Clinicopathological and prognostic significance of SPARC expression in gastric cancer: A meta-analysis and bioinformatics analysis

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Abstract. Secreted protein acidic and rich in cysteine (SPARC) is a member of the extracellular matrix glycoprotein family that binds to calcium ions. It may bind to a variety of proteins in the extracellular matrix and also compete with cell membrane surface receptors for growth. In the present study, the relationship between SPARC expression in gastric cancer tissues and the clinicopathological characteristics and prognosis of patients with gastric cancer were systematically evaluated. A meta-analysis and bioinformatics analysis were performed using the PubMed, Chinese National Knowledge Infrastructure, Kaplan-Meier (KM)-plotter, The Cancer Genome Atlas (TCGA), Gene Expression Profiling Interactive Analysis (GEPIA), University of ALabama at Birmingham CANcer (UALCAN), Human Protein Atlas (HPA) and Timer databases. SPARC was mainly expressed in tumor mesenchymal cells. The meta-analysis indicated that SPARC expression was higher in gastric cancer tissues than in normal tissues. SPARC was associated with the degree of differentiation and distant metastasis. K-M plotter results indicated that high SPARC expression was negatively associated with overall survival, post-progression survival and progression-free survival rates of patients. According to the Oncomine, GEPIA, UALCAN and HPA databases, SPARC mRNA and protein expression was upregulated in gastric cancer vs. normal tissues and was negatively associated with poor patient prognosis. In the TCGA database, univariate analysis indicated that lymph node metastasis and distant metastasis were associated with the prognosis of patients with gastric cancer. Cox multifactorial analysis suggested that high SPARC expression, age and distant metastasis were important factors affecting the survival time of patients with gastric cancer. Analysis with the Timer database indicated that SPARC was closely associated with the proportion of 7 immune-cell infiltrates in gastric cancer. These findings indicated that high expression of SPARC may be a potential marker of tumorigenesis and metastasis in patients with gastric cancer.

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Introduction

Gastric cancer is a digestive tract tumor that seriously threatens human health and life and is the third leading cause of cancer-associated death worldwide (1). In recent years, although the incidence of gastric cancer has decreased worldwide, the incidence and mortality rate of gastric cancer in China have both risen (2). Therefore, improving the diagnostic rate of early gastric cancer and finding new therapeutic targets and prognostic indicators are important directions of current gastric cancer research.

SPARC, also known as osteoadhesive protein, is a calcium-binding glycoprotein whose structure and function are regulated by calcium ions. It belongs to the stromal cell protein family, which inhibits cell adhesion and promotes tumor cell proliferation, invasion and metastasis (3). The SPARC protein has three functional domains: Amino acid terminal Ca-binding region, Cu-binding region and extracellular Ca-binding region. Because of the three functional regions of SPARC, it may participate in cell proliferation and angiogenesis; however, to the best of our knowledge, no previous study has determined whether serum calcium and copper levels affect the growth of cancer (4). SPARC is mainly expressed in mesenchymal cells and its expression may inhibit the synthesis of mechanistic proteins and alter the composition and structure of mesenchymal stroma (5). It may also increase the synthesis of mechanistic degradation enzymes, thus promoting tumor cells to break through the basement membrane of blood vessels and lymphatic vessels for distant metastasis (6). In addition, SPARC can induce gastric tumor cells to become round in shape and have an anti-adhesion role, thereby improving the invasive ability of gastric tumor cells (7).

In most studies on cancer published to date, SPARC was indicated to be abnormally expressed and closely related to the

biological behavior of malignant tumors, such as cancer cell invasion and metastasis. SPARC inhibits the mitogenic effect of VEGF in human microvascular endothelium and reduces the tyrosine phosphorylation of the protein kinase activated by VEGF, further attenuating the activity of VEGF (8). High expression of SPARC in gastric cancer mesenchyme inhibits the progression of gastric cancer, while VEGF promotes the development of this type of cancer. SPARC inhibits tumor angiogenesis by regulating VEGF expression. As the expression of SPARC decreases, the inhibitory effect gradually decreases and tumor microvessels become more and more numerous, causing cancer cells to metastasize to distant sites (9). SPARC regulates extracellular matrix components and has a role in promoting the secretion of TGF-β1 protein, which reduces the adherence of gastric tumor cells, enhances their concentration dependence, and inhibits their growth and replication (10).

Previous studies have indicated that SPARC expression is elevated in colorectal, renal and prostate cancers (11-13). High SPARC expression is closely associated with tumor development and has an important role in tumor invasion and metastasis, leading to poor prognosis. In the present study, a meta-analysis and bioinformatics analysis were performed to analyze the relationship between SPARC expression and the clinicopathological characteristics and prognosis of gastric cancer.

Materials and methods

Literature search and data extraction. The published literature was obtained by searching the Pubmed and CNKI databases (May 2022) using the following key words: 'SPARC' AND 'gastric' (OR 'stomach') AND 'cancer' (OR 'carcinoma' OR 'tumor'). The inclusion criteria were as follows: i) Patients with gastric cancer; ii) immunohistochemical staining for SPARC expression; iii) article containing SPARC protein expression and clinicopathological features; iv) none of the patients received any medical treatment prior to surgery. The exclusion criteria were as follows: i) Patients received chemotherapy, radiation therapy or other treatment prior to surgery; ii) the article type was abstract, case report, review or meeting; iii) SPARC expression was detected by western blot or reverse transcription (RT)-PCR; iv) repeated publications.

Data extraction and quality assessment. The main information of the articles was extracted by two authors (JS and ZGF). The information extracted included the following: First author, year of publication, country, antibody company, number of cases and controls, expression changes and quality score assessment. The quality scores of the included articles were independently completed by two authors based on the Newcastle Ottawa Oncomine Scale (14).

Bioinformatics analysis. Using the Human Protein Atlas (HPA) database (www.proteinatlas.org), the protein expression of SPARC in normal gastric tissues and gastric cancer tissues was analyzed and the survival curves of patients with gastric cancer were drawn. The prognostic significance of SPARC mRNA expression was analyzed in gastric cancer using the Kaplan-Meier (KM)-plotter database (https://kmplot.com/analysis). The Oncomine database (www.oncomine.org) was used to analyze the SPARC mRNA expression levels in gastric cancer tissues and normal tissues. According to The Cancer Genome Atlas (TCGA) database (www.cancer.gov), the raw data were integrated, the expression of SPARC mRNA in gastric cancer was analyzed and its association with the clinicopathological and prognostic data of patients was determined. SPARC expression in gastric cancer was also analyzed using the Gene Expression Profiling Interactive Analysis (GEPIA; http://gepia.cancer-pku.cn/) and University of ALabama at Birmingham CANcer (UALCAN; http://ualcan.path.uab.edu/index.html) databases and the relationship between SPARC expression and patient prognosis was examined. The TIMER database (https://cistrome.shinyapps.io/timer/) was used to investigate the relationship between SPARC gene expression and clinical outcomes and immune-cell infiltration.

Statistical analysis. Revman version 5.3 (The Cochrane Institute) was used for the present analysis. The expression of SPARC was estimated using odds ratios (ORs) and 95% CIs. The heterogeneity of included articles was tested with the χ^2 test and if there was no statistically significant heterogeneity among studies ($P>0.1$, $I^2\leq 50\%$), a fixed-effects model was used. If there was significant heterogeneity among the studies ($P<0.1$, $I^2\geq 50\%$), a random-effects model was used. Funnel plots were drawn to assess publication bias and its asymmetry was quantified using Begg's test and Egger's test. Cox risk regression models were used for the univariate and multivariate analyses. This model analyzed the effect of risk factors, the hazard ratio and 95% CI. $P<0.05$ was considered to indicate a statistically significant difference. All data analyses were performed with SPSS 17.0 software (SPSS, Inc.).

Results

Characteristics of included studies. As illustrated in Fig. 1, a total of 9 eligible studies were chosen for inclusion in the present analysis (9,10,15-21). The main characteristics of the included studies are presented in Table I. Information on the expression of SPARC in gastric cancer tissues, as well as clinicopathological characteristics of patients, including histological type, tumor location, TNM stage, degree of differentiation, distant metastasis, lymph node metastasis, gender and age, was extracted.

Association between SPARC expression and clinicopathological characteristics of patients with gastric cancer. Forest plots for the association of SPARC with various parameters of patients with gastric cancer are provided in Fig. 2. The expression of SPARC in gastric cancer tissue was higher than that in normal gastric mucosal tissue ($P<0.05$; Fig. 2A). The meta-analysis further indicated that SPARC expression was not associated with the histological type ($P>0.05$; Fig. 2B), tumor location ($P>0.05$; Fig. 2C), TNM stage ($P>0.05$; Fig. 2D), lymph node metastasis ($P>0.05$; Fig. 2G), gender ($P>0.05$; Fig. 2H) and age ($P>0.05$; Fig. 2I). However, SPARC was associated with the degree of differentiation ($P<0.05$; Fig. 2E) and distant metastasis ($P<0.05$; Fig. 2F).

Publication bias. As presented in Fig. 3, funnel plots were used to detect heterogeneity among studies. Sensitivity analysis is

Table I. Main characteristics of studies included in the present meta-analysis.

First author	Year	Country	Antibody supplier	Cases	Controls	Risk of cancer associated with high SPARC expression	Quality (NOS)	(Refs.)
Li	2014	China	BIOSS	65	90	Increased	7	(10)
Li	2014	China	NS	46	61	Increased	8	(15)
Yang	2012	China	ZSGB-BIO	61	80	Increased	8	(9)
Dong	2011	China	BIOSS	95	123	Increased	8	(17)
Li	2015	China	ZYMED	95	108	Increased	8	(16)
Ma	2019	China	CST	91	192	Increased	7	(18)
Franke	2009	China	Germany	38	40	Increased	8	(19)
Wang	2004	China	ZYMED	25	40	Increased	8	(20)
Zhao	2009	China	Santa Cruz Biotechnology, Inc.	144	436	Increased	8	(21)

ZSGB, Zhongshan Goldenbridge Bio; CST, Cell Signaling Technology; NS, not specified; NOS, Newcastle Ottawa Scale; SPARC, secreted protein acidic and rich in cysteine.

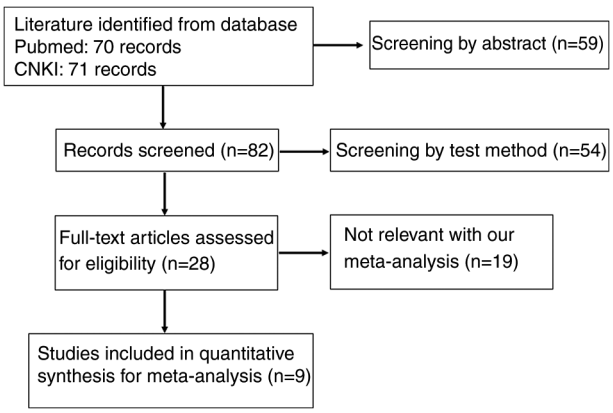

Figure 1. Flow diagram of article selection. CNKI, Chinese National Knowledge Infrastructure.

used to assess the impact of a single study on summary results, deleting one study at a time from the summary analysis. Based on Egger's test, there was no significant publication bias in the present meta-analysis.

Clinicopathological and prognostic significance of SPARC expression in gastric cancers. According to KM-plotter, it was indicated that higher SPARC expression was negatively associated with overall survival (OS) rates (P<0.05; Fig. 4A), even after the stratification of the patients by TNM stage, distant metastasis, perforation, treatment, Lauren's classification and Her2 status (P<0.05; Table II). These findings were the same for female patients, N1-N3 stage and well-differentiated tumors (P<0.05; Table II). In addition, higher SPARC expression was negatively associated with post-progression survival rates (P<0.05; Fig. 4A), even after the stratification of the patients by lymph node metastasis, distant metastasis and Lauren's classification (P<0.05; Table II). This was also the same for female patients with gastric cancer, those with TNM stage II-IV, treated with surgery alone or adjuvant therapy other than 5-FU, as well as Her2-negative tumors (P<0.05; Table II). The first progression survival rate during the entire treatment period of the patients with high expression of SPARC was significantly lower than that in the low expression group, and this was also the case in the subgroups stratified by tumor size and treatment (P<0.05; Fig. 4A and Table II).

According to the Oncomine database, SPARC mRNA expression was higher in gastric cancer tissue compared with that in normal tissues (P<0.05; Fig. 4B), even when cases were stratified as diffuse, intestinal and mixed-type carcinoma. Higher SPARC expression was negatively associated with OS rates based on the UALCAN database (P<0.05; Fig. 5A). Based on the UALCAN database, SPARC was also indicated to be highly expressed in gastric cancer tissues and high SPARC expression was strongly associated with grade, stage, lymph node metastasis, TP53 status and *Helicobacter pylori* infection status (Fig. 5B-G), but there was no significant difference between sexes or among different age groups (Fig. 5H and I).

The GEPIA database indicated that SPARC expression was higher in gastric cancer than in normal tissue and was positively correlated with the TNM stage (P<0.05; Fig. 6A-C).

SPARC expression was not significantly associated with OS according to the GEPIA and ONCOLNC databases (P>0.05; Fig. 6D and E); however, higher SPARC expression was negatively associated with OS rates based on the HPA (P<0.05; Fig. 6F). A univariate survival analysis performed in the TCGA database indicated that distant metastasis and lymph node metastasis were positively associated with the prognosis of patients with gastric cancer (P<0.05; Table III). Furthermore, multivariate analysis suggested that high SPARC expression, age and distant metastasis were important factors affecting patients' survival (P<0.05; Table IV). An analysis in the Timer database indicated that SPARC expression was closely associated with the proportion of 7 immune-cell infiltrates in gastric cancer (B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils and dendritic cells; P<0.05; Fig. 7A). When the degree of macrophage infiltration decreases, the survival time of cancer patients increases. However, survival and prognosis in cancer patients were negatively correlated

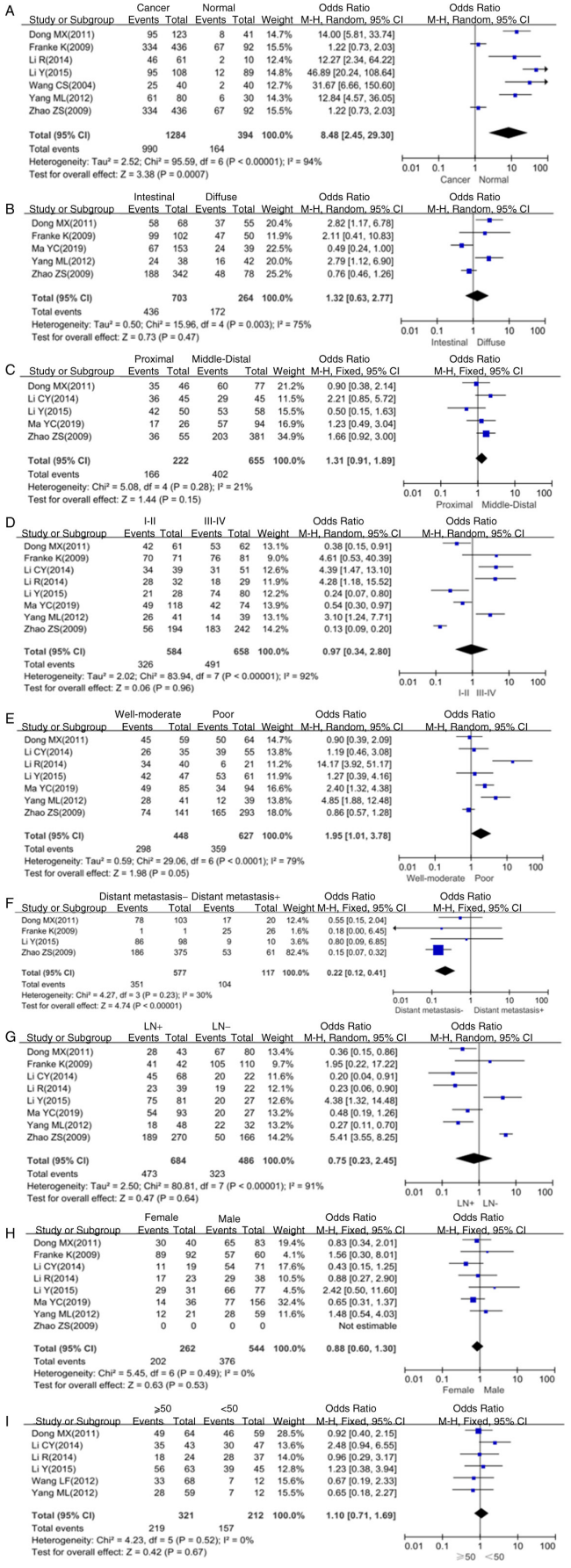

Figure 2. Forest plots of the expression of secreted protein acidic and rich in cysteine in gastric cancer. (A) Cancer vs. normal, (B) histological type, (C) tumor location, (D) TNM stage, (E) differentiation, (F) distant metastasis, (G) lymph node metastasis, (H) gender and (I) age. M-H, Mantel-Haenszel; df, degrees of freedom.

with SPARC expression (P<0.05; Fig. 7B). As presented in Fig. 7C, based on DNA copy variation data, it was found that diploid/normal is more common than deep deletion in CD8+, CD4+T cells, macrophages, neutrophils and dendritic cells, which is related to the deletion and gain at arm level.

Discussion

SPARC is a calcium-binding glycoprotein with multiple functions, promoting the following effects: Tumor-cell detachment, invasion and metastasis, matrix composition changes, basement membrane degradation and endothelial cell migration, and angiogenesis and cell growth stimulation (22). As a potential cell cycle inhibitor, SPARC may act as a cyclin to cause cell cycle arrest in G1 phase. The carboxyl terminal of region IV in the extracellular calcium binding region of SPARC contains a calcium binding site with high affinity, which may release active peptides after binding with calcium to act on endothelial cells and inhibit the proliferation of endothelial cells, thus affecting the biological activity of SPARC (23). It may bind to the dimer of platelet-derived growth factor (PDGF), thereby changing the structure of the dimer, which hinders the binding of PDGF to cell surface receptors, leading to the regulation of cell growth (24). In ovarian cancer, SPARC may inhibit the activation of ERK mediated by β-fibroblast growth factor and VEGF in endothelial cells and may also inhibit the phosphorylation levels of MAPK and ERK (25).

The strongly positive expression rate and score of SPARC in liver cancer tissues were significantly higher than those in normal liver tissues, which may promote tumor invasion and metastasis, demonstrating that it may act as a diagnostic tool for liver cancer. In addition, SPARC expression was different in liver cancer tissues with different Tumor, Nodes, American Joint Committee on Cancer stages and tumor differentiation. Univariate and multivariate survival analyses indicated that strongly positive expression of SPARC was a prognostic factor affecting OS and disease-free survival of patients with liver cancer, providing evidence that the SPARC expression pattern may aid the prognostication of liver cancer (26-28).

A previous study indicated that the expression of SPARC was significantly higher in colorectal cancer tissues, and was positively associated with tumor differentiation and metastasis, suggesting that SPARC has a role in tumor invasion and metastasis (29). Studies on colon cancer suggested that SPARC has the effect of inhibiting tumor angiogenesis, which is related to the expression of VEGF. The function of SPARC in tumors is the same: SPARC has the effect of inhibiting tumor angiogenesis, but it has a significant negative correlation with the expression of VEGF. It is well-known that VEGF is able to promote tumor blood angiogenesis; therefore, SPARC is mainly expressed in tumor stroma, and the anti-angiogenesis effect of SPARC may be achieved by regulating the expression of VEGF (29,30). SPARC is associated with distant metastasis and lymph node metastasis in malignant melanoma and may be used as a predictor of melanoma prognosis.

Another study, which used a transgenic mouse model, demonstrated that high expression of SPARC in prostate stromal adenocarcinoma inhibits the growth of cancer cells

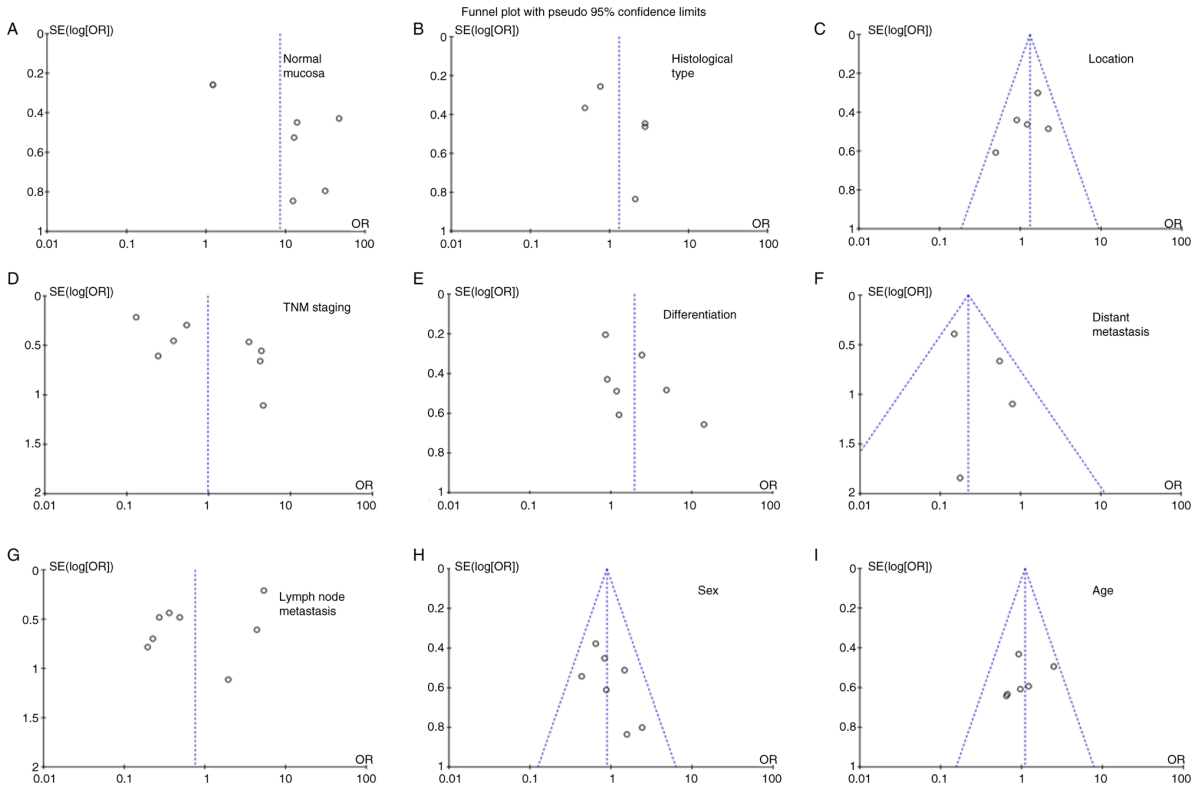

Figure 3. Funnel plot for testing publication bias for the association of SPARC with gastric cancer. Publication bias was also tested for the association between SPARC expression and clinicopathological features of gastric cancer, including (A) gastric mucosa, (B) histological type, (C) location, (D) TNM staging, (E) differentiation, (F) distant metastasis, (G) lymph node metastasis, (H) sex and (I) age. SPARC, secreted protein acidic and rich in cysteine; OR, odds ratio; SE, standard error.

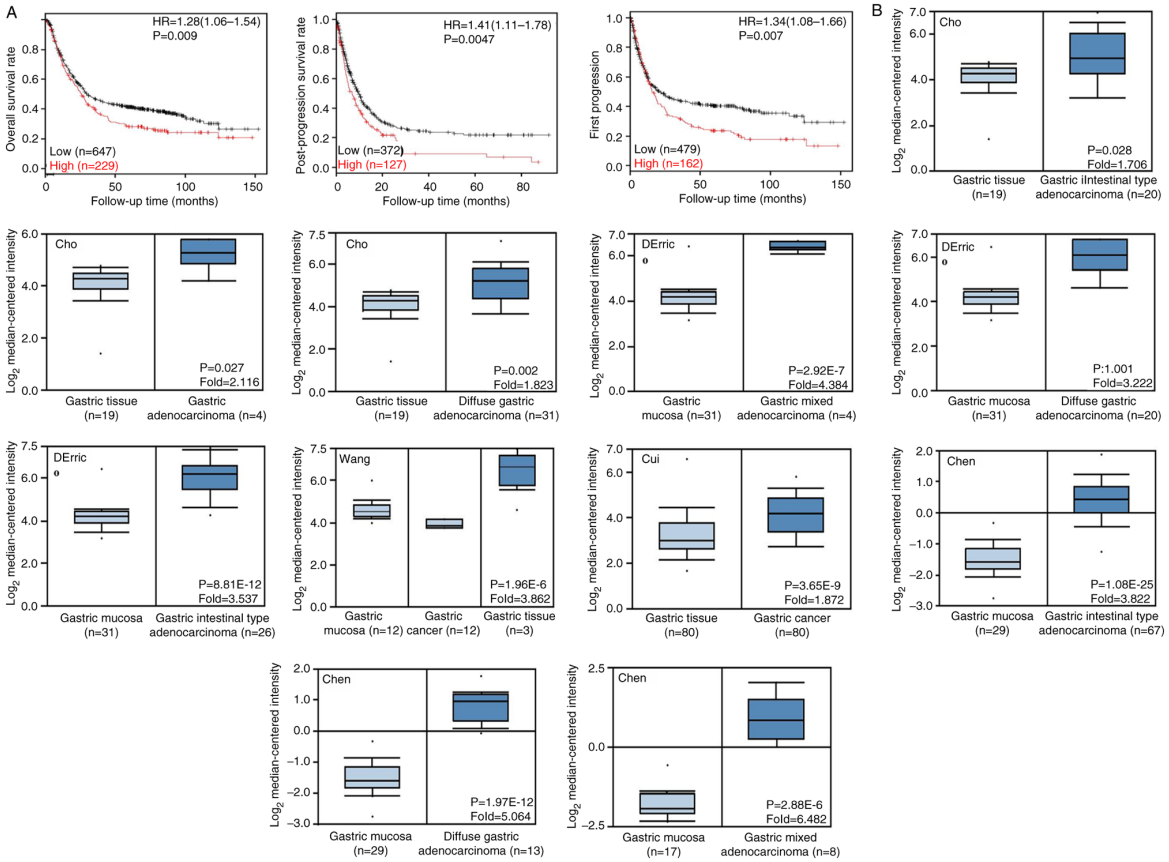

Figure 4. Prognostic value of SPARC mRNA expression in patients with gastric cancer according to the (A) Kaplan-Meier plotter and (B) Oncomine databases. SPARC, secreted protein acidic and rich in cysteine. HR, hazard ratio.

Table II. Prognostic significance of secreted protein acidic and rich in cysteine mRNA (high vs. low) in gastric cancer.

Clinicopathological features	Overall survival		Post-progression survival		First progression	
	Hazard ratio	P-value	Hazard ratio	P-value	Hazard ratio	P-value
Sex						
Female	1.80 (1.26-2.57)	0.0011	2.05 (1.33-3.17)	0.00093	1.84 (1.25-2.73)	0.0019
Male	1.22 (0.99-1.51)	0.065	1.26 (0.97-1.63)	0.087	1.17 (0.91-1.51)	0.23
TNM staging						
1	0.21 (0.05-0.95)	0.026	0.30 (0.04-2.55)	0.25	0.27 (0.06-1.22)	0.068
2	2.08 (1.03-4.22)	0.037	2.29 (1.10-4.77)	0.023	1.77 (0.91-3.46)	0.088
3	1.50 (1.12-2.01)	0.0066	2.40 (1.55-3.70)	$4.7x10^{-5}$	1.80 (1.24-2.60)	0.0017
4	1.62 (1.10-2.38)	0.013	1.77 (1.10-2.84)	0.017	1.47 (0.97-2.22)	0.066
Tumor stage						
2	1.90 (1.24-2.92)	0.0028	2.11 (1.34-3.32)	0.00094	1.74 (1.14-2.64)	0.0089
3	1.55 (1.09-2.22)	0.015	1.67 (1.14-2.45)	0.0081	1.46 (1.03-2.07)	0.034
4	3.72 (1.23-11.26)	0.013	1.56 (0.62-3.94)	0.34	3.22 (1.43-7.25)	0.0032
Nodal stage						
0	1.67 (0.71-3.96)	0.24	3.28 (1.00-10.68)	0.038	1.66 (0.70-3.93)	0.24
1-3	2.08 (1.60-2.72)	$3.5x10^{-8}$	2.16 (1.61-2.90)	$1.4x10^{-7}$	1.97 (1.53-2.55)	$1.2x10^{-7}$
1	2.44 (1.61-3.71)	$1.4x10^{-5}$	2.50 (1.58-3.95)	$5.1x10^{-5}$	2.30 (1.55-3.42)	$2.1x10^{-5}$
2	1.89 (1.20-2.99)	0.0057	1.81 (1.11-2.94)	0.015	2.07 (1.31-3.27)	0.0015
3	1.89 (1.09-3.71)	0.021	1.94 (1.08-3.47)	0.023	1.44 (0.85-2.43)	0.17
Metastasis stage						
0	1.80 (1.36-2.39)	$3.7x10^{-5}$	2.07 (1.52-2.82)	$2.0x10^{-6}$	1.76 (1.34-2.31)	$3.3x10^{-5}$
1	1.95 (1.08-3.54)	0.025	3.18 (1.41-7.18)	0.0036	1.38 (0.76-2.51)	0.29
Perforation						
-	1.66 (1.12-2.48)	0.012	1.37 (0.74-2.52)	0.31	1.63 (1.11-2.40)	0.011
Treatment						
Surgery alone	1.71 (1.23-2.38)	0.0014	1.85 (1.35-2.53)	$8.8x10^{-5}$	1.56 (1.17-2.09)	0.0022
5-FU-based adjuvant	0.58 (0.39-0.87)	0.0069	0.72 (0.48-1.08)	0.11	0.62 (0.42-0.92)	0.016
Other adjuvant	4.21 (1.74-10.19)	0.00053	4.11 (1.69-10.02)	0.00075	3.75 (1.71-8.23)	$4.0x10^{-4}$
Degree of differentiation						
Well-differentiated	2.97 (1.24-7.11)	0.01	-	-	-	-
Moderately differentiated	1.59 (0.79-3.21)	0.19	0.61 (0.24-1.58)	0.31	1.76 (1.33-3.45)	0.096
Poorly differentiated	1.38 (0.91-2.11)	0.13	0.69 (0.37-1.30)	0.25	1.53 (0.94-2.51)	0.087
Lauren's classification						
Intestinal type	1.69 (1.16-2.45)	0.0054	1.57 (1.04-2.38)	0.03	1.56 (1.09-2.22)	0.014
Diffuse type	2.17 (1.53-3.06)	$7.8x10^{-6}$	2.33 (1.58-3.42)	$1.0x10^{-5}$	2.07 (1.46-2.94)	$2.9x10^{-5}$
Mixed type	2.77 (0.97-7.93)	0.049	-	-	2.21 (0.79-6.20)	0.12
Her2 status						
-	1.43 (1.14-1.81)	0.0023	1.87 (1.39-2.52)	$3.1x10^{-5}$	1.42 (1.09-1.85)	0.0085
+	1.45 (1.08-1.96)	0.013	1.36 (0.93-1.98)	0.11	1.29 (0.91-1.82)	0.16

by affecting the cell cycle, thereby limiting the progression of prostate cancer (31,32). The expression of SPARC in breast cancer tissues is higher than that in normal tissues and its expression in tumor stromal cells is even higher than that in tumor cells. Studies have indicated that SPARC expression is positively associated with histological grade and TNM stage: Univariate analysis and Cox multivariate analysis suggested that lymph node metastasis, distant metastasis, age and TNM stage were negatively associated with the prognosis of patients with breast cancer. However, analysis with KM-plotter indicated that low expression of SPARC was negatively associated with OS, post-progression survival and distant metastasis. Metastasis and TNM stage are important factors affecting the survival time of patients with breast cancer and SPARC expression may be a good indicator of prognosis in patients with breast cancer (33). At the same time, SPARC expression was found in the MDA-MB-231 breast cancer cell line and to promote breast cancer metastasis to the lung (34).

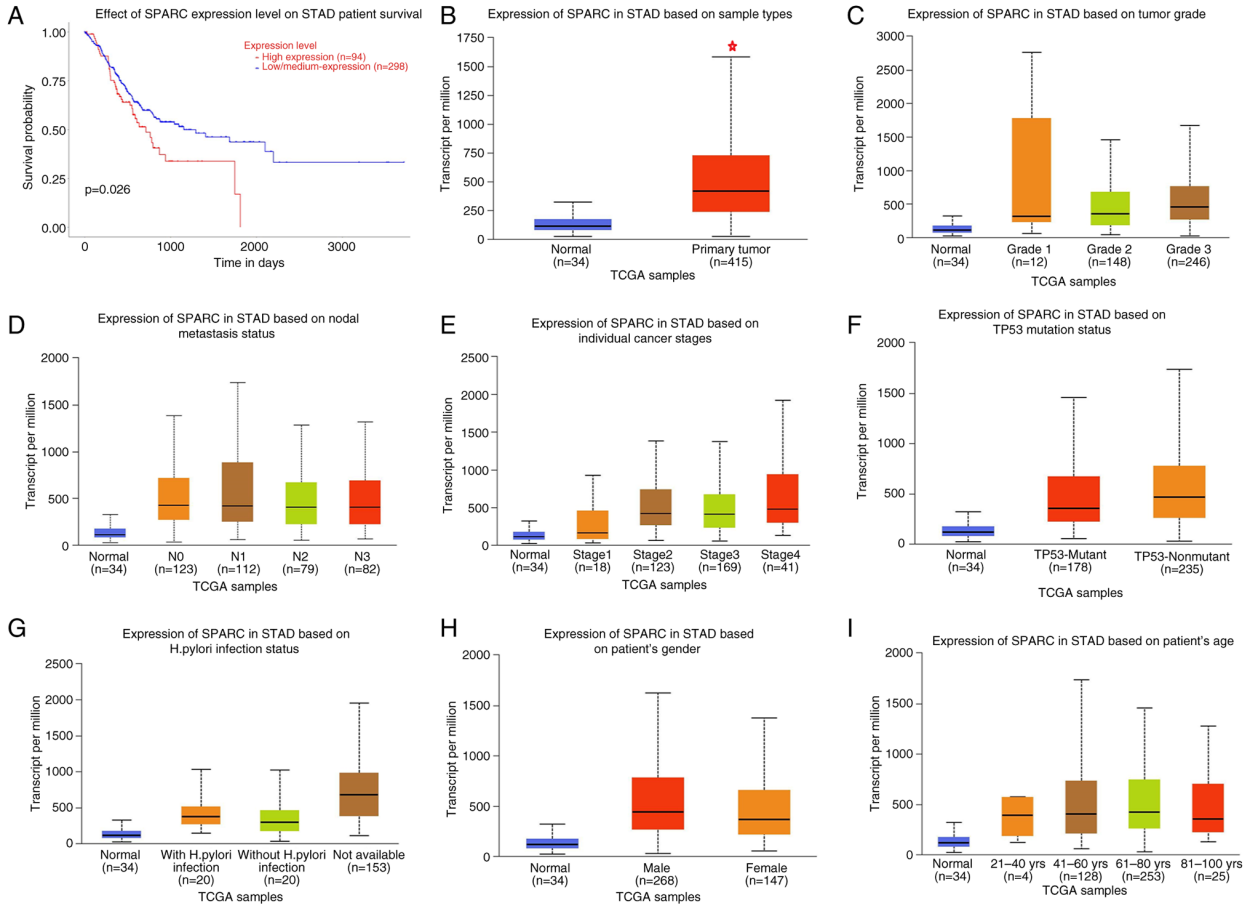

Figure 5. Prognostic value of SPARC mRNA expression in patients with gastric cancer according to the UALCAN database. (A) Overall survival, (B) SPARC was higher expressed in gastric cancer than normal tissues, (C) tumor grade, (D) node metastasis status, (E) individual cancer stages, (F) TP53 mutation status, (G) *Helicobacter pylori* infection status, (H) gender and (I) age. *P<0.05. SPARC, secreted protein acidic and rich in cysteine; TCGA, The Cancer Genome Atlas; STAD, stomach adenocarcinoma.

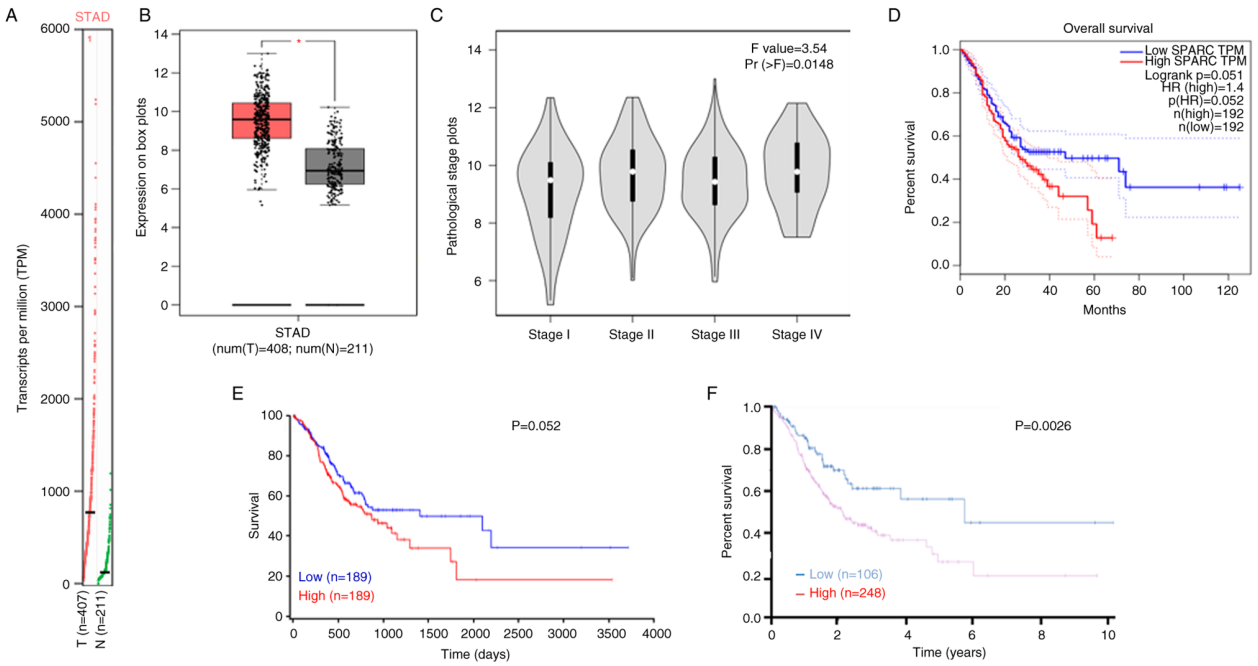

Figure 6. Prognostic value of SPARC mRNA expression in patients with gastric cancer according to the GEPIA, HPA and ONCOLNC databases. Based on the gene expression Profile (A) and box plots (B) in the GEPIA database, we found that SPARC expression was higher in gastric cancer than in normal tissue and (C) was negatively correlated with the TNM stage. The relationship between SPARC expression in gastric cancer and overall survival of patients based on the (D) GEPIA, (E) ONCOLNC and (F) HPA databases. *P<0.05. T, tumor; N, normal; SPARC, secreted protein acidic and rich in cysteine; HR, hazard ratio; GEPIA, Gene Expression Profiling Interactive Analysis; HPA, Human Protein Atlas; STAD, stomach adenocarcinoma.

Table III. Univariate analysis of prognostic risk factors in patients with gastric cancer.

Characteristic	Patients, n (%)	Relative risk (95% CI)	P-value
Sex			
Female	127 (37.1)	Ref.	
Male	215 (62.9)	1.030 (0.696-1.524)	0.883
Age, years			
<60	114 (33.3)	Ref.	
≥60	228 (66.7)	1.342 (0.880-2.049)	0.173
TNM stage			
I/II	46 (14.1)	Ref.	
III/IV	280 (85.9)	1.605 (0.857-3.006)	0.139
Invasion			
-	17 (5.0)	Ref.	
+	322 (95.0)	6.58 (0.915-47.62)	0.061
Lymph node metastasis			
-	107 (32.4)	Ref.	
+	223 (67.6)	2.066 (1.279-3.344)	0.003
Distant metastasis			
-	303 (92.9)	Ref.	
+	23 (7.1)	3.040 (1.686-5.464)	<0.001
Degree of differentiation			
Well-differentiated	10 (2.4)	Ref.	
Moderately-poorly differentiated	400 (97.6)	1.193 (0.946-1.684)	0.314

CI, confidence interval; TNM, tumor-nodes-metastasis.

Table IV. Multivariate analysis of clinicopathological variables influencing the survival of patients with gastric cancer.

Clinicopathological parameters	Relative risk (95% CI)	P-value
SPARC expression (+)	0.014 (0.001-0.190)	0.001
Age (≥60 years)	1.857 (1.105-2.999)	0.011
Sex (female)	0.898 (0.581-1.390)	0.631
Depth of invasion (T2-4)	5.451 (0.687-43.275)	0.109
Lymph node metastasis (+)	1.892 (0.982-3.645)	0.057
Distant metastasis (+)	3.056 (1.555-6.006)	0.001
TNM staging (III/IV)	0.649 (0.257-1.636)	0.359

CI, confidence interval; TNM, tumor-nodes-metastasis; SPARC, secreted protein acidic and rich in cysteine.

Previous studies used small interfering RNA to inhibit SPARC in high-expressing cell lines and found that the proliferation and survival of gastric cancer cells in the SPARC-knockdown group were significantly reduced, which was confirmed in a tumor formation experiment in nude mice (35,36). The detection of 10 commonly used gastric cancer cell lines indicated that 8 cell lines had SPARC promoter methylation and 7 of them had loss of SPARC expression. After pyrimidine nucleoside treatment, SPARC expression was restored to normal levels in all cell lines. The phenomenon of SPARC promoter methylation provides a new direction for gastric cancer prognostication and selection of therapeutic targets (37). Liao *et al* (38) and Li *et al* (39) found SPARC, one of the genes closely related to the occurrence of gastric cancer, through database screening of differentially expressed genes, and determined that the SPARC gene is closely related to the prognosis of patients with gastric cancer through KM-plotter and TCGA database analyses. However, in the present study, the expression of SPARC in gastric cancer tissue was examined through a meta-analysis and the relationship between its expression and clinical characteristics of patients was analyzed. The TCGA and KM-plotter databases were also used to analyze the prognosis of patients with SPARC gene expression, but the relationship between SPARC mRNA expression and clinicopathological characteristics of patients with gastric cancer was assessed in more detail. Furthermore, the expression of SPARC protein and mRNA in gastric cancer was examined in three additional databases, GEPIA, HPA and UALCAN, making the results more convincing. The influence of SPARC on immune-cell infiltration in gastric cancer was also analyzed through the Time database. The present results comprehensively explain the significance of the SPARC gene for patients with gastric cancer and lay a foundation for future research.

The expression of SPARC mRNA in gastric cancer tissue as determined by RT-PCR was significantly higher than that in normal tissue and immunohistochemical analysis

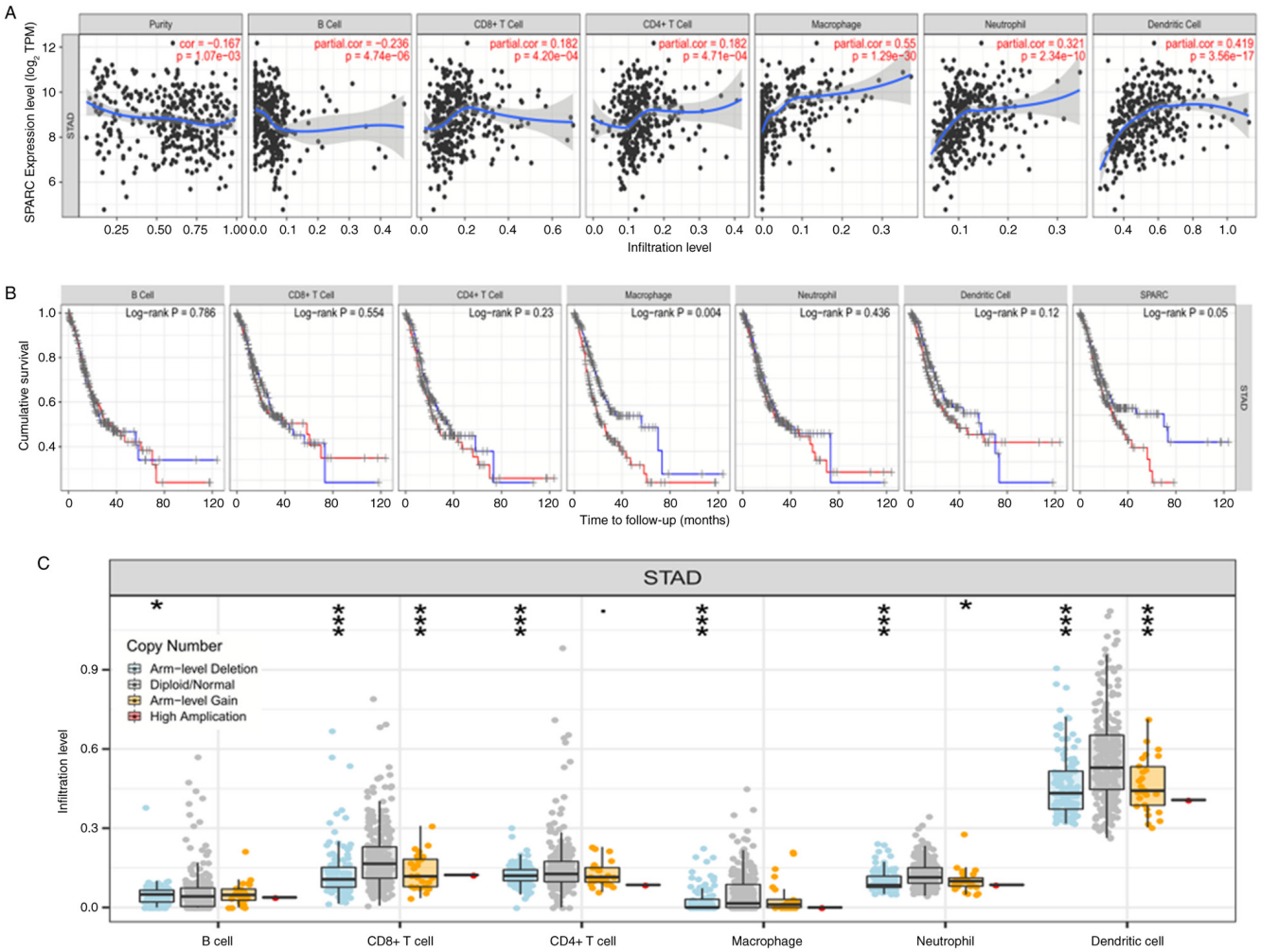

Figure 7. Association of SPARC with immune-cell infiltration in gastric cancer tissue. (A) Association between SPARC expression and immune cell infiltrates in gastric cancer. (B) Association between degree of immune cell infiltration and prognosis and SPARC expression and survival of patients with gastric cancer. (C) Based on DNA copy variation data, it was found that diploid/normal is more common than deep deletion in CD8+CD4+ T cells, macrophages, neutrophils and dendritic cells, which is related to the deletion and gain at arm level. *P<0.05; ***P<0.001. SPARC, secreted protein acidic and rich in cysteine; cor, correlation coefficient; STAD, stomach adenocarcinoma.

demonstrated that SPARC was highly expressed in interstitial cells, while its expression was lower in normal mucosal cells in tumor nuclei. High SPARC expression was negatively associated with TNM stage and lymph node metastasis (40,41). This is consistent with the present analysis, which indicated that SPARC expression was higher in gastric cancer tissues than in normal tissues. High SPARC expression was negatively associated with the degree of differentiation and distant metastasis. Furthermore, the KM-plotter analysis indicated that high SPARC mRNA expression was negatively associated with OS, post-progression and first progression survival rates of patients. Univariate analysis suggested that lymph node metastasis and distant metastasis were associated with the prognosis of patients with gastric cancer. Cox multifactorial analysis indicated that high SPARC expression, age and distant metastasis were independent factors affecting the survival time of patients with gastric cancer. In the TCGA database, the number of stratified samples of indicators included is not completely consistent, which may have led to inconsistent results regarding the TNM stage, lymph node metastasis and distant metastasis in the univariate analysis. Univariate analysis is the effect of each clinicopathological feature on prognosis. Multivariate analysis is a statistical analysis method that takes prognosis as the dependent variable and other pathological characteristics as independent variables, establishes a linear or nonlinear mathematical model to estimate the quantitative relationship between multiple variables, and uses sample data for analysis. Therefore, the results of the single-factor and multi-factor analysis may be different.

In conclusion, SPARC protein and mRNA expression is upregulated in gastric cancer. SPARC is positively associated with lymph node metastasis and distant metastasis of gastric cancer. High expression of SPARC may be a potential marker of tumorigenesis and metastasis in patients with gastric cancer.

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Availability data and materials

All data generated or analyzed during this study are included in this published article. The expression level of SPARC was analyzed using Oncomine. In addition, the prognostic significance of SPARC mRNA was analyzed using the KM-plotter, GEPIA, HPA, UALCAN, Timer, ONCOLNC and TCGA databases. The data for the meta-analysis were obtained from the studies listed in Table I.

Authors' contributions

JS and ZGF performed the meta-analysis and wrote the manuscript. JS and YKB analyzed the data from databases. The authenticity of the raw data was confirmed by JS and YKB. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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