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Clinicopathological and Prognostic Significance of Expression of B-Cell-Specific Moloney Murine Leukemia Virus Insertion Site 1 (BMI-1) Gene and Protein in Gastrointestinal Stromal Tumors

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Background:	Gastrointestinal stromal tumor (GIST) is an uncommon visceral sarcoma that arises predominantly in the gastrointestinal tract. Since GISTs are encountered infrequently and inflexible to traditional therapy, the aim of the present study was to explore the correlation of B-cell-specific Moloney murine leukemia virus insertion site 1 (BMI-1) mRNA and BMI-1 protein levels with the clinicopathological characteristics and prognosis significance of GISTs.
Material/Methods:	GIST tissues and normal tissues were collected from 156 patients who had undergone surgical treatment. RT-qPCR and immunohistochemistry were used to measure the BMI-1 mRNA and protein levels in GIST tissues and normal tissues. Univariate survival analysis was used for determination of the factors that affect prognosis of GIST patients. Cox proportional hazards model was plotted to determine the independent risk factors for prognosis of GIST patients.
Results:	The BMI-1 mRNA and protein levels in GIST tissues were higher than those in normal tissues. BMI-1 mRNA and positive protein levels were correlated with the National Institutes of Health (NIH) risk grade, tumor diameter and infiltration, and metastasis. There was a short survival period for the patients with a positive protein level and a high mRNA level of BMI-1. The site of primary tumor, tumor diameter, NIH risk grade, infiltration, and metastasis, as well as BMI-1 mRNA and protein levels were independent risk factors for prognosis of GIST patients.
Conclusions:	Taken together, these findings suggest there might be a relationship between BMI-1 mRNA and protein levels, and clinicopathological characteristics, including NIH risk grade, tumor size as well as infiltration and metastasis, of GIST patients. In addition, BMI-1 mRNA and protein levels were identified as independent risk factors for prognosis of GIST patients.
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Background

Gastrointestinal stromal tumor (GIST) is considered the most common mesenchymal tumor of the digestive tract [1]. GISTs are common in men and women around the world including Europe and the United States, and GISTs have a high incidence of 10 to 20 per million [2]. GIST patient symptoms include abdominal pain, gastrointestinal bleeding or palpable mass, and other symptoms [3]. In addition, among malignancies of the digestive tract, GIST has been reported to arise in the GI tract, with the stomach being the most frequent site (60–70%), followed by the small intestine (20–30%), and then the esophagus, colon, and rectum (<10%) [4,5]. GISTs are thought to originate from interstitial cells of Cajal (ICC), which are distributed around the myenteric plexus and muscularis propria, and which serve as not only coordinators of gut motility, but also as electrical pacemakers modulating the GI tract motility [6]. The independent risk factors for GISTs have been reported to include mitotic index, tumor size, site of primary tumor, and tumor rupture; at present, surgical resection is a popular treatment for primary and localized GISTs, with a goal to completely remove the tumor while avoiding tumor rupture and injury to the pseudo capsule [2]. Some previous studies have provided evidence that there is a significant association between relative B-cell-specific Moloney murine leukemia virus integration site 1 (BMI-1) levels and a variety of cancers such as gastric cancer and colon cancer [7,8].

With a location on chromosome 10p12.22, which is involved in chromosomal translocations in leukemia, BMI-1 gene is a significant member of polycomb group, and BMI-1 plays an important role in determining the cellular phenotype in all kinds of therapy-resistant cancers and it is one of the major cancer stem cell factors, with responsibility for the treatment failure in glioma [9]. As a polycomb-group protein, BMI-1 has a role in the regulation of gene expression through chromatin remodeling [10]. BMI-1 has been identified as not only a transcriptional repressor with an elevated level in cancers, but also as a prognostic predictor of therapy response and survival period for a variety of tumors [11]. A previous study revealed an association between high BMI-1 gene expression and the development and prognosis of many tumors; the transformation of epithelial-ectomesenchymal tissue might be promoted by higher expression of BMI-1, which is also closely related to advanced cancer stages, cancers with serious histology, as well as patients survival [12]. Through the cooperation of c-myc, BMI-1 has a capacity to suppress the expression of tumor inhibitor genes such as p16Ink4a and p19Arf, thus preventing apoptosis and accelerating cell proliferation [13]. Furthermore, aberrant BMI-1 expression has been reported to be related to multiple classifications of carcinoma and hematologic malignancies such as B-cell non-Hodgkin lymphoma, colorectal cancer, gastric carcinoma, and esophageal squamous cell carcinoma [14].

Moreover, recent research results have suggested that the expression of BMI-1 has a relationship to unfavorable prognosis and treatment failure for various cancers [15]. In addition, accumulative reports have provided evidence that BMI-1 overexpression is closely correlated with poor prognosis in various diseases [16,17]. A previous report concerning GISTs has come to the same conclusion, that enforced BMI-1 could contribute to poor prognosis of GISTs [18]. Therefore, in the present study, we not only studied the expression of BMI-1 in GISTs, but also did regression analysis and identified some independent factors for prognosis of GISTs, in an attempt to identify the clinicopathological significance and prognostic value of BMI-1 in GISTs.

Material and Methods

This study was performed with approval from the Ethics Committee in the First Affiliated Hospital of Xi'an Jiaotong University. All the patients provided written informed consents.

Study participants

GIST tissues were collected from 156 GIST patients who had undergone surgical resection at the First Affiliated Hospital of Xi'an Jiaotong University from January 1, 2011 to January 1, 2013. All patients were diagnosed according to the diagnostic criteria of GISTs [19]. The included patients consisted of 87 males and 69 females, whose ages ranged from 21 to 70 years, with the mean age of 45.68±15.63 years. The normal tissue samples were obtained from the resection margin of more than 2 cm away from the patients' tumor edges. Patients were included in this study if they had the tumor removed through surgical resection and the tumor was clinically diagnosed as stromal tumor; if they were not treated with any drugs or other therapies; and if they had complete clinical records and other related pathological materials. The biological behavior of GISTs was classified according to the National Institutes of Health (NIH) consensus on risk evaluation standards in 2008 [20]; all the study participants were classified as: very low-grade (n=12), low-grade (n=47), medium-grade (n=53), or high-grade (n=47).

RNA isolation and quantitation

TRIzol reagent (Invitrogen Inc., Carlsbad, CA, USA) was applied to extract the total RNA in GIST tissues and normal tissues. Reverse transcription was conducted using reverse transcription Moloney murine leukemia virus (MMLV), diethylpyrocarbonate (DEPC)-treated water of RNasin inhibitor and RNasin kit. Then RT-qPCR was performed, the reaction conditions included a warm start at 94°C for 5 min, proceeded by 28 cycles of a 94°C pre-denaturation for 30 sec, 55°C denaturation for 30 sec,

72°C annealing for 1 min, and 72°C extension for 10 min. Then, RNA was preserved at 4°C. After reactions, the computer showed the standard curves of internal control of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and the primer sequences were as follows: forward BMI-1: 5'-GCTTCAAGATGGCCGCTTG-3'; reverse BMI-1: 5'-TTCTCGTTGTTCGATGCATTTC-3'; forward GADPH: 5'-GCTGAACGGGAAGCTCACTG-3', reverse GADPH: 5'-GTGCTCAGTGTAGCCCAGGA-3'. The relative expressions of amplified products as $2^{-\Delta\Delta Ct}$ was calculated according to ΔCt, which was the difference of Ct values between the expression of target genes and the expression of internal control gene: $\Delta Ct = Ct_{target\ gene} - Ct_{internal\ control\ gene}$. Each sample was established using 3 duplicated wells and the relative expressions of amplified products were calculated respectively. The quantitative value was extracted and determined at random.

Immunohistochemistry

GIST tissues and normal tissues of all patients were immersed in 10% paraformaldehyde (pH=7.4), then primary antibody mouse anti-human was added, samples were placed at 37°C for 2 hours or incubated in a refrigerator overnight. After rinsing 3 times with phosphate buffered saline (PBS), the samples were incubated with the secondary antibody rabbit anti-mouse at 37°C for 20 min and washed with PBS (3 times, 5 min each time). Then PBS was removed, and each tissue section was stained with diaminobenzidine (DAB) and observed under a microscope until the staining results were satisfactory. Subsequently, the sections were counterstained, differentiated, back to blue, dehydrated, permeabilized, and sealed with neutral gum. Then all dried sections were observed under the microscope.

Evaluation of immunohistochemistry results

Immunohistochemistry results were evaluated by 2 experienced pathological doctors. The evaluation standards of positive results of BMI-1 were as follows: with reference to the percentage of positive cells to total cells, 5 fields of views at high magnification were selected at random for each section, with 200 cells counted in each field of view. Then the average-value of positive cells was figured. Cell samples were considered positive if more than 5% of cells were considered positive, and the cell samples were regarded as negative if less than or equal to 5% were regarded as negative.

Follow-up

Follow-up visits during the survival period were performed for all GIST patients. An analysis of the correlation of BMI-1 expression with GIST patients' survival period was performed. The follow-up visit was started at the date of the resection treatment up until May 2016, with a total follow-up period of 36 months, with follow-up twice every month. All patients were visited through telephone communication or checking the pathological developments on return visits. All of the 156 cases finished follow-up and no patients were lost to follow-up.

Statistical analysis

SPSS 21.0 software (IBM Corp. Armonk, NY, USA) was used for all statistical analysis. The chi-square test or the Fisher's exact probability method were plotted to clarify the difference between the positive expression of BMI-1 and the clinicopathological characteristics in GIST tissues. Mean ± standard deviation (SD) was employed for the expression of measurement data, with the t-test was used for the statistical analysis. $P<0.05$ was considered as statistical significance.
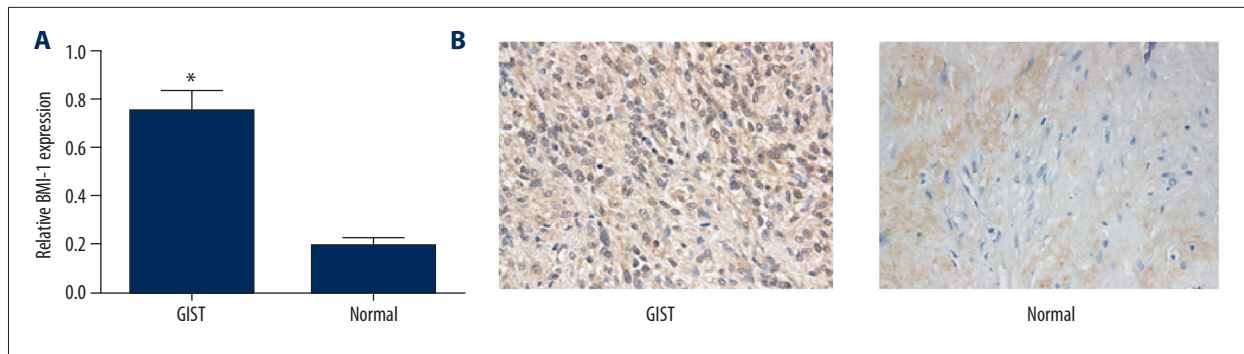
Results

Elevated mRNA and protein levels of BMI-1 were identified in GISTs

The mRNA expression of BMI-1 in GIST tissues and normal tissues was detected by RT-qPCR. The results showed that the mRNA expression of BMI-1 in normal tissues was 0.757±0.021, and that in GIST tissues, it was 0.197±0.029, revealing that mRNA expression of BMI-1 in GIST tissues was higher compared to normal tissues ($P<0.001$) (Figure 1A). To study the correlation of protein levels of BMI-1 and GISTs, protein levels of BMI-1 in GIST tissues and normal tissues were measured using immunohistochemistry. The results suggested that protein levels of BMI-1 were visualized in the cell membrane and cell cytoplasm of tumor cells in GIST tissues, with brown-yellow in cell membranes and cytoplasm and no staining visible in cell nucleus, while there were little visible protein levels of BMI-1 in normal tissues (Figure 1B). Among the 156 cases of GIST tissues, there were 115 cases with positive expressions; the positive expression rate was 73.72%. Among the 156 cases of normal tissues, there were 18 cases of positive expressions; the positive expression rate was 11.54%. Therefore, there was a higher positive expression of BMI-1 in GIST tissues compared to normal tissues ($P<0.001$). This evidence showed a vital association of mRNA and protein levels of BMI-1 and GISTs.

BMI-1 mRNA and protein expressions were correlated to the clinicopathological characteristics in GISTs

Subsequently, the relationship of mRNA and protein expressions of BMI-1 and the clinicopathological characteristics in GISTs were tested (Table 1). There was no statistical significance between mRNA and protein expressions of BMI-1 and the risk factors of age, gender, site of primary tumor, and histological classification in GISTs (all $P>0.05$). In addition, mRNA and protein expressions of BMI-1 were obviously correlated with

Figure 1. The RT-qPCR and immunohistochemistry results demonstrated that the relative BMI-1 mRNA and protein expressions in GIST tissues was higher than in normal tissues. (**A**) mRNA expression of BMI-1 was elevated in GIST tissues detected by RT-qPCR. (**B**) Results of immunohistochemistry indicated that positive expression rate of BMI-1 was higher in GIST tissues. * $P<0.01$ versus normal tissues; BMI-1 – B-cell-specific Moloney murine leukemia virus insertion site 1; GIST – gastrointestinal stromal tumor.

Table 1. Relationship of BMI-1 mRNA and protein expressions and the clinicopathological characteristics in GISTs.

Variables	Clinicopathological characteristics	Case (n)	BMI-1 mRNA expression	P	BMI-1 protein expression		P
					+	–	
Age (year)	≤55	90	0.762±0.085	0.405	61	29	0.354
	>55	66	0.751±0.076		40	26	0.432
Gender	Male	87	0.748±0.083	0.107	54	33	0.229
	Female	69	0.769±0.077		47	22	0.084
Site of primary tumor	Stomach	95	0.749±0.085	0.314	58	37	<0.001
	Small intestine	38	0.768±0.076		29	9	<0.001
	Colon and rectum	23	0.771±0.068		14	9	<0.001
Histological classification	Spindle cell	110	0.754±0.086	0.534	71	39	0.354
	Epithelioid cell	30	0.772±0.054		23	7	0.432
	Mixed cell classification	16	0.751±0.089		7	9	0.229
NIH criteria for risk stratification	Very low-risk	15	0.678±0.063	<0.001	2	13	0.084
	Low-risk	47	0.696±0.052		21	26	<0.001
	Medium-risk	53	0.771±0.051		42	11	<0.001
	High-risk	41	0.838±0.063		36	5	<0.001
Tumor diameter	r <2 cm	39	0.685±0.066	<0.001	14	25	0.354
	2 cm ≤ r ≤5 cm	58	0.735±0.055		32	26	0.432
	5 cm < r ≤10 cm	41	0.817±0.045		38	3	0.229
	r ≥10 cm	18	0.847±0.068		17	1	0.084
Infiltration and metastasis	No	99	0.715±0.061	<0.001	49	50	<0.001
	Yes	57	0.831±0.054		52	5	<0.001

BMI-1 – B-cell-specific Moloney murine leukemia virus integration site 1; GISTs – gastrointestinal stromal tumors; NIH – National Institutes of Health.

Table 2. Univariate survival analysis of the 156 cases of patients with GISTs.

Variables	Wald	P	Exp (B)	95% CI for Exp (B)
Age	0.152	0.696	0.764	0.198~2.954
Gender	0.609	0.435	1.560	0.511~4.766
Site of primary tumor	4.876	0.027	2.386	1.103~5.164
Histological classification	0.356	0.551	1.294	0.556~3.011
NIH criteria for risk stratification	4.356	0.037	2.672	1.062~6.724
Tumor diameter	4.781	0.029	2.257	1.088~4.681
BMI-1 protein levels	4.206	0.040	9.905	1.107~88.642
BMI-1 mRNA levels	4.242	0.039	4.985	1.081~22.986
Infiltration and metastasis	5.475	0.019	4.209	1.263~14.032

BMI-1 – B-cell-specific Moloney murine leukemia virus integration site 1; GISTs – gastrointestinal stromal tumors; C.I. – confidence interval; NIH – National Institutes of Health.

different NIH risk grades, different tumor diameters, as well as infiltration and metastasis (all $P<0.001$). All these results indicated that BMI-1 mRNA and protein expressions were correlated to some of the clinicopathological characteristics in GISTs.

Univariate analysis for the prognosis of the patients with GISTs

In the following experiments, correlations of prognosis of the patients with GISTs and site of primary tumor, NIH risk grade, tumor diameter, BMI-1 mRNA and protein levels, as well as infiltration and metastasis were analyzed by a univariate analysis. The mean survival period of all patients was 27.53±12.50 months. According to the results of the univariate analysis, the prognosis of the patients with GISTs had a correlation with the site of primary tumor, NIH risk grade, tumor diameter, BMI-1 mRNA and protein levels, as well as infiltration and metastasis (all $P<0.05$), while was no association with the histological classifications, age, and gender (all $P>0.05$) (Table 2). Patients with GI tract as the site of primary tumor had a longer survival period than those with colorectum as the site of primary tumor ($P<0.05$). There was a higher survival rate for GIST patients with short tumor diameter when compared with those with long tumor diameter ($P<0.05$). GIST patients with a low NIH risk grade had a higher survival rate than patients with a high NIH risk grade ($P<0.05$). GIST patients with a negative BMI-1 protein level had a longer survival period than patients with a positive BMI-1 protein level ($P<0.05$). There was a longer survival period for GIST patients with low mRNA expression of BMI-1 in comparison with GIST patients having high mRNA expression of BMI-1 ($P<0.05$). In addition, GIST patients with no recurrence of infiltration and metastasis had a higher survival rate than patients with recurrence of infiltration and metastasis ($P<0.05$) (Figure 2). Our results found a close association

between prognosis of patients with GISTs and site of primary tumor, NIH risk grade, tumor diameter, BMI-1 mRNA and protein levels, as well as infiltration and metastasis.

Cox regression analysis to determine independent risk factors for the prognosis of GIST patients

Finally, Cox proportional hazards model was used for the analysis of the clinicopathological features which had influences on the prognosis of GIST patients according to the univariate analysis. The results of Cox proportional hazards analysis showed that there were several independent risk factors for the prognosis of GIST patients, which included tumor diameter, NIH risk grade, and BMI-1 mRNA and protein levels (all $P<0.05$) (Table 3).

Discussion

As a kind of GI mesenchymal tumor, GIST has had an increased incidence rate in recent years, and GIST patients suffer disease recurrence with no response to chemotherapy or radiation therapy [21]. According to some previous studies, there are correlations between BMI-1 expression and several classifications of solid tumors, such as colorectal cancer and gastric cancer, suggesting a role in tumor cell growth and survival, and as such, BMI-1 has not only a diagnostic value but also a prognostic potential for these cancers [22,23]. Thus, the present study aimed to explore the association between BMI-1 mRNA and protein levels and clinicopathological characteristics in GISTs, and importantly, fully evaluate the prognostic values of BMI-1 in the patients with GISTs.

With an involvement in the self-renewal of cancer stem cells, BMI-1 might lead to tumor initiation, like bone and soft tissue
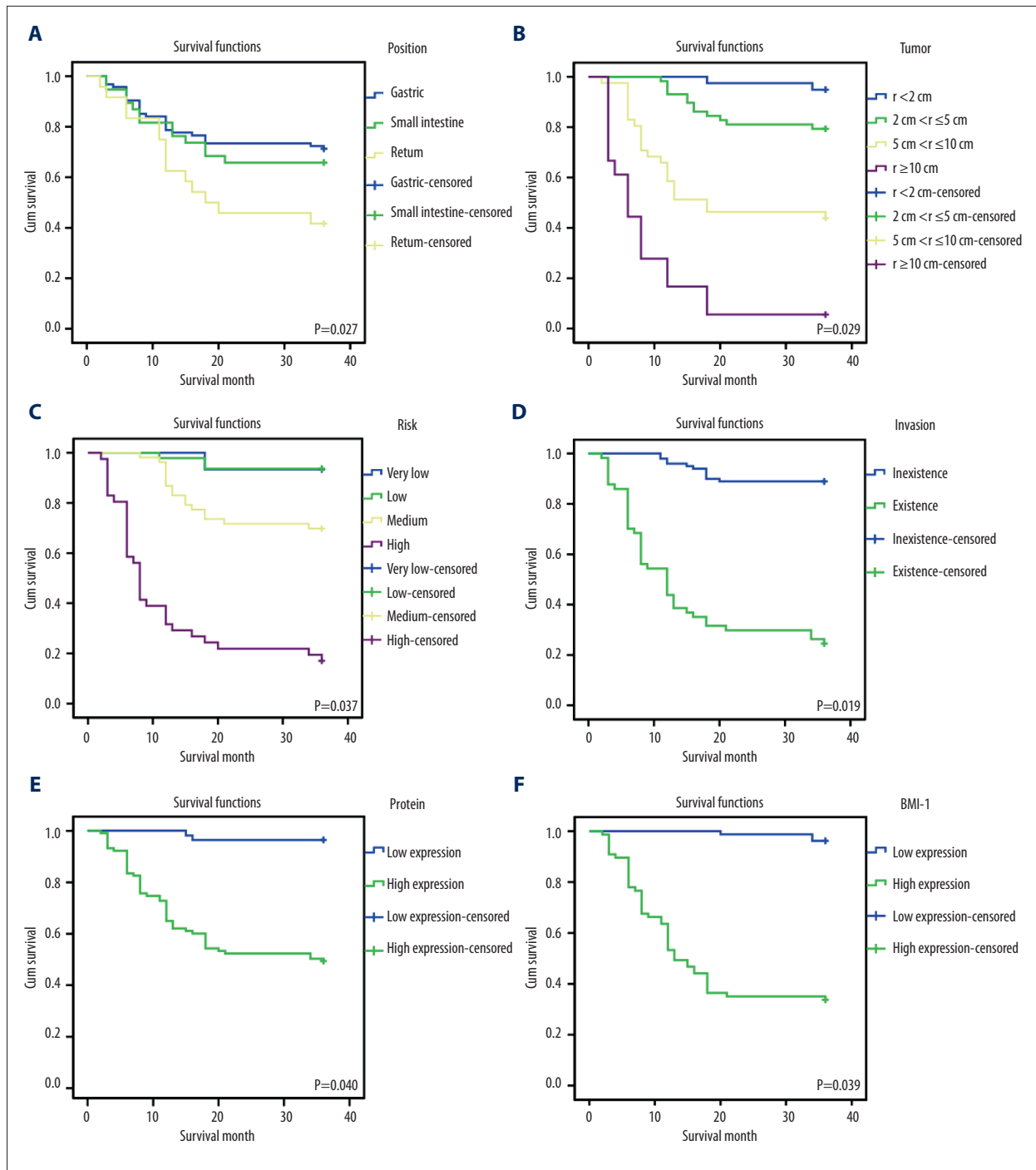
Figure 2. Prognosis of the patients with GISTs is implicated in the site of the disease recurrence, NIH risk grade, tumor diameter, BMI-1 mRNA and protein levels, as well as infiltration and metastasis. (**A**) Survival rates of patients with GISTs in gastrointestinal tract were higher. (**B**) Survival rates of patients with small-diameter GISTs were higher. (**C**) Survival rates of patients with GISTs in relative low NIH risk grade were higher. (**D**) Survival rates of patients without infiltration and metastasis were higher. (**E**) Patients experiencing GISTs with negative BMI-1 protein expression exhibited elevated survival rates. (**F**) Patients suffering from GISTs with poor mRNA expressions of BMI-1 had higher survival rates. $P<0.05$=statistically significant; BMI-1 – B-cell-specific Moloney murine leukemia virus insertion site 1; mRNA – micro-RNA; GISTs – gastrointestinal stromal tumors; NIH – National Institutes of Health; mean ± standard deviation; t-test was performed for statistical analysis; chi-square test or the Fisher's exact probability method were plotted to clarify the difference between the positive expression of BMI-1 and the clinicopathological characteristics in GIST tissues.

Table 3. The influence of tumor diameter, NIH risk grade, BMI-1 mRNA and protein levels on GIST patients.

Variables	Wald	P	Exp (B)	95% CI for Exp (B)
Site of primary tumor	2.187	0.139	1.293	0.920~1.816
NIH criteria for risk stratification	13.541	<0.001	2.748	1.604~4.709
Tumor diameter	11.365	0.001	2.065	1.355~3.149
BMI-1 protein levels	3.892	0.049	4.319	1.010~18.478
BMI-1 mRNA levels	4.824	0.028	4.220	1.168~15.251
Infiltration and metastasis	3.709	0.054	2.120	0.987~4.556

BMI-1 – B-cell-specific Moloney murine leukemia virus integration site 1; GIST – gastrointestinal stromal tumor; NIH – National Institutes of Health; C.I. – confidence interval.

tumors and gliomas [24,25]. Furthermore, BMI-1 has demonstrated a capacity to control cell proliferation and invasion as an oncogene through cooperation with c-myc in the oncogenesis of mouse lymphomas [26,27]. In our study, GIST tissues had a higher BMI-1 mRNA expression as well as positive protein levels, when compared with normal tissues. In addition, it has been previously reported that there is also a correlation between overexpression of BMI-1 and advanced pathological stages as well as poor overall survival in esophageal squamous cell carcinoma [28]. The results of our study provided further evidence that there were different BMI-1 mRNA and protein levels in GIST tissues, which had a relationship with several factors such as NIH risk grades, tumor diameters, as well as infiltration and metastasis. Furthermore, GIST tissues with higher NIH risk grade and longer tumor diameter were found to have increasing expressions of BMI-1 mRNA and protein levels; there was also an elevation of GIST tissues with the occurrence of infiltration and metastasis. In accordance with these findings, several studies indicated that risk factors, including NIH risk grade, tumor size, mitotic figure count, as well as Ki67 expression, served as pathological indicators, which also had a significant correlation with the recurrence risk of GISTs [29,30]. It has previously been reported that BMI-1 expression was enforced in gastric cancer, which could be regarded as the independent negative prognostic factor, indicating that it can be a therapeutic target [31]. Wang et al. proposed that promoted expression of BMI-1 was linked to the enhanced proliferation and growth in GIST cells [18]. Our results revealed that there was a correlation between BMI-1 mRNA and protein levels and clinicopathological characteristics of GISTs.

Recent research result revealed that with upregulation in gastric cancer, BMI-1 was related to lower survival rates of patients with GISTs [32,33]. According to the results of our study, the mean survival time of GIST patients was 27.53±12.50 months. The higher levels of BMI-1 mRNA and proteins were significantly correlated with GIST patients' survival time, and specifically, GIST patients with a positive protein level of BMI-1 had a lower survival rate in comparison to those with a negative protein expression of BMI-1. A previous study found a decreased level of the INK4 locus proteins (P16INK4a/p14ARF), which were demonstrated as 2 significant tumor suppressors, in colorectal carcinomas with moderate or strong BMI-1 expression. BMI-1 can potentially regulate p16-pRb and p53-p21 pathways of senescence by downregulating p16INK4A and p14ARF, which indicated that the colorectal carcinogenesis had a close correlation with the regulation of BMI-1 protein through repressing the INK4a/ARF proteins [34,35]. Moreover, a previous study demonstrated that BMI-1 mRNA and protein levels were obviously elevated in the cells of oral squamous cell carcinomas [36]. Evidence on similar topics suggests that overexpression of BMI-1 mRNA and protein had a negative impact on survival of colon cancer patients and lower expression of BMI-1 might predict longer survival of patients with colon cancer [37]. Thus, BMI-1 mRNA and protein level might be correlated with an unfavorable prognosis as well as a short survival period for GIST patients.

Conclusions

This study provides evidence that there was an association between BMI-1 mRNA and protein levels and clinicopathological characteristics and progression of GISTs, and that unfavorable prognosis might be generated from overexpression of BMI-1 mRNA and protein. In addition, the study results suggest that BMI-1 mRNA and protein levels could act as a prospective prognostic predictor and novel therapeutic target. However, the GIST patients enrolled in this study received a limited period of follow-up, and the small sample size of this study might have an influence on the accuracy of the experimental results. Therefore, further study about the effect of mRNA and protein levels of BMI-1 on GISTs is still needed.

Conflict of interest

None.

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