

Expression and clinical correlation of Survivin and PTEN in gastric cancer patients

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Abstract. Reports on the correlation between the expression of Survivin/phosphatase and tensin homolog (PTEN) proteins and clinical factors in gastric cancer (GC) are varied, and the sample sizes were also not sufficient. The present study aimed to detect the expression of Survivin and PTEN proteins in GC patients on the basis of a greater number of specimens and to analyze the correlation with clinical features and survival. The results revealed that the Survivin expression rates in GC, normal tissues and metastatic lymph nodes were 72% (232/322), 5% (6/120) and 80% (36/45), respectively, while the PTEN expression rates were 34% (109/322), 92.5% (111/120) and 24.4% (11/45), respectively, and the differences between cancer and normal tissue or metastatic lymph nodes were significant for both proteins ($P<0.05$). The expression of Survivin was significantly associated with gross type, depth of invasion, distant metastasis, tumor, necrosis and metastasis (TNM) stage and vascular invasion, while PTEN expression was predominantly associated with age, tumor size, invasion depth, TNM stage and lymphatic invasion in GC patients ($P<0.05$). The expression of both was associated with postoperative metastasis and metastatic site ($P=0.007$ and $P=0.011$ for Survivin, and $P=0.002$ and $P=0.005$ for PTEN). There was a negative association between the expression levels of Survivin and PTEN ($P=0.001$, $r=-0.524$). The expression levels of both were also associated with prognosis. The expression of Survivin and PTEN protein exhibit opposing trends in GC, which may indicate adverse biological effects in the occurrence of GC. The Survivin and PTEN expression levels are likely to be an important molecular event in gastric

tumorigenesis and may be considered as molecular markers of GC progression and reliable prognostic indicators of GC.

Introduction

Gastric cancer (GC) comprises >1,000,000 new cases with an estimated 783,000 deaths reported worldwide in 2018, which renders it the fifth most common malignancy and the third primary cause of cancer-related mortality (1). GC also rates third in morbidity and second in mortality in China (2). The curative treatment for GC remains the complete excision of primary tumors with proper lymphadenectomy, since the curative effects of neoadjuvant therapy have been disappointing to date. Even some GC patients with the same TNM stage have a different prognosis and treatment outcome. Thus, researchers are focusing on identifying the molecular biomarkers and development-related targets of treatment. Treatment of the disease at an earlier stage may be key to improving the prognosis of patients with GC.

Survivin has been depicted as the smallest member of the 'inhibitor of apoptosis' family with a unique structure (3). Survivin is frequently observed to be overexpressed in malignancies when compared with normal tissues (4). As regards its functions, Survivin plays a regulatory role in cell division and the inhibition of apoptosis, induces angiogenesis, and plays a vital role in cancer progression (5). Survivin blocks apoptosis induced by a variety of pro-apoptotic stimuli, including chemotherapy and radiation, in numerous malignancies (6). In addition, an increased level of Survivin is correlated with a poorer outcome in various malignancies (4,7-10); however, certain studies have indicated that an increased expression of Survivin splice variants may represent a favorable marker of survival in some malignancies (11,12).

Phosphatase and tensin homologue deleted on chromosome 10 (PTEN), also known as mutated in multiple advanced cancers (MMAC), was identified in 1997 by two independent research groups as a candidate tumor suppressor gene that was located at the human chromosome 10q23, a site frequently damaged in primary human malignancies (13,14). The loss of PTEN function can occur via a series of genetic or epigenetic abnormalities, such as point chromosomal deletions, mutations, promoter hypermethylation and post-translational modifications (15,16), and may result in various human malignancies,

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including renal cancer (17), pancreatic cancer (18), glioma (19), colorectal cancer (20), breast cancer (21), endometrial cancer (22), melanoma (23) and myeloid malignancies (24).

Although previous studies have reported enhanced expression of Survivin and a decreased expression of PTEN in GC, the level and correlation of Survivin and PTEN variations have not yet been fully elucidated. Although some studies have depicted their expression patterns in GC and analyzed the association of these expression patterns with clinical characteristics and prognosis (25,26), the outcomes have been controversial or dubious due to the insufficiency of sample sizes (27,28). Therefore, on the base of a relatively larger sample size, the present study further investigated Survivin and PTEN expression in GC in order to determine their expression levels, their effects on patient survival and clinical significance in GC.

Materials and methods

GC patients and specimens. A total of 322 primary gastric adenocarcinoma samples, 120 matched normal controls (situated 15 cm from the tumor margin) and 45 metastatic lymph nodes, which had been selected from the Tumor Hospital Affiliated to Xin Jiang Medical University between January, 2009 and December, 2012, were included in this study. Patient characteristics are shown in Table I. The study protocol was approved by the Review Board of Xin Jiang Tumor Hospital of Xin Jiang Medical University (approval no. 20090102, January 2, 2009) and all procedures followed the principles of the Declaration of Helsinki. All subjects provided written informed consent prior to participation. All patients had undergone radical primary tumor excision. All patients, apart from those with stage IV disease, underwent radical surgery (D2) followed by standard chemotherapy. None of the patients had received preoperative chemotherapy or radiotherapy. All cases were staged in accordance with the guidelines of the American Joint Committee on Cancer and the 2010 Cancer Staging manual of the Union for International Cancer Control (25). The data on clinical follow-up were obtained from the hospital record department. The overall survival (OS) time was calculated from the date of primary surgery to the date of death. The disease-free survival (DFS) time was measured from the date of primary radical surgery to the date of onset of local recurrence or distant metastasis. The patients who died due to surgery or other causes were eliminated from this study.

Immunohistochemistry (IHC). The streptavidin-biotin peroxidase complex (SP) method was used for the IHC assay and was completed with a commercially available SP-kit (SP-9000; OriGene Technologies, Inc.). All tumor specimens that were embedded in paraffin were cut into 4- μ m sections and rehydrated in a gradient series of alcohols following deparaffinization. The slides were boiled for antigen retrieval in 10 mM sodium citrate buffer (pH 6.0) and quenched with 3% H₂O₂ for 15 min to block endogenous peroxidase activity. Non-specific binding was prevented by incubating the slides with 5% goat serum (OriGene Technologies, Inc.) in PBS for 30 min at room temperature. The slides were treated with

rabbit polyclonal anti-human Survivin (cat. no. RAB-0536; NeoMarkers, Inc.) antibody (1:100) (ready to use) or mouse monoclonal anti-human PTEN (cat. no. 17A; NeoMarkers, Inc.) antibody (ready to use, 1:50) at room temperature for 2 h, followed by incubation with biotinylated goat anti-rabbit IgG (HRP; 1:10,000; cat. no. ab6721) and streptavidin-peroxidase (cat. no. TS-060-HR; Thermo Fisher Scientific, Inc.) for 1 h at room temperature. Diaminobenzidine was used for visualizing the peroxidase binding at room temperature for 1 h. The slides were counterstained lightly with hematoxylin at room temperature for 1 h and visualized under a light microscope (magnification, x100). PBS was employed as a negative control in the IHC assay.

Evaluation of IHC staining. A tumor cell cytoplasm that stained brown under a light microscope was considered as positive staining. The cells were scored grossly based on the intensity of staining and the percentage of positive tumor cells (26). The intensity of staining (I) was scored as follows: The absence of staining as 0 points; weak staining as 1 point; and moderate to strong staining as 2 points. The percentage of positive tumor cells (P) was divided into three grades as follows: None or <10% of tumor cells with positive staining as 0 points; 10-50% as 1 point; and >50% as 2 points. The total score was calculated as (I) x (P) and the outcome was graded as 0, 1+, 2+ or 3+. All stained slides were scored independently by two individual pathologists. The evaluation was performed twice, with the evaluator having no knowledge of the patient's diagnosis or prognosis. A total of two pathologists jointly examined the cases and came to an agreement towards any inconsistent results of the samples.

Statistical analysis. The SPSS software package (version 18.0 SPSS Inc.) was used for correlation analysis between categorical variables. The difference in the clinical features between the positive and negative groups was assessed using the Chi-squared or Fisher's exact tests. The patient OS and DFS were calculated using the Kaplan-Meier method. Univariate and multivariate analysis was performed to analyze the factors that were determined to be significant for OS by the Cox proportional hazards model. All experiment were performed in triplicate. P<0.05 was considered to indicate a statistically significant difference.

Results

General data of the samples. Among the 322 cases examined, there were 206 (63.9%) males and 116 (36.1%) females, with a mean age of 62 years (range, 25 to 87 years). A total of 296 (91.9%) cases were categorized as differentiated type and 26 (8.1%) as undifferentiated type (including mucinous adenocarcinoma and signet-ring cell carcinoma). The invasion depth was T1 in 14 (4.3%), T2 in 54 (16.8%), T3 in 133 (41.3%) and T4 in 121 (37.6%) patients. As regards TNM staging, 31 patients had stage I disease, 78 had stage II, 159 had stage III and 54 had stage IV disease. In total, 212 cases exhibited regional lymph node metastasis. The follow-up data were complete in 292 cases and the median duration of follow-up was 38 months (range, 8-110 months) after primary

Table I. Survivin and PTEN expression in gastric cancer and normal tissues.

Tissue	N	Survivin		P-value	PTEN		P-value
		-	+		-	+	
GC tissue	322	90 (28)	232 (72)	<0.001 ^a	213 (66)	109 (34)	<0.001 ^a
ANT	120	114 (95)	6 (5)	<0.001 ^b	9 (7.5)	111 (92.5)	<0.001 ^b
LNM	45	9 (4.2)	36 (13.1)	0.208 ^c	34 (75.6)	11 (24.4)	0.102 ^c

^acomparison between GC and ANT. ^bcomparison between GC and LNM. ^ccomparison between ANT and LNM. ANT, adjacent normal tissue; LNM, lymph node metastasis; GC, gastric cancer; PTEN, phosphatase and tensin homolog.

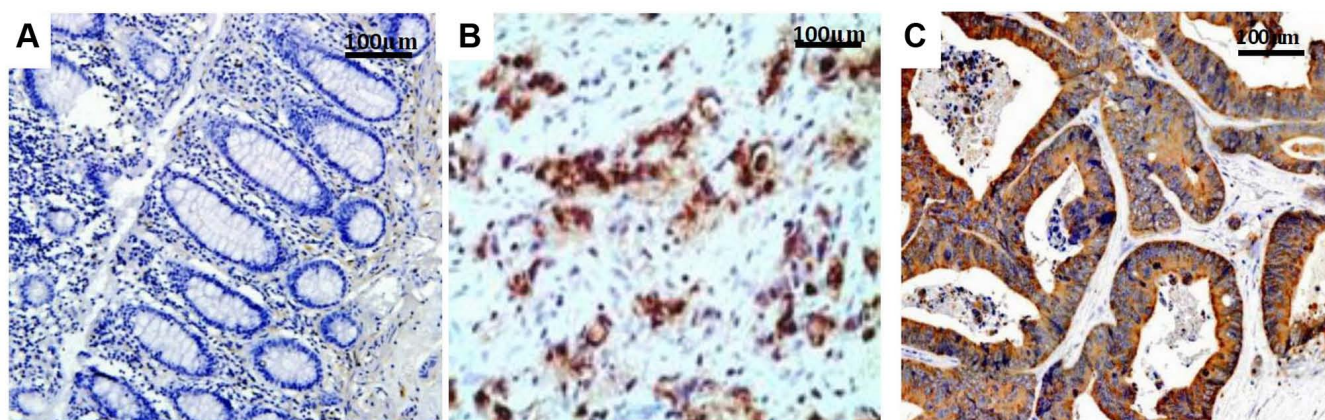


Figure 1. Survivin expression. (A) GC tissue, (B) Adjacent normal tissue and (C) metastatic lymph node. The staining level demonstrated gradual increase in the sequence of GC tissue, adjacent normal tissue and metastatic lymph node. GC, gastric cancer.

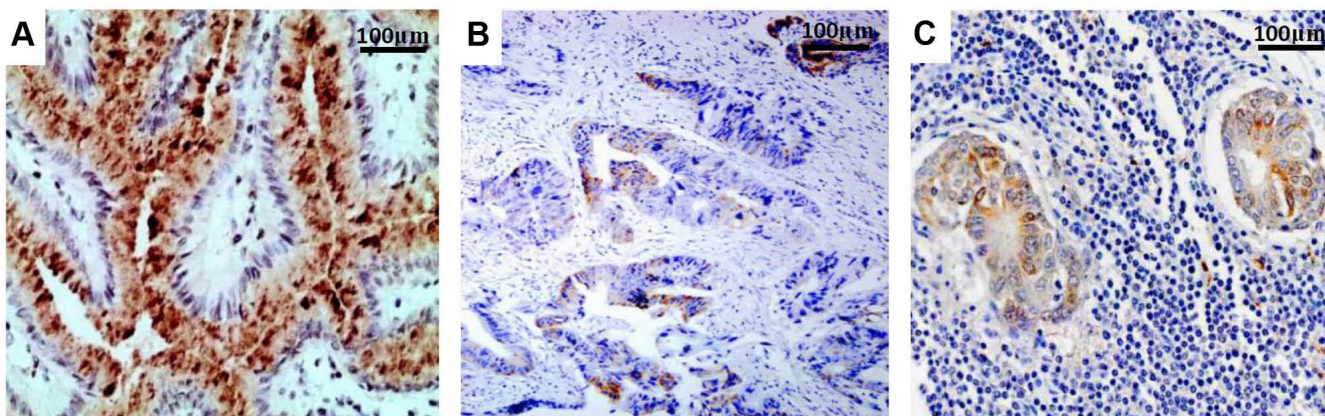


Figure 2. PTEN expression. (A) GC tissue, (B) Adjacent normal tissue and (C) metastatic lymph node. The staining level showed a gradual decreasing trend in the throughout the GC tissue, adjacent normal tissue and metastatic lymph node, respectively. GC, gastric cancer; PTEN, phosphatase and tensin homolog.

surgery. A total of 30 patients were lost during follow-up. The follow-up rate was 90.67%.

Expression of Survivin or PTEN in GC, normal tissues and metastatic lymph nodes. Survivin expression was located mainly in the cytoplasm and cell membrane, with minimal expression in the nucleus (Fig. 1), while PTEN expression was observed in both the cytoplasm and nucleus (Fig. 2). The Survivin expression rates in the GC, normal tissues and

metastatic lymph nodes were 72% (232/322), 5% (6/120) and 80% (36/45), respectively (Fig. 1), while the PTEN expression rates were 34% (109/322), 92.5% (111/120) and 24.4% (11/45), respectively (Table I). The primary GC tissues and metastatic lymph nodes expressed significantly increased levels of Survivin and decreased levels of PTEN compared with the normal mucosal tissues ($P<0.001$). However, the difference in Survivin or PTEN expression between the GC tissues and metastatic lymph nodes was not statistically

Table II. The correlation between Survivin and PTEN expression and clinicopathological factors.

Clinicopathological factors	N=322	PTEN expression			Survivin expression		
		(-) n (%)	(+) n (%)	P-value	(-) n (%)	(+) n (%)	P-value
Age	≤60	34 (36.6)	109 (47.6)	0.071	102 (49)	41 (36)	0.024 ^a
	>60	59 (63.4)	120 (52.4)		106 (51)	73 (64)	
Sex	Male	58 (62.4)	148 (64.6)	0.701	131 (63)	75 (65.8)	0.616
	Female	35 (37.6)	81 (35.4)	0.846	77 (37)	39 (34.2)	
Race	Han	89 (95.7)	218 (95.2)	0.404	196 (94.2)	111 (97.4)	0.201
	Uyghur	4 (4.3)	11 (4.8)		12 (5.8)	3 (2.6)	
Blood type	A	32 (34.4)	80 (34.8)	0.973	75 (36.1)	37 (32.5)	0.813
	B	37 (39.8)	78 (34.1)		71 (34.1)	44 (38.6)	
	AB	4 (4.3)	22 (9.6)		18 (8.7)	8 (7)	
	O	20 (21.5)	49 (21.4)		44 (21.2)	25 (21.9)	
Tumor size	≤4	16 (17.2)	38 (16.6)	0.022 ^a	33 (15.9)	21 (18.4)	0.012 ^a
	4-8	65 (69.9)	163 (71.2)		157 (75.5)	71 (62.3)	
	>8	12 (12.9)	28 (12.2)		18 (8.7)	22 (19.3)	
Gross type	Fungus	35 (37.6)	93 (40.6)	0.883	88 (42.3)	40 (35.1)	0.193
	Ulcerous	38 (40.9)	113 (49.3)		97 (46.6)	54 (47.4)	
	Invasive	18 (21.4)	23 (10.0)		23 (11.1)	20 (17.5)	
	Well	18 (19.4)	35 (15.3)		27 (13)	26 (22.8)	
Histology	Moderate	58 (62.4)	147 (64.2)	0.668	142 (68.3)	63 (55.3)	0.208
	Poor	8 (8.6)	16 (7)		14 (6.7)	10 (8.8)	
	Papillary adenocarcinoma	3 (3.2)	11 (4.8)		9 (4.3)	5 (4.4)	
	Mucinous adenocarcinoma	5 (5.4)	17 (7.4)		13 (6.3)	9 (7.9)	
	Signet ring	1 (1.1)	3 (1.3)		3 (1.4)	1 (0.9)	
Tumor site	Antrum	27 (29)	77 (33.6)	0.001 ^a	67 (32.2)	37 (32.5)	0.884
	Body	28 (30.1)	69 (30.1)		61 (29.3)	36 (31.6)	
	GEJ	38 (40.9)	83 (36.2)		80 (38.5)	41 (36)	
Infiltration depth	T1	5 (5.4)	9 (3.9)	0.206	5 (2.4)	9 (7.9)	0.001 ^a
	T2	28 (30.1)	26 (11.4)		28 (13.5)	26 (22.8)	
	T3	44 (47.3)	89 (38.9)		83 (39.9)	50 (43.9)	
	T4	16 (17.2)	105 (45.9)		92 (44.2)	29 (25.4)	
LN metastasis	None	37 (39.8)	73 (31.9)	0.005 ^a	60 (28.8)	50 (43.9)	0.025 ^a
	≤7	39 (41.9)	121 (52.8)		117 (56.3)	43 (37.7)	
	>7	17 (18.3)	35 (15.3)		31 (14.9)	21 (18.4)	
Distant metastasis	No	86 (92.5)	182 (79.5)	<0.001 ^a	169 (81.3)	99 (86.8)	0.199
	Yes	7 (7.5)	47 (20.5)		39 (18.8)	15 (13.2)	
TNM staging	I	22 (23.7)	9 (3.9)		7 (3.4)	24 (21.1)	
	II	15 (16.1)	63 (27.5)		53 (25.5)	25 (21.9)	
	III	49 (52.7)	110 (48)	0.045	109 (52.4)	50 (43.9)	0.098
	IV	7 (7.5)	47 (20.5)		39 (18.8)	15 (13.2)	
Vascular invasion	No	75 (84.3)	214 (91.8)	0.130	195 (86.7)	77 (79.4)	0.022
	Yes	14 (14.8)	19 (8.2)		30 (13.3)	20 (20.6)	
Lymphatic invasion	No	101 (88.6)	171 (82.2)	0.152	201 (87.4)	71 (77.2)	0.327
	Yes	13 (11.4)	37 (17.8)		29 (12.6)	21 (22.8)	
CEA	≤3.5	18 (20)	58 (27.9)	0.071	52 (27.4)	24 (22.2)	0.327
	>3.5	72 (80)	150 (72.1)		138 (72.6)	84 (77.8)	

^aP<0.05. GEJ, gastroesophageal junction; LN, lymph node; CEA, carcinoembryonic antigen; PTEN, phosphatase and tensin homolog.

significant (P=0.208 for Survivin and P=0.102 for PTEN), although Survivin expression was slightly increased and

PTEN expression was slightly decreased in the metastatic lymph nodes compared with in the cancerous tissues. Among

Table III. Correlation between Survivin or PTEN expression and related factors of prognosis.

Prognostic factors	Survivin			PTEN		
	-N (%)	+N (%)	P-value	-N (%)	+N (%)	P-value
Local recurrence						
No	74 (88.1)	195 (90.3)	0.577	184 (88.5)	105 (92.1)	0.303
Yes	10 (11.9)	21 (9.7)		24 (11.5)	9 (7.9)	
Postoperative metastasis						
No	62 (72.1)	100 (54.9)	0.007	90 (53.3)	72 (72.7)	0.002
Yes	24 (27.9)	82 (45.1)		79 (46.7)	27 (27.3)	
Metastatic site						
No	61 (70.9)	100 (54.9)	0.011	89 (52.7)	72 (72.7)	0.005
Single	13 (5.1)	59 (32.4)		55 (32.5)	17 (17.2)	
PD	12 (14)	23 (12.7)		25 (14.8)	10 (10.1)	
Median DFS	61	31	<0.001	31	70	<0.001
Median OS	73	39	<0.001	37	71	<0.001

OS, overall survival; DFS, disease-free survival; PTEN, phosphatase and tensin homolog.

Table IV. Relation between Survivin and PTEN expression.

Factor	PTEN		P-value	r
	+	-		
Survivin				
+	44	185	<0.001	-0.531
-	70	23		

PTEN, phosphatase and tensin homolog.

the 236 tissues with positive Survivin expression, there were 75 cases with weak staining (32.3%), 97 cases with moderate staining (41.8%) and 64 with strong staining (27.6%). Among the 109 tissues with positive PTEN expression, 44 exhibited weak staining (40.4%), 35 demonstrated moderate staining (32.1%) and 30 displayed strong staining (27.5%).

Association between the expression of Survivin or PTEN and clinical factors. The expression of Survivin was significantly associated with gross type, depth of invasion, distant metastasis, TNM stage and vascular invasion, while PTEN expression was predominantly associated with age, tumor size, invasion depth, TNM stage and lymphatic invasion in patients with GC ($P<0.05$; Table II). The expression of both was associated with postoperative metastasis and metastatic site ($P=0.007$ and $P=0.011$ for Survivin, and $P=0.002$ and $P=0.005$ for PTEN) (Table III). Correlation analysis also revealed a negative correlation between Survivin and PTEN expression ($P=0.001$, $r=-0.531$, Table IV); the higher the expression of Survivin, the lower the expression of PTEN.

Survival analysis. The results of survival analysis by the Kaplan-Meier method are presented in Fig. 3. The 1-,

3- and 5-year survival rates of all patients were 91.9, 53.8 and 27.7%, respectively. A statistically significant difference was observed in OS or DFS between the Survivin- or PTEN-positive and -negative patients ($P<0.001$ and $P=0.001$). The patients who were Survivin⁺ or PTEN⁻ had lower OS and DFS compared with those who were Survivin⁻ or PTEN⁺. Multivariate analysis using the Cox model was performed to analyze relevant prognostic factors in GC patients. The survival rate of the patients was significantly associated with invasion depth, advanced TNM stage, postoperative metastasis, tumor size and the Survivin and PTEN expression level ($P<0.05$; Table V). The OS and DFS of the patients who were simultaneously Survivin⁺ and PTEN⁻ were the lowest compared to the others (patients with Survivin⁺ and PTEN⁺ or Survivin⁻ and PTEN⁻ or Survivin⁻ and PTEN⁺) ($P=0.001$ and $P=0.001$).

Discussion

Survivin is observed in a number of human malignancies but is almost undetectable in normal tissues. Survivin expression is associated with a diminished apoptotic index, a poorer survival rate and an increased recurrence risk in the majority of tumors (29-31). Data on the expression of Survivin in different gastric tissues are limited, particularly in large sample analyses. Bury *et al* (32) reported that the Survivin expression rate was 73.17% in GC patients and Gu *et al* (25) found that Survivin was expressed at a rate of 62.9% (44/70) in GC tissues and 0% (0/20) in adjacent normal tissues; both studies had small sample sizes. In the present study, the expression rate of Survivin was 72% in malignant tissues, 5% in adjacent normal tissues and 80% in metastatic lymph nodes. Survivin expression was increased in malignant tissues and the expression in metastatic lymph nodes was the highest. These findings suggested that the upregulation of Survivin may be closely associated with malignant transformation and the invasive behavior of GC.

Table V. Cox regression model for univariate and multivariate analyses of prognostic factors in gastric cancer.

Prognostic factor	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age	0.824 (0.619-1.097)	0.184	1.436 (0.600-3.435)	0.416
Sex	0.995 (0.742-1.334)	0.975	1.108 (0.786-1.562)	0.557
Ethnicity	0.580 (0.314-1.069)	0.081	1.623 (0.728-4.121)	0.473
Blood type	0.805 (0.543-1.193)	0.28	0.814 (0.522-1.269)	0.363
Tumor site	1.066 (0.900-1.264)	0.459	0.723 (0.329-1.847)	0.513
Histological type	0.799 (0.629-1.016)	0.067	0.831 (0.603-1.145)	0.258
Gross type	1.109 (0.706-1.743)	0.652	0.780 (0.465-1.309)	0.347
Tumor size	0.994 (0.741-1.203)	0.054	1.426 (1.091-1.862)	0.009 ^a
Lymphatic invasion	1.241 (0.934-2.623)	0.042 ^a	0.582 (0.124-1.690)	0.164
Vascular invasion	2.251 (1.283-3.421)	0.084	1.324 (0.452-4.378)	0.87
Invasion depth	1.852 (1.532-2.237)	0.001 ^a	1.383 (1.130-1.693)	0.002 ^a
LN metastasis	1.527 (1.267-1.840)	0.021 ^a	0.589 (0.402-0.970)	0.098
Distant metastasis	2.726 (1.959-3.792)	0.002 ^a	0.460 (0.218-0.973)	0.102
TNM Staging	2.089 (1.746-2.499)	0.001 ^a	1.988 (1.581-2.502)	0.001 ^a
Local recurrence	1.227 (0.786-1.918)	0.368	0.824 (0.481-1.411)	0.481
Postoperative metastasis	2.933 (2.178-3.950)	0.001 ^a	1.561 (1.100-2.215)	0.013 ^a
Metastatic site	1.616 (1.359-1.927)	0.001 ^a	0.672 (0.429-1.054)	0.083
PTEN	0.219 (0.158-0.304)	0.001 ^a	0.228 (0.157-0.332)	0.001 ^a
Survivin	5.889 (4.020-8.626)	0.001 ^a	4.514 (2.964-6.876)	0.001 ^a
CEA	0.774 (0.555-1.080)	0.14	0.933 (0.558-1.546)	0.231

^aP<0.05. LN, lymph node; PTEN, phosphate and tensin homolog; CEA, carcinoembryonic antigen.

The association between the expression of Survivin and invasion depth or metastatic lymph node in GC remains unclear. Lins *et al* (27), reported that Survivin expression was not associated with the depth of invasion, lymph node metastasis or differentiation. However, Gu *et al* (25) demonstrated that Survivin expression was associated with tumor differentiation, depth of invasion and lymph node metastasis. The data of the present study also indicated that the expression of Survivin was associated with gross type, invasion depth, distant metastasis, TNM stage, vascular invasion, postoperative metastasis and metastatic site. Wang *et al* (33), concluded that a positive Survivin expression in the nuclei was associated with prognosis, although its positive expression in the cytoplasm was not associated with prognosis in GC. Chen *et al* (34), found that the upregulation of Survivin was associated with a worse survival rate in GC in 11 studies compared with the normal group. The results of the present study also supported the hypothesis that patients with positive Survivin expression exhibit shorter OS and DFS compared with those with negative Survivin expression.

There is increasing evidence to indicate that PTEN is a pivotal element that participates in the process of cancer development and progression (35), and that it is a prognostic and predictive biomarker in cancer (36). Li *et al* (37) reported positive expression of PTEN in 41.2% (47/114) of cases, while a reduction or loss of PTEN expression was detected in over half of GC cases (58.7%, 67/114). Zhu *et al* (38), found that the percentage of PTEN expression in GC samples (48%, 77/159) was significantly lower compared with that in adjacent normal tissue (75%, 113/151). The present study demonstrated

that PTEN expression in GC (34%) and metastatic lymph nodes (24.4%) was downregulated compared with in normal tissues (92.5%). PTEN expression in metastatic lymph nodes was lower compared with that in GC tissues, although the difference did not reach statistical significance. Therefore, the loss or diminished expression of PTEN in malignant tissues of the stomach may be a major general event in the progression of GC.

Reports on the associations between PTEN expression and clinicopathological factors are inconsistent. Bai *et al* (39) demonstrated that age, differentiation, TNM classification, depth of invasion and distant metastasis were negatively associated with the expression of nuclear PTEN. Furthermore, the lower level of nuclear PTEN expression was also associated with a good prognosis. Li *et al* (37) found that the loss of PTEN expression was associated with distant metastasis and advanced clinical stage, but not with prognosis. The data of the present study demonstrated that PTEN expression was associated with age, tumor size, invasion depth, TNM stage, lymph node metastasis, lymphatic invasion, postoperative metastasis and metastatic site. Patients with positive PTEN expression had higher OS compared with those with negative PTEN expression. Therefore, low expression of PTEN may be a critical biomarker for GC progression and may be closely associated with cancer invasiveness and metastasis.

The correlation analysis in the present study demonstrated a negative correlation between Survivin and PTEN expression. Lu *et al* (40), demonstrated that the expression of PTEN was negatively correlated with the expression of Survivin in cervical intraepithelial neoplasia and cervical

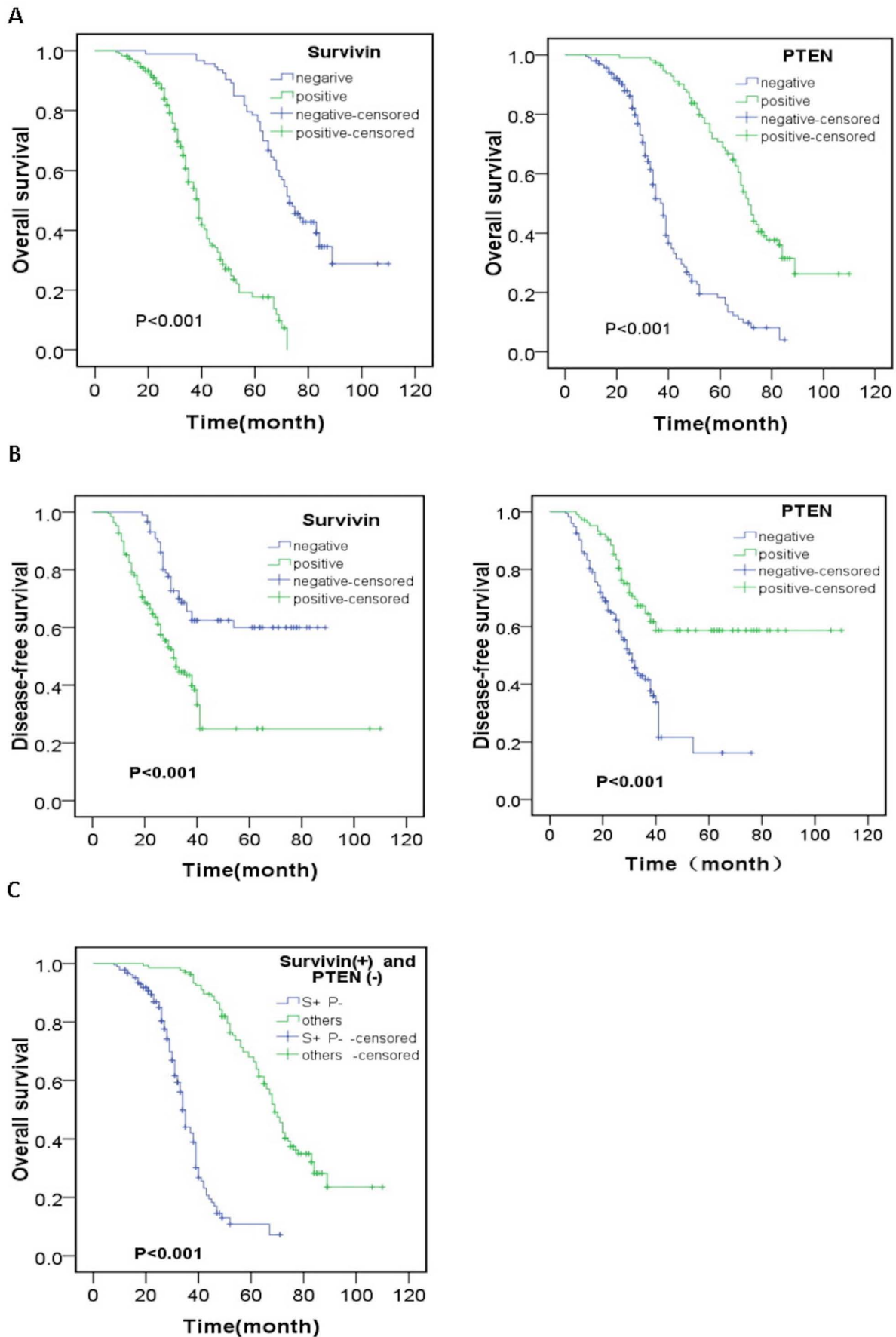


Figure 3. Correlation between expression level of Survivin or PTEN in GC and survival. (A) The difference in overall survival between Survivin or PTEN positive and negative patients. (B) The difference in disease free survival between Survivin or PTEN positive and negative patients. (C) The difference in overall survival between patients with simultaneous Survivin⁺, PTEN⁻ and patients with others (patients with Survivin⁺ and PTEN⁺ or Survivin⁻ and PTEN⁻ or Survivin⁻ and PTEN⁺). GC, gastric cancer; PTEN, phosphatase and tensin homolog.

squamous cell carcinoma. Wu *et al* (41), found that PTEN overexpression suppressed the growth of bladder cancer cells and significantly induced apoptosis via the downregulation of Survivin and caspase cascade activation. As previously demonstrated, following treatment with aspirin, Hep-2 cells exhibited a significant upregulation of PTEN and the inhibition of nuclear factor (NF)- κ B and Survivin, the downstream targets of the PTEN/protein kinase B (AKT) signaling pathway, suggesting that the anticancer molecular mechanism of aspirin may be associated with the inhibition of tumor invasion and the induction of apoptosis by regulating the activity of the PTEN/AKT/NF- κ B/Survivin signaling pathway (42). The aforementioned findings suggest that there may be an association between Survivin and PTEN.

In conclusion, Survivin and PTEN exhibit a negative association in GC, which may indicate that Survivin functions as an oncogene while PTEN plays the role of tumor suppressor gene in GC occurrence. PTEN and Survivin expression are likely important molecular events in gastric tumorigenesis and may be used as molecular markers of GC progression and reliable prognostic indicators of GC. The patient's odds of recurrence, metastasis and survival may be predicted preliminarily by detecting the Survivin and PTEN expression in GC tissue before treatment. The major limitation of the present study is that there wasn't the chance to perform the experiments *in vitro* and *in vivo* for further functional corroboration of the two genes, which is the main emphasis of future research.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

AY and HW conceived and designed the present study. RT acquired and analyzed the data and drafted the initial manuscript. DR assisted with the collection of the clinicopathological materials and the overall statistics. AR and ZZ helped perform the IHC experiment. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The present study was approved by the Review Board of Xin Jiang Tumor Hospital of Xin Jiang Medical University (Urumqi, China; approval no. 20090102), and performed in accordance with The Declaration of Helsinki.

All subjects provided written informed consent prior to participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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