = 0.806), and funnel plot (Fig. 6) showed no evidence of obvious asymmetry for OS. Additionally, Begg's test showed no publication bias in analysis of lymph node metastasis(P = 0.308), TNM stage(P = 0.296) and invasion depth (P = 0.296).

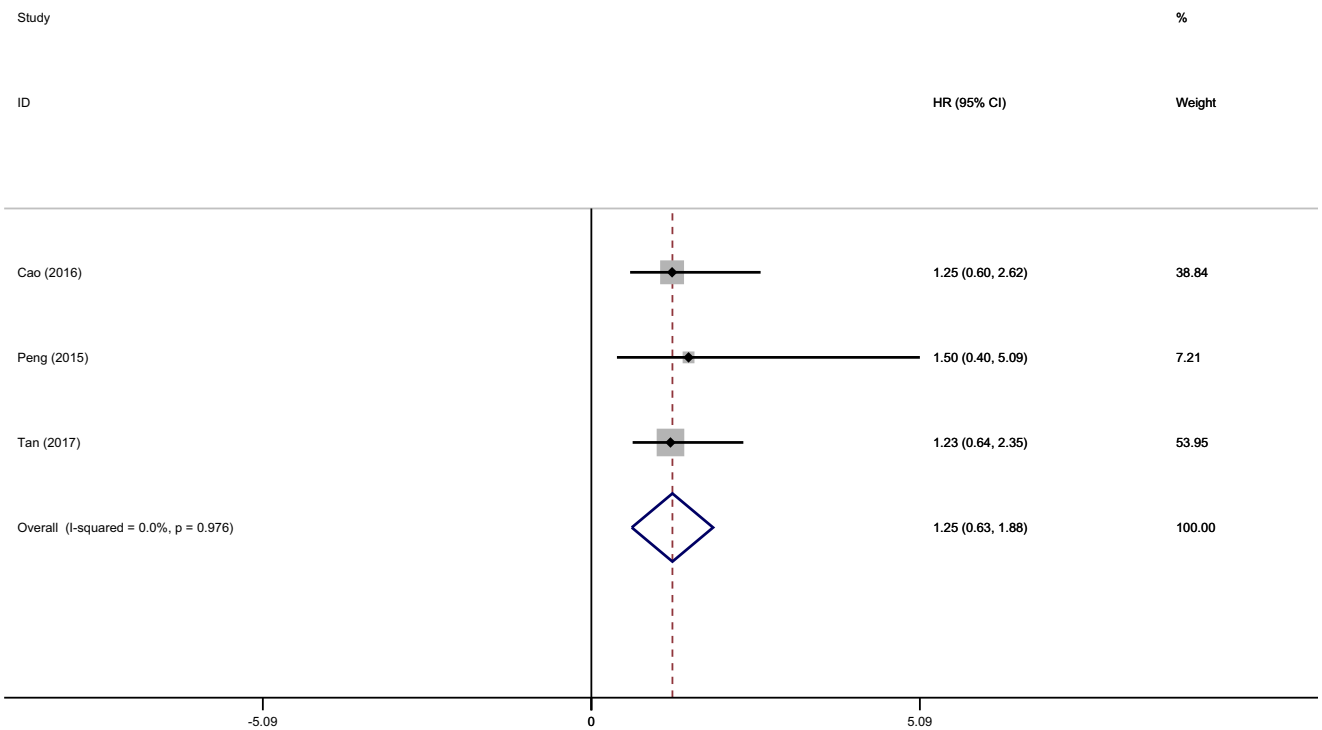

Fig. 5 Forest plot of HRs for the association between high SPRY4-IT1 expression and invasion depth in digestive system malignancy patients

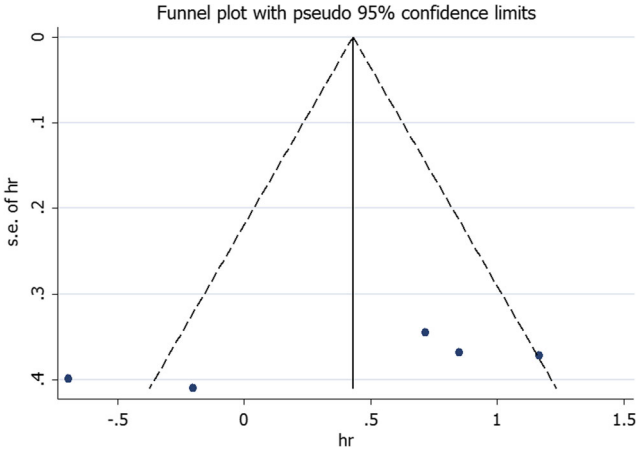

Fig. 6 Funnel plot of the publication bias for the analysis of SPRY4-IT1 in OS in digestive system malignancy patients

Discussion

Digestive system tumors include liver cancer, gastric cancer, esophageal cancer, colorectal cancer and pancreatic cancer, the high morbidity and mortality rate of digestive system cancers remain a critical health problem worldwide [14]. As the early symptoms of digestive system malignancies are not obvious, and lead to the current clinical diagnosis is difficult to accurately, thus, seeking a new tumor biomarkers or new therapeutic targets has become the key to clinical work. In recent years, lncRNA discovery and its functional research has promoted the development of tumor biology greatly. Numbers of studies [7, 15, 16] have shown that some abnormal expression of lncRNAs is related to the occurrence and development of tumors, suggesting that lncRNA can be used as tumor prevention, biomarkers or targets for prognosis.

SPRY4-IT1, a newly discovered lncRNA, was identified in adipose tissue and is transcribed from the second intron of the SPRY4 gene, located at 5q31.3 [17]. In recent years, there are many important findings that SPRY4-IT1 can mediate epithelial–mesenchymal transition pathway to promote tumor metastasis [18]. SPRY4-IT1 was also found to modulate the proliferation and migration of estrogen receptor-negative breast cancer cells by regulating target ZNF703 and to influence tumor growth [19]. These efforts are to understand the functional role of SPRY4-IT1 in the progression of cancer, although the underlying molecular mechanisms involved in cancer progression are largely unclear, but we have gained some revelation that targeting SPRY4-IT1 may be beneficial to human cancer treatment. Among the many studies, like peng's [11] studies indicated that overexpression of SPRY4-IT1 was significantly associated with poor prognosis in gastric cancer. But xie's [12] studies found low SPRY4-IT1 expression indicated a shorter overall survival. Due to existence of the different conclusions, we collected relevant articles and carried out a quantitative meta-analysis to explore the relationship between SPRY4-IT1 expression levels with prognosis in malignant digestive tumors.

In this meta-analysis, screening was conducted through a series of selection criteria, which eventually included 5 studies on 3 categories of malignancies for a total of 518 patients. The results demonstrate that overexpression of SPRY4-IT1 is associated with poor over survival in malignant digestive tumors. Despite the heterogeneity is obvious, which may be related to the sample size, Meanwhile, we performed a sensitivity analysis, after excluding the Xie study, the observed heterogeneity disappeared and the results did not change, this shows that our results are reliable and stable. Furthermore, we analyzed the clinicopathological parameters. The results showed that increased expression level of SPRY4-IT1 was positively correlated with lymph node metastasis, TNM stage and invasion depth. Due to the limited number of studies we did not carry out funnel plot to assess bias, but Begg's test showed no publication bias.

However, there are several limitations in this meta-analysis, the main limitation is all of the studies came from China and did not include the patients of other countries. Another limitation is that only studies published in English were selected, which may cause language bias despite there was no evidence of publication bias in this meta-analysis. The last limitation is the number of studies was relatively small. Consolidate the above limitations, it is need to be conduct larger-size and better design studies to confirm our results.

Conclusion

In conclusion, our meta-analysis revealed that elevated SPRY4-IT1 is a predictor of poor prognosis, higher incidence of metastasis, higher risk of deep tumor invasion and advanced TNM stage. Thus, lncRNA SPRY4-IT1 may serve as a potential prognostic marker in malignant digestive tumors.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interests regarding the publication of this paper.

Abbreviations *HR*, hazard ratios; *CI*, confidence interval; *OS*, overall survival; *CRC*, colorectal cancer; *GC*, gastric cancer; *ESCC*, esophageal squamous

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