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Original contribution

Overexpression of serum response factor is correlated with poor prognosis in patients with gastric cancer☆,☆☆

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Summary Serum response factor (SRF) is highly expressed in many tumors, including gastric cancer. However, the exact prognostic utility of SRF in patients with gastric cancer remains unclear. Therefore, in this study, we investigated the expression and prognostic value of SRF in patients with gastric cancer. SRF expression was detected by immunohistochemistry in 149 gastric cancer samples. The relationship between SRF expression and clinicopathological characteristics along with the prognostic significance of SRF in disease-free survival and overall survival of patients was analyzed. We found that the expression of SRF was significantly increased in gastric cancer tissues compared with adjacent noncancerous tissues. Overexpression of SRF was significantly correlated with histologic differentiation, invasion depth, lymph node metastasis, and TNM stage. Furthermore, disease-free survival rate and overall survival rate were both significantly lower for patients with high SRF expression. Multivariate Cox regression analysis identified high SRF expression as an independent prognostic factor for disease-free survival but not for overall survival. Our findings indicate that overexpression of SRF may play an important role in human gastric cancer recurrence and prognosis. SRF may serve as a predictive marker for prognosis of gastric cancer.

1. Introduction

Gastric cancer (GC) is one of the most common malignant tumors, especially in East Asia. The incidence of GC is estimated to be 951 600 new cases per year worldwide, with about half of the new cases in East Asia [1]. Although the incidence and mortality of GC are decreasing in developing countries, GC still represents the third leading cause of cancer-associated deaths worldwide [2]. A large proportion of patients with GC are diagnosed at advanced stages accompanied with lymph

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node metastasis or distant metastasis, when the disease is incurable. Although great progress has been made in early diagnosis and treatment in recent years, the outcome of GC patients remains poor. Even in the case of curative intent, the 5-year survival is still very low [3,4]. Developing new prognostic markers is of great importance for patients with GC.

Serum response factor (SRF) is a member of the MCM1, agamous, deficiencies, and SRF box family of transcription factors [5]. So far, DNA binding sites for SRF, also named serum response elements, have been found in the promoters of 50 different genes, including immediate early genes like c-fos, Egr-1, and muscle-specific genes [5,6]. SRF has been shown to be involved in cellular processes such as cell proliferation, differentiation, apoptosis, and angiogenesis [7-9]. Recently, the overexpression of SRF has been reported in some digestive system tumors, such as hepatocellular carcinoma, colorectal cancer, and esophageal cancer [10-12]. Besides matrix metalloproteinases 2 and 9, SRF can modulate the Wnt/β-catenin pathway and plays an important role in hepatocellular carcinoma progression [13]. In colorectal cancer, SRF enhances cell motility and invasiveness through modulating E-cadherin/β-catenin expression [11]. Esophageal cancer exhibits increased expression of SRF, and blocking SRF expression inhibits tumor cell proliferation and invasion through regulating β-catenin and cyclin D1 [12]. These findings indicate that SRF may act as a prometastatic factor during tumor metastasis.

High expression of SRF has also been found in GC tissues [14]. SRF may play an important role in the invasion and migration of GC cells [15,16]. However, the association between SRF and prognosis of GC has not been completely elucidated. In this study, we investigated the expression of SRF in surgical specimens of GC tissues and paired adjacent noncancerous (ANC) tissues by immunohistochemistry, analyzed the correlation between SRF expression and clinicopathological characteristics, and further analyzed the prognosis value of SRF expression for disease-free survival (DFS) and overall survival (OS), hoping to clarify the prognostic value of SRF in GC patients and give more clues for the treatment and prevention of GC.

2. Materials and methods

2.1. Tumor samples

This study was approved by the Ethics Committee of the Fourth Military Medical University, and informed consent was acquired in accordance with the Declaration of Helsinki. A total of 149 GC and ANC tissues were collected from patients who underwent surgical resection in Xijing Hospital from June 2006 to June 2009. All tissue samples were obtained from patients without undergoing any medical treatment before surgery. Histomorphology of all primary tumors specimens was confirmed with hematoxylin-eosin staining according to the TNM system of the American Joint Committee on Cancer or Union for International Cancer Control [17,18]. Each tissue sample was collected along with detailed patient information including age, sex, tumor location, tumor size, tumor differentiation, Lauren type, depth of invasion, lymph node metastasis, distant metastasis, and TNM stage.

2.2. Immunohistochemistry

Immunohistochemistry was performed using the Dako EnVision+ Kit (Dako, Carpinteria, CA) and detected by Dako Liquid DAB+, which is based on a horseradish peroxidase–labeled polymer conjugated with secondary antibodies. Paraffin-embedded tissues were cut into 4-μm-thick sections, mounted onto polylysine-coated slides, deparaffinized in xylene, rehydrated through an ethanol gradient, and rinsed with distilled water. To block endogenous peroxidase activity, the slides were treated with 1% H_2O_2 in methanol. For antigen retrieval, the sections were incubated in citrate buffer for 15 minutes at 95°C and then treated with 10% normal goat serum for 40 minutes at 37°C to block nonspecific binding sites. The tissue slides were incubated with an anti-SRF monoclonal antibody (1:100; Santa Cruz Biotechnology, Santa Cruz, CA) overnight at 4°C. The primary antibody was detected using the Dako EnVision+ Kit. Reaction products were visualized by the Dako Liquid DAB+ Substrate-Chromogen System and then counterstained with hematoxylin. Negative controls were obtained by incubating samples with normal mouse serum.

2.3. Immunohistochemical staining analysis

All immunostained sections were observed by 2 independent pathologists in a blind manner. According to methods described by recent studies, SRF expression scoring was based on both immunostaining intensity and extensity [19,20]. The staining intensity of positive cells was graded as follows: 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). The percentage of positive cells was determined semiquantitatively by assessing the whole tumor section, and each sample was scored as follows: 0 (negative), 1 (1%-25%), 2 (26%-50%), 3 (51%-75%), and 4 (76%-100%). Total scores of 0 to 12 was finally calculated and graded as follows: I, scores 0 to 1; II, 2 to 4; III, 5 to 8; and IV, 9 to 12. If the total score differed between the 2 pathologists, an agreement was reached by rescoring the slides together with a third pathologist. For further survival analysis, grades I and II represented low expression, and grades III and IV represented high expression.

2.4. Patient follow-up

In this study, all patients were regularly followed up at outpatient clinics for a period of 60 months. Tumor biomarkers,

upper gastrointestinal endoscopy, and abdominal ultrasonography were performed every 3 months, and computed tomography was also performed if necessary. The diagnosis of recurrence or distant metastasis was based on imaging techniques such as upper gastrointestinal endoscopy, ultrasonography, computed tomography, magnetic resonance imaging, and position emission tomography, and cytologic analysis if possible [21]. DFS was defined as the time from surgery to the first occurrence of any following events: recurrence, distant metastasis, or death from any cause without documentation of a cancer-related event. OS was defined as the time from surgery to the day the patient died. The end point for follow-up was set at the 60th month, and the survival time was also set at the 60th month for those who survived for more than 5 years.

2.5. Statistical analysis

Statistical analysis and graphic presentation were performed using the SPSS 22.0 software package (IBM, Armonk, NY). Differences between GC tissues and ANC tissues and associations between SRF expression and clinicopathological characteristics were analyzed using the Mann-Whitney test. Survival curves were estimated using the Kaplan-Meier method, and differences in survival distributions were evaluated by using the log-rank test. Relevant prognostic factors were identified through univariate Cox regression analysis and then multivariate Cox regression analysis. P values <.05 were considered statistically significant.

3. Results

3.1. Immunohistochemical detection of SRF in GC and ANC tissues

Positive staining of SRF was mainly found in the nucleus, and cytoplasmic staining was also found in some cancer cells. In addition to the staining observed in carcinoma cells, smooth muscle cells and endothelial cells also showed positive nuclear staining for SRF (Fig. 1). In GC tissues, SRF expressions of grade I, grade II, grade III, and grade IV were found in 30, 42, 49, and 28 patients, respectively, whereas in ANC tissues, SRF expressions of grade I, grade II grade III, and grade IV were found in 54, 54, 28, and 13 patients, respectively. The expression level of SRF in GC tissues was higher than that in ANC tissues (Table 1, $P < .001$).

3.2. Correlation between SRF expression and clinicopathological characteristics

According to the statistical results of immunostaining, the correlations between SRF expression and clinicopathological characteristics are shown in Table 2. High SRF expression was found in moderately and poorly differentiated GC tissues when compared with expression in well-differentiated GC tissues ($P = .012$). Because a statistically significant difference was detected between T1/T2 and T3/T4 tumors, the overexpression of SRF was correlated with the depth of invasion,

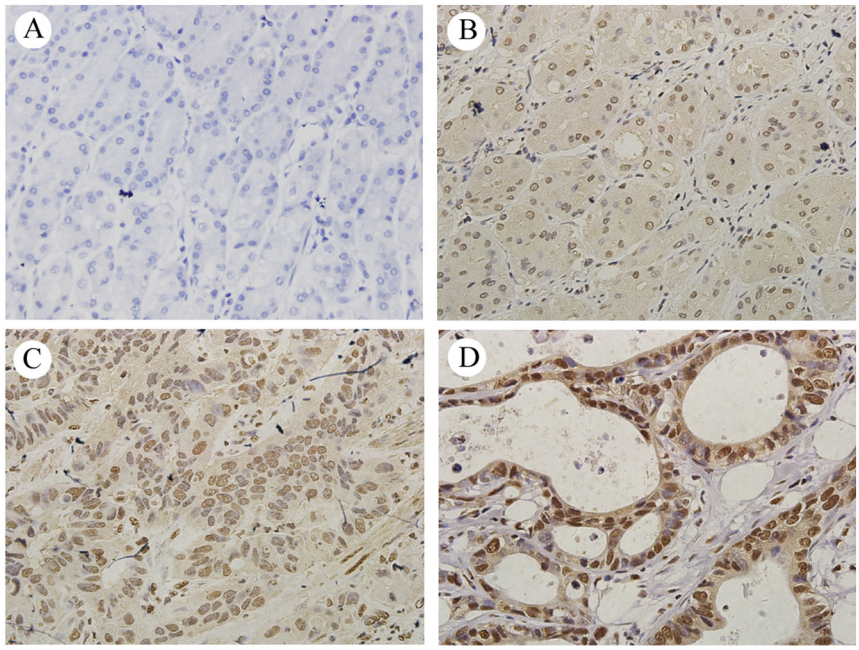

Fig. 1 Representative illustration of immunohistochemical grade of SRF in gastric carcinoma and ANC tissues. A, Grade I. B, Grade II. C, Grade III. D, Grade IV.

Table 1 The expression of SRF in GC tissues and ANC tissues

Group	Cases	SRF expression				*P*
		I	II	III	IV	
GC tissues	149	30	42	49	28	<.001 *
ANC tissues	149	54	54	28	13	

* $P < .05$ was considered significant.

especially in T3 and T4 carcinomas ($P = .001$). SRF expression was also associated with lymph node metastasis, and GC specimens from patients with lymph node metastasis tended to have higher expression ($P = .004$). Furthermore, the expression of SRF was increased in stage III/IV tumors compared with expression in stage I/II tumors ($P = .001$). The expression of SRF was not correlated with the patient's sex, age, tumor location, tumor size, or existence of distant metastasis (Fig. 2).

3.3. SRF expression is associated with DFS of patients with GC

During follow-up, there were 124 deaths and 25 surviving patients. The correlation between DFS of patients and SRF expression level was evaluated through Kaplan-Meier analysis, and the results showed that patients with high SRF expression had shorter DFS than did those with low SRF expression (Fig. 3A; log-rank test, $P < .001$). The postoperative median

Table 2 Relationship between SRF expression and clinicopathological features in patients with GC

Clinical parameters	Cases	SRF expression				*P*
		I	II	III	IV	
Sex						.646
Male	97	22	26	33	16	
Female	52	8	16	16	12	
Age (y)						.608
<50	75	16	24	19	16	
≥50	74	14	18	30	12	
Tumor location						.895
Cardia	37	8	8	15	6	
Body/antrum	112	22	34	34	22	
Tumor size (cm)						.479
≥5	73	18	18	24	13	
<5	76	12	24	25	15	
Differentiation						.012 *
Well	68	20	22	13	13	
Moderate/Poor	81	10	20	36	15	
Lauren type						.716
Diffuse	80	18	22	24	16	
Intestinal	69	12	20	25	12	
Depth of invasion						.001 *
T1/T2	48	19	11	12	6	
T3/T4	101	11	31	37	22	
Lymph node metastasis						.004 *
Negative	56	16	19	15	6	
Positive	93	14	23	34	22	
Distant metastasis						.939
Without	136	27	40	42	27	
With	13	3	2	7	1	
TNM stage						.001 *
I/II	80	24	22	24	10	
III/IV	69	6	20	25	18	

* $P < .05$ was considered significant.

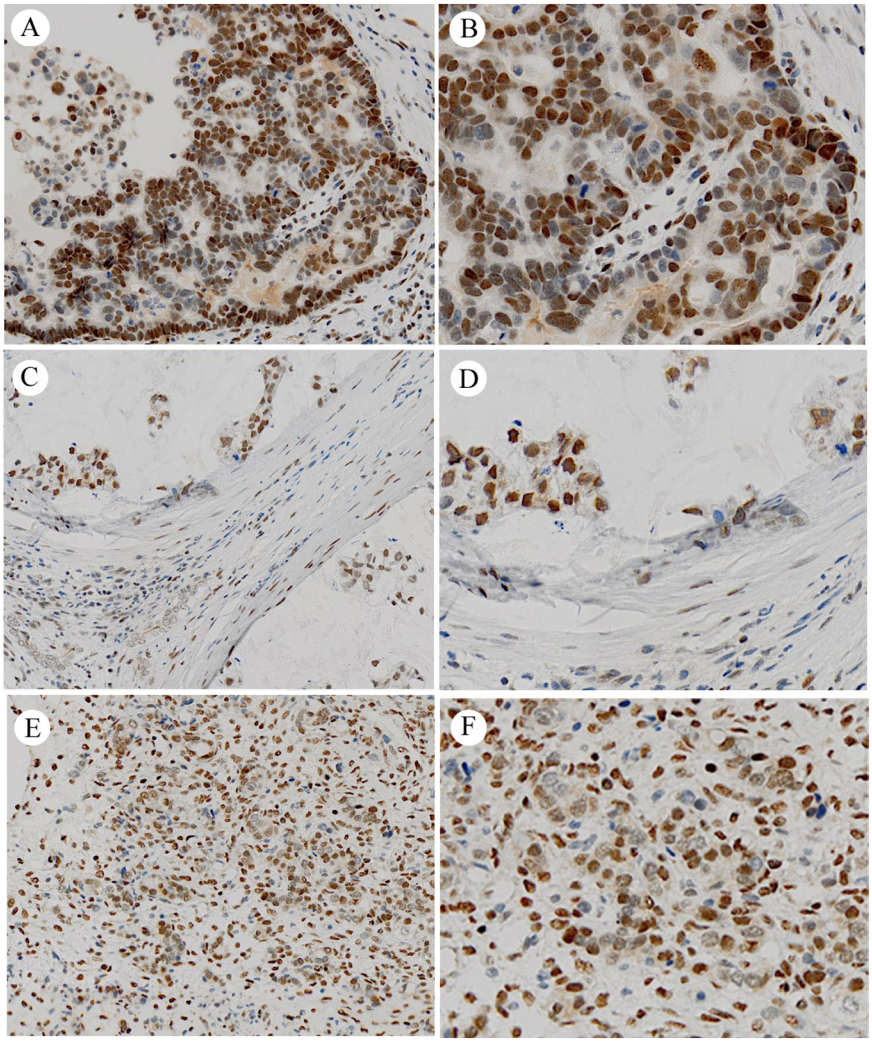

Fig. 2 Representative illustration of SRF expression in invasion sites of GC including the lymph node, ovary, and liver. A, High SRF expression in lymph node tissue with GC metastasis (original magnification ×100). B, High SRF expression in lymph node tissue with GC metastasis (×200). C, High SRF expression in ovary tissue with GC metastasis (×100). D, High SRF expression in ovary tissue with GC metastasis (×200). E, High SRF expression in liver tissue with GC metastasis (×100). F, High SRF expression in liver tissue with GC metastasis (×200).

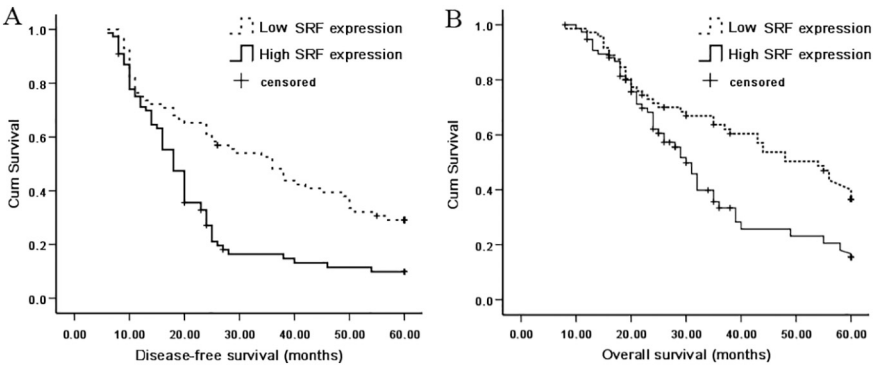

Fig. 3 Kaplan-Meier survival curves for DFS and OS in GC patients. A, Kaplan-Meier survival curve for DFS of patients and SRF expression ($P < .001$). B, Kaplan-Meier survival curve for OS of patients and SRF expression ($P = .005$).

Table 3 Univariate Cox regression analysis for DFS and OS in GC patients

Factors	DFS			OS		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Sex: male *vs* female	0.820	0.553-1.215	.322	0.867	0.559-1.345	.525
Age: <50 y *vs* ≥ 50 y	1.221	0.847-1.760	.284	1.145	0.756-1.734	.522
Location: cardia *vs* body/antrum	0.954	0.623-1.461	.829	0.753	0.477-1.188	.222
Size: <5 cm *vs* ≥5 cm	1.066	0.740-1.535	.732	1.007	0.666-1.523	.974
Differentiation: well *vs* moderate/poor	2.039	1.396-2.979	<.001 *	1.978	1.290-3.034	.002 *
Lauren type: diffuse *vs* intestinal	1.037	0.718-1.497	.846	1.178	0.779-1.783	.438
Depth of invasion: T1/T2 *vs* T3/T4	2.123	1.391-3.242	<.001 *	2.061	1.288-3.298	.003 *
Lymph node metastasis: negative *vs* positive	2.358	1.566-3.549	<.001 *	2.886	1.790-4.653	<.001 *
Distant metastasis: without *vs* with	3.784	2.087-6.861	<.001 *	3.402	1.609-7.195	.001 *
TNM stage: I/II *vs* III/IV	1.921	1.327-2.780	.001 *	2.564	1.679-3.915	<.001 *
SRF expression: low *vs* high	2.054	1.405-3.002	<.001 *	1.825	1.190-2.800	.006 *

* $P < .05$ was considered significant.

DFS time of patients with high SRF expression was 18 months (95% confidence interval [CI], 15.728-20.272), whereas that of patients with low SRF expression was 36 months (95% CI, 26.044-45.956). Patients with high SRF expression had a 2.054-fold higher risk of relapse than did those with low SRF expression (95% CI, 1.405-3.002; $P < .001$). Tumor differentiation, depth of invasion, lymph node metastasis, distant metastasis, and TNM stage were found to be associated with DFS of patients. However, sex, age, tumor location, tumor size, and Lauren type were not found to be associated with DFS (Table 3).

In multivariate analysis, the Cox proportional hazard model was adjusted for differentiation status, depth of invasion, lymph node metastasis, distant metastasis, TNM stage, and SRF expression level. The results indicated that high SRF expression was an independent prognostic factor of DFS for patients with GC ($P = .020$). In addition, differentiation status, lymph node metastasis, and distant metastasis were also independent prognostic factors for DFS. However, depth of invasion and TNM stage were not shown to be independent prognostic factors for DFS (Table 4).

3.4. SRF expression is associated with OS of patients with GC

Kaplan-Meier analysis for postoperative OS showed that patients with high SRF expression had poorer OS than did those with low SRF expression (Fig. 3B; log-rank test, $P = .005$). The postoperative median OS time of patients with high SRF expression was 30 months (95% CI, 15.728-20.272), whereas that of patients with low SRF expression was 54 months (95% CI, 26.044-45.956). The patients with high SRF expression had a 1.825-fold higher risk of relapse than did those with low SRF expression (95% CI, 1.190-2.800; $P = .006$). In addition, differentiation status, depth of invasion, lymph node metastasis, distant metastasis, and TNM stage were also found to be associated with OS of patients. However, sex, age, tumor location, tumor size, and Lauren type were not found to be associated with OS of patients (Table 3).

In multivariate analysis, the Cox proportional hazard model was adjusted for differentiation status, depth of invasion, lymph node metastasis, distant metastasis, TNM stage, and SRF expression level. The results showed that high lymph

Table 4 Multivariate Cox regression analysis for DFS and OS in GC patients

Factors	DFS			OS		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Differentiation: well *vs* moderate/poor	1.594	1.070-2.374	.022 *	1.476	0.943-2.311	.088
Depth of invasion: T1/T2 *vs* T3/T4	1.301	0.787-2.151	.305	0.961	0.535-1.726	.895
Lymph node metastasis: negative *vs* positive	1.734	1.108-2.714	.016 *	2.135	1.271-3.587	.004 *
Distant metastasis: without *vs* with	3.630	1.917-6.872	<.001 *	2.631	1.196-5.788	.016 *
TNM stage: I/II *vs* III/IV	1.023	0.643-1.628	.923	1.665	0.956-2.898	.071
SRF expression: low *vs* high	1.613	1.079-2.410	.020 *	1.407	0.898-2.205	.136

* $P < .05$ was considered significant.

node metastasis and distant metastasis were independent prognostic factors of OS for patients with GC ($P = .004$ and $P = .016$, respectively). However, SRF expression level, differentiation status, and TNM stage were shown not to be independent prognostic factors for OS (Table 4).

4. Discussion

In this study, we comprehensively analyzed SRF expression in GC tissues and investigated its prognostic value in patients with GC. According to the immunostaining results, we found that the expression of SRF was higher in GC tissue than in ANC tissue. Moreover, SRF was significantly associated with tumor differentiation, depth of invasion, lymph node metastasis, and TNM stage. However, SRF expression was not correlated with age, sex, tumor location, tumor size, Lauren type, or distant metastasis. Our data were compatible with the pro-oncogenic role identified for SRF overexpression in other digestive system tumors and suggested that SRF might play an important role in GC invasion, progression, and metastasis.

The role of SRF in GC has been explored by some studies. SRF was found to be highly expressed in human GC cells where it participates in regulating the invasion and migration of GC cells as well as altered expression of E-cadherin and β-catenin [14]. The prevalence of SRF methylation alteration was consistently and coordinately associated with gastric carcinoma metastasis [22]. Our group previously showed that SRF promotes GC cell migration, invasion, and metastasis both in vitro and in vivo. SRF downregulates E-cadherin by transactivating miR-199a-5p in metastatic GC cells, and miR-199a-5p promotes epithelial to mesenchymal transition in GC cells and regulates Wnt/β-catenin signaling. The SRF/miR-199a-5p/E-cadherin pathway leads to both inhibition of E-cadherin and SRF-induced epithelial to mesenchymal transition [15]. Recently, another research group also showed that overexpressing SRF in fibroblasts significantly enhances the invasion and migration of GC cells in vitro and in vivo. SRF upregulates αSMA and stromal-derived factor 1 (SDF1) expression in fibroblasts. SRF contributes to GC metastasis through its role in the crosstalk between cancer cells and fibroblasts, and the SDF1-CXCR4 axis may play a crucial role in the SRF-mediated crosstalk between cancer cells and fibroblasts [16]. Furthermore, miR-101-3p and miR-647 have been found to be functioning as tumor suppressors of proliferation and invasion in GC through targeting the SRF/HOTAIR axis and SRF/MYH9 axis, respectively [23,24].

In our study, Kaplan-Meier analysis of survival curves revealed significantly shorter disease-free and overall 5-year survival of patients with higher SRF levels, indicating that high SRF protein level is a marker of poor prognosis for patients with GC. Besides SRF expression, differentiation status, depth of invasion, lymph node metastasis, distant metastasis, and TNM stage were also found to be associated with DFS of patients with GC in univariate survival analysis. However, SRF expression still kept its prognostic value for DFS in multivariate survival analysis besides tumor differentiation status, lymph node metastasis, and distant metastasis. Univariate survival analysis also indicated that SRF expression, tumor differentiation status, depth of invasion, lymph node metastasis, distant metastasis, and TNM stage were associated with OS of patients with GC. However, multivariate COX regression analysis showed that lymph node metastasis and distant metastasis, but not SRF expression, had prognostic value for OS. These results clarified that SRF was an independent prognostic factor for DFS but not for OS.

The prognostic value of SRF has been found in some cancers. Increased SRF expression in prostate cancer is associated with biochemical recurrence following radical prostatectomy, and during the disease progression from localized prostate cancer to castration resistance and bone metastases, patient survival was inversely correlated with nuclear SRF expression in the context of docetaxel resistance [25,26]. SRF induces the epithelial to mesenchymal transition with resistance to sorafenib in hepatocellular carcinoma, which might lead to poor patient survival [27]. A new study showed that SRF was also involved in microRNA-647–suppressed invasion and metastasis of GC and might be an unfavorable factor for survival of GC patients [24]. Combined with these studies, our results confirmed that SRF was an independent unfavorable factor for GC DFS, suggesting that SRF might have potential value in predicting the recurrence of GC.

There were some limitations in our study. This was a retrospective study with a restricted sample size. Furthermore, further studies needed to be taken to understand better the molecular mechanism of SRF in GC, such as the relationship with *Helicobacter pylori* infection, based on current evidence. Finally, more prospective studies are needed to validate the prognostic value of SRF to be used in routine clinical practice.

In conclusion, this study demonstrated that SRF was highly expressed in GC tissues, and the patients exhibiting SRF overexpression had a shorter survival time. Furthermore, SRF was found to be an independent prognostic factor for DFS but not for OS. These data suggested that SRF might be a useful marker for predicting the prognosis of patients with GC and could also serve as a molecular marker of GC relapse.

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References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.

[2] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.

[3] Rahman R, Asombang AW, Ibdah JA. Characteristics of gastric cancer in Asia. World J Gastroenterol 2014;20:4483-90.
[4] Cutsem E, Sagaert X, Topal B, et al. Gastric cancer. Lancet 2016;388: 2654-64.
[5] Norman C, Runswick M, Pollock R, et al. Isolation and properties of cDNA clones encoding SRF, a transcription factor that binds to the c-fos serum response element. Cell 1988;55:989-1003.
[6] Chai J, Tarnawski AS. Serum response factor: discovery, biochemistry, biological roles and implications for tissue injury healing. J Physiol Pharmacol 2002;53:147-57.
[7] Posern G, Treisman R. Actin' together: serum response factor, its co-factors and the link to signal transduction. Trends Cell Biol 2006;16: 588-96.
[8] Taylor A, Halene S. The regulatory role of serum response factor pathway in neutrophil inflammatory response. Curr Opin Hematol 2015;22: 67-73.
[9] Franco CA, Li Z. SRF in angiogenesis: branching the vascular system. Cell Adh Migr 2009;3:264-7.
[10] Park MY, Kim KR, Park HS, et al. Expression of the serum response factor in hepatocellular carcinoma: implications for epithelial-mesenchymal transition. Int J Oncol 2007;31:1309-15.
[11] Choi HN, Kim KR, Lee JH, et al. Serum response factor enhances liver metastasis of colorectal carcinoma via alteration of the E-cadherin/beta-catenin complex. Oncol Rep 2009;21:57-63.
[12] He X, Xu H, Zhao M, et al. Serum response factor is overexpressed in esophageal squamous cell carcinoma and promotes Eca-109 cell proliferation and invasion. Oncol Lett 2013;5:819-24.
[13] Kwon CY, Kim KR, Choi HN, et al. The role of serum response factor in hepatocellular carcinoma: implications for disease progression. Int J Oncol 2010;37:837-44.
[14] Zhao M, Xu H, He X, et al. Expression of serum response factor in gastric carcinoma and its molecular mechanisms involved in the regulation of the invasion and migration of SGC-7901 cells. Cancer Biother Radiopharm 2013;28:146-52.
[15] Zhao X, He L, Li T, et al. SRF expedites metastasis and modulates the epithelial to mesenchymal transition by regulating miR-199a-5p expression in human gastric cancer. Cell Death Differ 2014;21: 1900-13.
[16] Qiao J, Liu Z, Yang C, et al. SRF promotes gastric cancer metastasis through stromal fibroblasts in an SDF1-CXCR4-dependent manner. Oncotarget 2016;7:46088-99.
[17] Edge SB, Byrd DR, Compton CC, Fritz AG. AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual. . 7th ed.New York: Springer; 2009.
[18] Sobin LH, Gospodarowicz MK, Wittekind C. International Union Against Cancer TNM Classification of Malignant Tumours. . 7th ed. New York: Wiley-Liss; 2010.
[19] Xie H, Song J, Du R, et al. Prognostic significance of osteopontin in hepatitis B virus–related hepatocellular carcinoma. Dig Liver Dis 2007;39: 167-72.
[20] Xie H, Song J, Liu K, et al. The expression of hypoxia-inducible factor-1alpha in hepatitis B virus–related hepatocellular carcinoma: correlation with patients' prognosis and hepatitis B virus X protein. Dig Dis Sci 2008;53:3225-33.
[21] Chu D, Zhang Z, Li Y, et al. Matrix metalloproteinase-9 is associated with disease-free survival and overall survival in patients with gastric cancer. Int J Cancer 2011;129:887-95.
[22] Liu Z, Zhang J, Gao Y, et al. Large-scale characterization of DNA methylation changes in human gastric carcinomas with and without metastasis. Clin Cancer Res 2014;20:4598-612.
[23] Wu X, Zhou J, Wu Z, et al. miR-101-3p suppresses HOX transcript antisense RNA (HOTAIR)–induced proliferation and invasion through directly targeting SRF in gastric carcinoma cells. Oncol Res 2017;25: 1383-90.
[24] Ye G, Huang K, Yu J, et al. MicroRNA-647 targets SRF-MYH9 axis to suppress invasion and metastasis of gastric cancer. Theranostics 2017;7: 3338-53.
[25] O'Hurley G, Prencipe M, Lundon D, et al. The analysis of serum response factor expression in bone and soft tissue prostate cancer metastases. Prostate 2014;74:306-13.
[26] Lundon DJ, Boland A, Prencipe M, et al. The prognostic utility of the transcription factor SRF in docetaxel-resistant prostate cancer: in-vitro discovery and in-vivo validation. BMC Cancer 2017;17:163.
[27] Bae JS, Noh SJ, Kim KM, et al. Serum response factor induces epithelial to mesenchymal transition with resistance to sorafenib in hepatocellular carcinoma. Int J Oncol 2014;44:129-36.