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Clinical Significance of Lysophosphatidic Acid Receptor-2 (LPA2) and Krüppel-Like Factor 5 (KLF5) Protein Expression Detected by Tissue Microarray in Gastric Adenocarcinoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The aim of this study was to evaluate lysophosphatidic acid receptor-2 (LPA2) and Krüppel-like factor 5 (KLF5) protein expression in gastric adenocarcinoma and their correlation with patient clinicopathological characteristics and prognosis.

Material/Methods: Fifty-one gastric adenocarcinoma tissue samples, 21 gastric intraepithelial neoplasia (GIN) samples, and 13 normal gastric tissue samples were collected to test for LPA2 and KLF5 expression by tissue microarray and immunohistochemistry assay. LPA2 and KLF5 positive expression rate between gastric adenocarcinoma, GIN, and normal gastric tissue were compared. The relationship between LPA2 expression, KLF5 expression, and patients' clinicopathological characteristics and prognosis were evaluated.

Results: The positive expression rate of LPA2 and KLF5 were statistical different in gastric adenocarcinoma, GIN, and normal gastric tissue ($P<0.05$). LPA2 positive expression was associated with tumor invasion depth, Lauren type, vascular invasion, local lymph node metastasis, and clinical stage ($P<0.05$). There was no correlation between LPA2 expression (hazard ratio [HR]=1.84, 95% confidence interval [CI]: 0.89–3.80, $P>0.05$), KLF5 expression (HR=1.13, 95% CI: 0.53–2.36, $P>0.05$), and gastric cancer patients' overall survival.

Conclusions: LPA2 and KLF5 protein expressions were differently expressed in gastric adenocarcinoma, GIN, and normal gastric tissue, and differences were correlated with patients' clinical characteristic. However, LPA2 and KLF5 expressions were not correlated with the patients' prognosis.

MeSH Keywords: Prognosis • Receptors, Lysophosphatidic Acid • Stomach Neoplasms

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Background

Gastric cancer is one of the most diagnosed malignant tumors and the third most common cause of cancer associated death globally [1]. The general prognosis of gastric cancer is poor because of advanced stages when first diagnosis for most patients [2,3].

The molecular mechanism of the occurrence and development of gastric cancer has not yet been fully elucidated. Recent studies have shown that overexpression of oncogenes and low expression of tumor suppressor genes play an important role in the occurrence and development of gastric cancer [4,5]. It has been reported in the literature that lysophosphatidic acid receptor (LPA) is highly expressed in human malignant tumors and is associated with poor clinical characteristics and prognosis [6–8]. LPA2 protein is encoded by the *LPA* gene, which is located in the 19.62–19.62 region of human chromosome 19. LPA2 is a G protein-coupled receptor which can bind with its ligand and then activate LPA signaling pathway, thereafter, promote cell proliferation and malignant transformation. It has been reported that LPA2 is highly expressed in solid tumors such as breast cancer and participates in biological behaviors of cancer cells proliferation and invasion [6]. Krüppel-like factor 5 (KLF5), the basic transcription element-binding protein 2 (BTEB2) in eukaryotes, is a zinc finger protein transcription factor, also known as intestinal-enriched KLF (IKLF). KLF5 can further regulate its targets genes expression by activating or inhibiting the transcription of target genes, and plays an important role in cell proliferation, differentiation, and apoptosis [9,10]. However, the expression of LPA2 and KLF5 in gastric cancer and their relationship with the occurrence and development of gastric cancer have rarely been reported.

Material and Methods

Patients

Fifty-one gastric cancer patients seen from March 2010 to March 2016 in Second People's Hospital of Jiuquan City, Gansu Province were included in this study. All the patients had pathological diagnosed gastric adenocarcinoma. In addition, 13 cases of normal gastric mucosa and 21 cases of gastric intraepithelial neoplasia (GIN) were selected for inclusion, including 12 cases of low-grade GIN and 9 cases of high-grade GIN. The general characteristics of the included cases presented in Table 1. This study was approved by the ethical committee of the Second People's Hospital of Jiuquan City, Gansu Province. The research related to human use has been complied with all the relevant national regulations, institutional policies, and was performed in accordance with the tenets of the Helsinki Declaration, and was approved by the Second People's Hospital of Jiuquan City, Gansu Province Institutional Review Board.

Methods

Instruments and equipment

The following instruments and reagents were used in this study: 1) rabbit anti-human LPA2 polyclonal antibody (Beijing Booshen Biotechnology Company, dilution number: bs-2881R, 1: 500); 2) anti-human KLF5 polyclonal antibody (Abcam, UK, 1: 600 dilution number: ab 24331); (3) instant SP9001 Kit (Beijing Zhongshan Jinqiao Biotechnology Company); 4) DAB enzyme substrate color reagent Kit (Beijing Zhongshan Jinqiao Biotechnology Company); 5) paraffin slicer (Leica Camera AG; Model: SHANDONAS-325); 6) OLYMPUSBX-40 microscope (Olympus); 7) constant-temperature bath (Grant Instruments), and 8) water purification system (Millipore Corporation).

Tissue microarray

The pathology slices were reviewed, the tissues were located under the microscope, and the location of the wax blocks was marked to determine the sampling site (Figure 1). A 2-mm hollow wax pattern was made with a tissue chip die. The tissue wax core was taken out at the marker site of the wax block by a tissue chip sampler with an inner diameter of 2 mm. The wax core was placed into the hole of the hollow wax pattern. A 6×7 tissue microarray was made, and the wax block of the tissue chip was sliced continuously at a thickness of 4 microns. The wax core was attached to the APES anti-stripping slide (Figure 2).

Immunohistochemistry

After dewaxing and gradient alcohol hydration, pH 6.0 citric acid was used to repair antigen under high temperature and high pressure. Then 3% hydrogen peroxide was used to remove endogenous enzyme activity for 10 minutes. Reagent A was applied and sealed at room temperature for 10 minutes. Primary and secondary antibodies were added by dripping after the antigen was retrieved. The tissues were developed and mounted for microscopic examination.

Determination of positive results

Two pathologists read the slices independently. Five visual fields were selected under high power microscopy to calculate the proportion of LPA positive cells in each visual field. The main positive cells were brown-yellow granules in cytoplasm/membrane. Results were qualitatively described as follows: positive cells <5% (–), positive cells 5~25% (+), positive

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Table 1. General characteristics of the included patients.

Characteristics	Poor differentiation (n=19)	Moderate differentiation (n=16)	Well differentiation (n=16)	High grade GIN (n=9)	Low grade GIN (n=12)	Normal (n=13)
Age	57.3±7.7	62.1±5.9	63.2±10.3	58.9±21.7	59.1±8.5	58.3±6.6
Gender						
Male	18	15	14	7	10	12
Female	1	1	2	2	2	1
Clinical stage						
I	5	5	12	NA	NA	NA
II	5	6	2	NA	NA	NA
III	6	4	2	NA	NA	NA
IV	3	1	0	NA	NA	NA
Tumor location						
Cardia	6	9	13	NA	NA	NA
Body of stomach	3	3	3	NA	NA	NA
Pylorus	10	4	0	NA	NA	NA
Invasion depth						
Mucosa or submucosa	2	2	7	NA	NA	NA
Muscularis	3	4	3	NA	NA	NA
Serosa	14	10	6	NA	NA	NA
Lauren type						
Intestinal type	10	16	16	NA	NA	NA
Diffuse type	9	0	0	NA	NA	NA
Vascular invasion				NA	NA	NA
Yes	8	5	0	NA	NA	NA
No	11	11	16	NA	NA	NA
Lymph node metastasis						
Yes	11	9	3	NA	NA	NA
No	8	7	13	NA	NA	NA
Tumor diameter						
≤5 cm	6	13	12	NA	NA	NA
>5 cm	13	3	4	NA	NA	NA

cells 25~50% (++), positive cells (++), positive cells (++) and positive cells >50% (+++).

Statistical analysis

Data in the present work was analyzed through Stata 11.0 statistical software (Stata Corporation, College Station, TX, USA). Measurement data and counted data expressed as mean ± standard deviation and rate. Comparisons were made by Fisher's exact test and F test. Differences were considered significant at $P<0.05$.

Results

LPA 2 expression in different groups

LPA2 was mainly expressed in the cytoplasm and cell membrane with brown granular (Figure 3). The positive expression rate was 89.5% (17 out of 19), 81.3% (13 out of 16), 25.0% (4 out of 16), 33.3% (3 out of 9), 25.0% (3 out of 12), and 23.1% (3 out of 13) for poor, moderate, well differentiation gastric adenocarcinoma, high grade GIN, low grade GIN, and normal gastric tissue respectively with statistical difference ($P<0.05$) (Table 2). The mRNA relative expression level of LPA2

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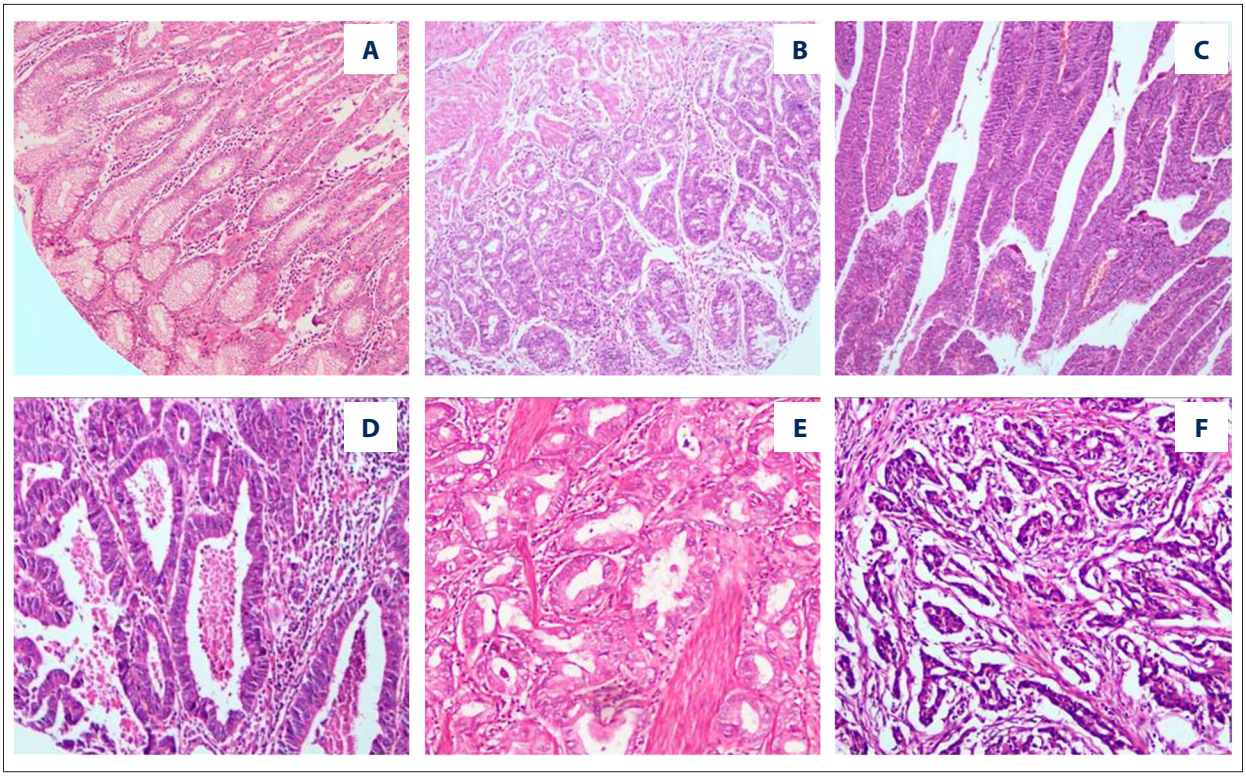

Figure 1. Hematoxylin and eosin (H&E) staining results of tissues of different groups: (**A**) normal gastric mucosa tissue; (**B**) low grade GIN; (**C**) high grade GIN; (**D**) well differentiation gastric adenocarcinoma tissue; (**E**) moderate differentiation gastric adenocarcinoma tissue; (**F**) poor differentiation gastric adenocarcinoma tissue); magnification 10x. GIN, gastric intraepithelial neoplasia.

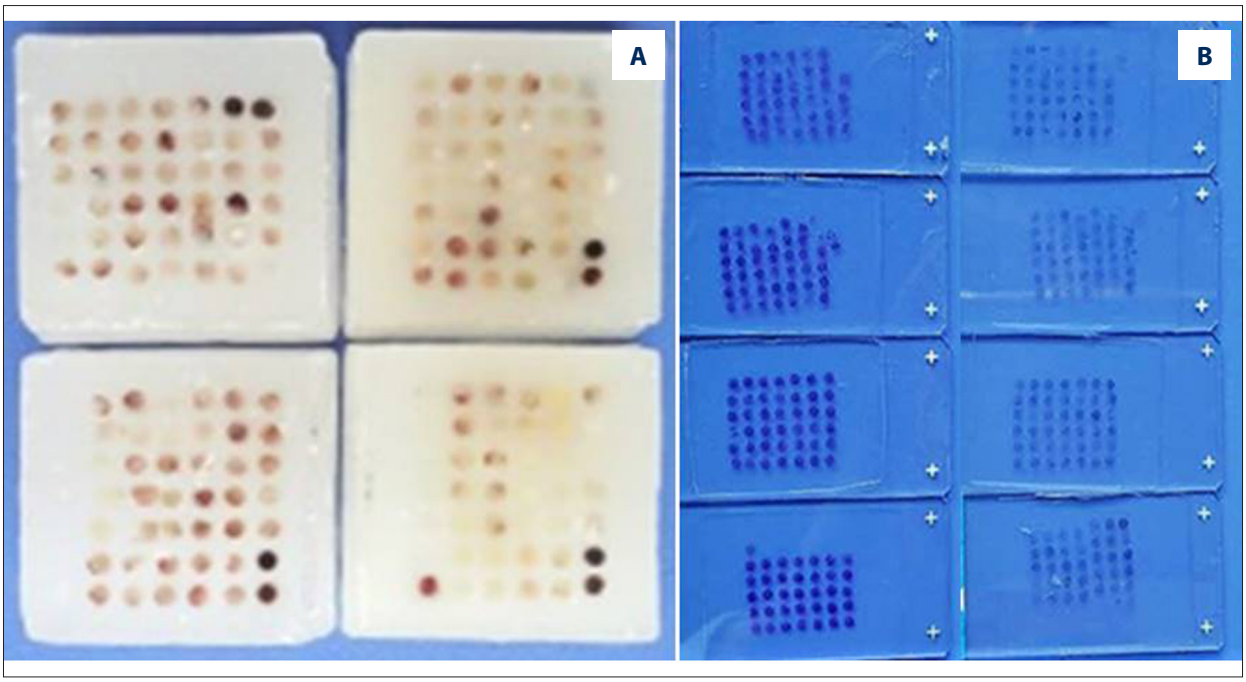

Figure 2. Tissue microarray for detection LPA2 and KLF5 expression: (**A**) paraffin blocks of tissue microarray; (**B**) sections of tissue microarray. LPA2 – lysophosphatidic acid receptor-2; KLF5 – Krüppel-like factor 5.

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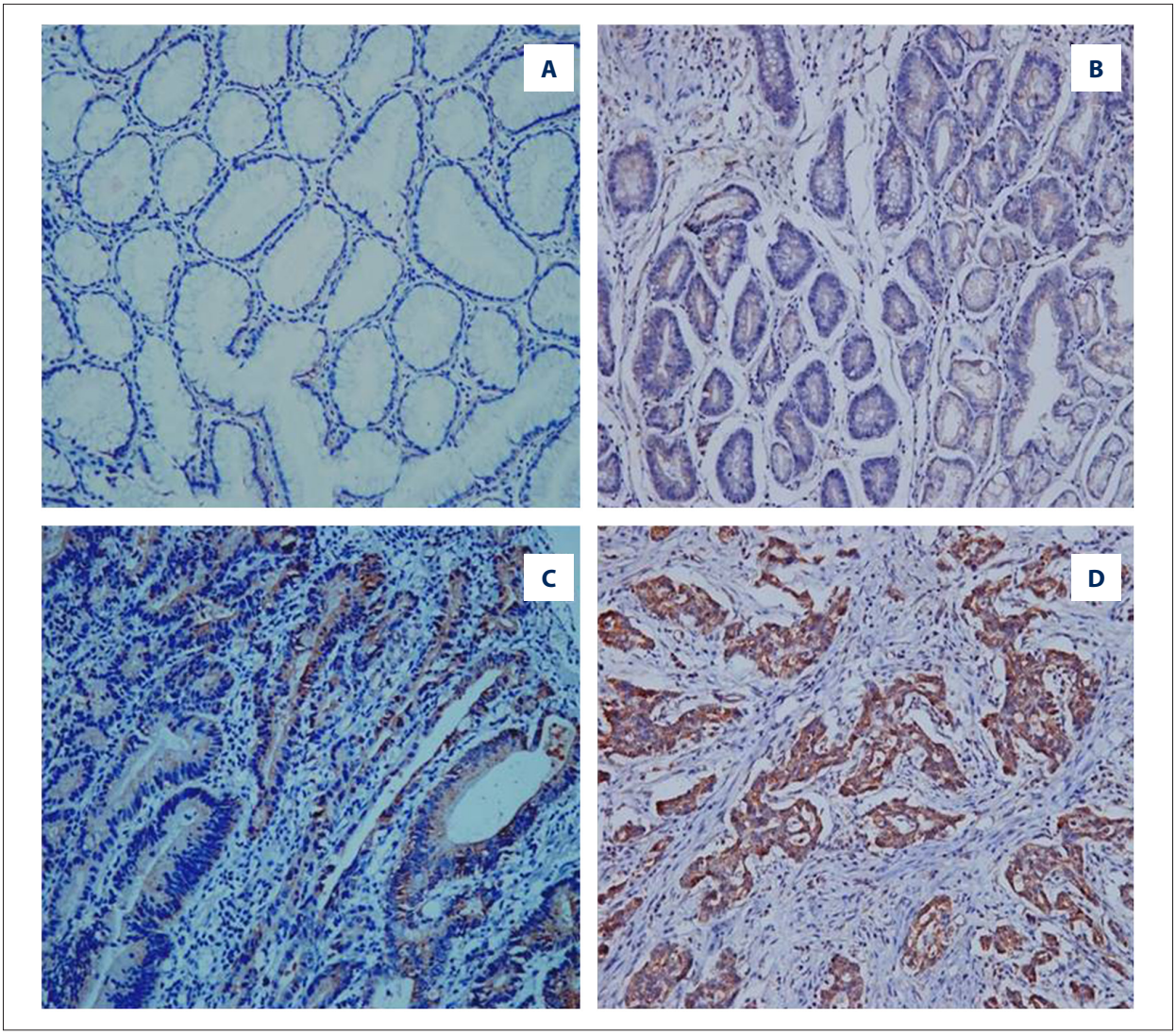

Figure 3. Immunohistochemical staining results of LPA2 expression of different groups: (**A**) positive expression of LPA2 in normal gastric mucosa tissue; (**B**) positive expression of LPA2 in low grade GIN; (**C**) positive expression of LPA2 in high grade GIN; (**D**) positive expression of LPA2 in gastric adenocarcinoma tissue); magnification 20×. LPA2 – lysophosphatidic acid receptor-2; GIN – gastric intraepithelial neoplasia.

Table 2. LPA2 Expression in different groups (n).

Histological category	Negative (n)	Positive (n)	Positive (%)
Gastric adenocarcinoma			
Poor (n=19)	2	17	89.5
Moderate (n=16)	3	13	81.3
Well (n=16)	12	4	25.0
GIN			
High grade GIN (n=9)	6	3	33.3
Low grade GIN (n=12)	9	3	25.0
Normal gastric tissue (n=13)	10	3	23.1

LPA2 – lysophosphatidic acid receptor-2; GIN – gastric intraepithelial neoplasia.

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Table 3. Correlation between LPA2 expression and clinicopathological characteristics (n).

Index	N=51	LPA2		Chi-square	*P*
		+ (n=34)	– (n=17)		
Gender				0.17	0.68
Male	47	32	15		
Female	4	2	2		
Age (years)				0.30	0.59
<50	8	6	2		
≥50	43	28	15		
Tumor location				0.96	0.62
Cardia	28	17	11		
Body of stomach	10	7	3		
Pylorus	13	10	3		
Lauren type				5.46	**0.02**
Intestinal type	42	25	17		
Diffuse type	9	9	0		
Vascular invasion				5.16	**0.02**
No	38	22	16		
Yes	13	12	1		
Lymph node metastasis				7.76	**0.01**
No	28	14	14		
Yes	23	20	3		
Clinical stage				8.71	**0.03**
I	22	10	12		
II	13	11	2		
III	12	9	3		
IV	4	4	0		
Invasion depth				11.63	**0.00**
Mucosa or submucosa	11	3	8		
Muscularis	10	6	4		
Serosa	30	25	5		
Tumor diameter				0.02	0.89
≤5 cm	35	23	12		
>5 cm	16	11	5		
Histological grade				0.00	0.96
Well	16	4	12		
Moderate	16	13	3		
Poor	19	17	2		

LPA2 – lysophosphatidic acid receptor-2.

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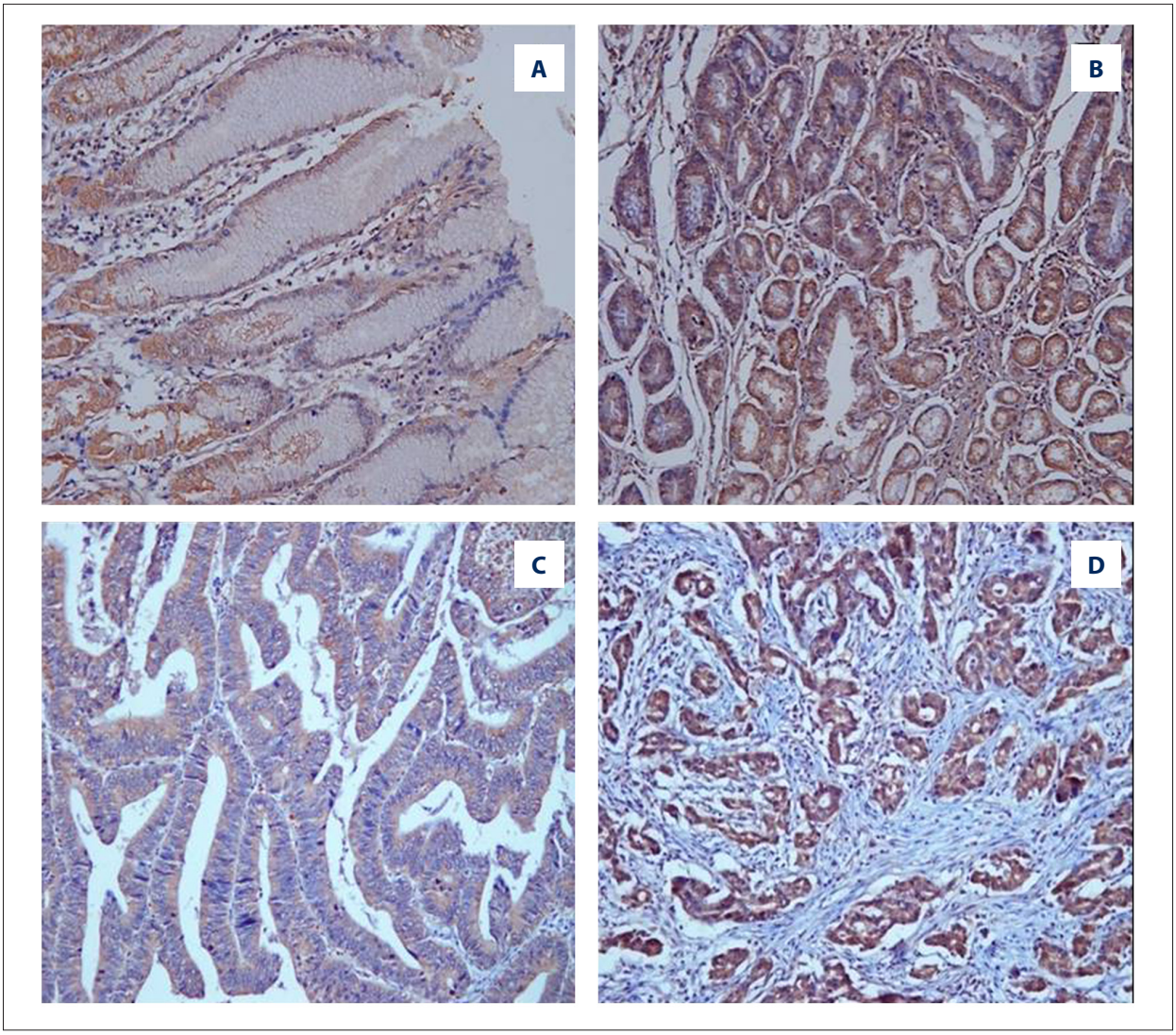

Figure 4. Immunohistochemical staining results of KLF5 expression of different groups: (**A**) positive expression of KLF5 in normal gastric mucosa tissue; (**B**) positive expression of KLF5 in low grade GIN; (**C**) positive expression of KLF5 in high grade GIN; (**D**) positive expression of KLF5 in gastric adenocarcinoma tissue); magnification 20×. KLF5 – Krüppel-like factor 5; GIN – gastric intraepithelial neoplasia

Table 4. KLF5 expression in different groups (n).

Histological category	Negative (n)	Positive (n)	Positive (%)
Gastric adenocarcinoma			
Poor (n=19)	4	15	78.9
Moderate (n=16)	4	12	75.0
Well (n=16)	4	12	75.0
GIN			
High grade GIN (n=9)	3	6	66.7
Low grade GIN (n=12)	5	7	58.3
Normal gastric tissue (n=13)	8	5	38.5

KLF5 – Krüppel-like factor 5; GIN – gastric intraepithelial neoplasia.

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Table 5. Correlation between KLF5 expression and clinicopathological characteristics (n).

Index	N=51	KLF5		Chi-square	*P*
		+ (n=39)	– (n=12)		
Gender				0.01	0.94
Male	47	36	11		
Female	4	3	1		
Age (years)				0.64	0.42
<50	8	7	1		
≥50	43	32	11		
Tumor location				0.46	0.79
Cardia	28	22	6		
Body of stomach	10	8	2		
Pylorus	13	9	4		
Lauren type				0.01	0.92
Intestinal type	42	32	10		
Diffuse type	9	7	2		
Vascular invasion				0.51	0.48
No	38	30	8		
Yes	13	9	4		
Lymph node metastasis				0.88	0.35
No	28	20	8		
Yes	23	19	4		
Clinical stage				5.41	0.14
I	22	16	6		
II	13	12	1		
III	12	7	5		
IV	4	4	0		
Invasion depth				1.28	0.53
Mucosa or submucosa	11	7	4		
Muscularis	30	24	6		
Serosa	10	8	2		
Tumor diameter				1.59	0.21
≤5 cm	37	30	7		
>5 cm	14	9	5		
Histological grade				0.07	0.78
Well	16	12	4		
Moderate	16	12	4		
Poor	19	15	4		

KLF5 – Krüppel-like factor 5.

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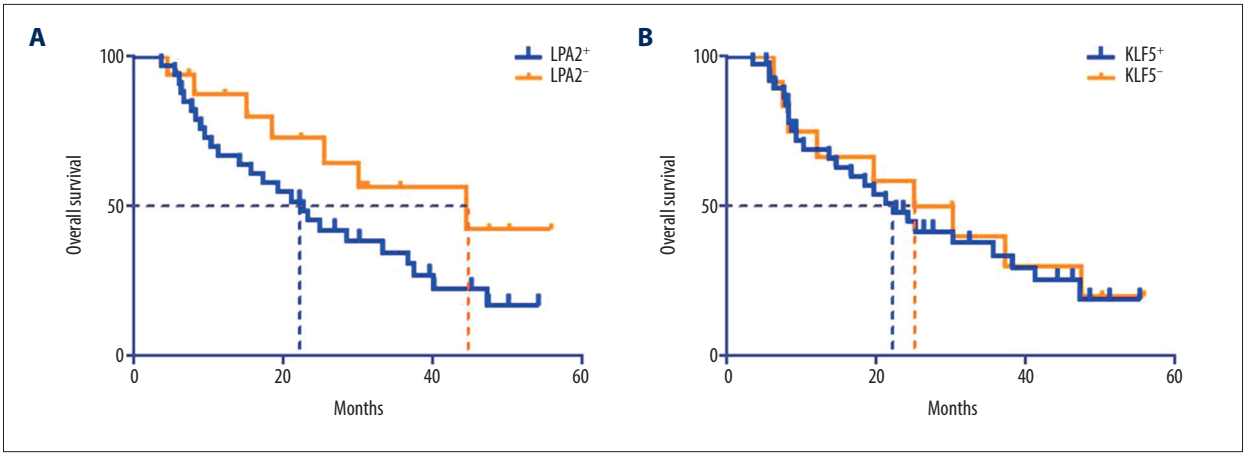

Figure 5. Survival curves f gastric adenocarcinoma patients between LPA2, KLF5 positive and negative groups: (**A**) LPA2; (**B**) KLF5. LPA2 – lysophosphatidic acid receptor-2; KLF5 – Krüppel-like factor 5.

was examined by real-time polymerase chain reaction (PCR) assay. The results showed that the LPA2 mRNA level of gastric adenocarcinoma and GIN were 0.045±0.018 and 0.021±0.009 respectively with statistical difference (P<0.05).

Correlation between LPA2 expression and clinicopathological features

LPA2 positive expression was not correlated with age, sex, location, diameter, or histological grade of the patients (P>0.05), but was correlated with depth of invasion, Lauren classification, vascular invasion, lymph node metastasis, and clinical stage (P<0.05) (Table 3).

KLF5 expression in different groups

KLF5 was mainly expressed in the cytoplasm, brown granular (Figure 4). The positive expression rate was 78.9% (15 out of 19), 75.0% (12 out of 16), 75.0% (12 out of 16), 66.7% (6 out of 9), 58.3% (7 out of 12), and 38.5% (5 out of 13) for poor, moderate, well differentiation gastric adenocarcinoma, high grade GIN, low grade GIN, and normal gastric tissue respectively with statistical difference (P<0.05) (Table 4). The mRNA of relative expression level of KLF5 was examined by real-time PCR assay. The results showed that the KLF5 mRNA level of gastric adenocarcinoma and GIN were 0.64±0.21 and 0.62±0.20 respectively without statistical difference (P>0.05).

Correlation between KLF5 expression and clinicopathological features

The positive expression of KLF5 protein was not correlated with age, sex, tumor location, tumor diameter, histological grade, depth of invasion, Lauren classification, vascular invasion, regional lymph node metastasis, or clinical stage (P>0.05), (Table 5).

LPA2, KLF5 expression and prognosis

There was no correlation between LPA2 (HR=1.84, 95% CI: 0.89–3.80, P>0.05), KLF5 (HR=1.13, 95% CI: 0.53–2.36, P>0.05) expression and patients' overall survival (Figure 5). For disease free survival (DFS), the difference was also not statistical different between LPA2 (HR=1.34, 95% CI: 0.68–3.12), KLF5 (HR=1.05, 95% CI: 0.46–2.14) positive and negative groups.

Discussion

Gastric cancer is one of the most diagnosed malignant tumor of digestive system and the third leading cause of cancer related death [11]. The development of gastric cancer is a multifactor, multi-gene and multi-step process [12,13]. It is also the result of the interaction of genetic and environmental factors. It involves the activation of oncogene and inactivation of anti-oncogene, activation of telomere and gene instability. In the process of tumorigenesis and development, although the activation of oncogenes is one of the main factors to promote tumorigenesis, the inactivation of tumor suppressor genes may play a more important role [14,15].

Generally, canceration seldom occurs directly from normal gastric mucosal epithelium. In most cases, the occurrence and development of gastric cancer is closely related to benign chronic gastric diseases and dysplasia of gastric mucosa. Precancerous diseases of gastric cancers refer to a number of clinical situations in which the risk of gastric cancer is significantly increased. Precancerous disease of gastric cancer includes chronic atrophic gastritis with or without intestinal metaplasia and malignant anemia, chronic gastric ulcer, remnant stomach, gastric polyp and gastric mucosal giant plica disease (Menetrier disease) after operation, and precancerous lesions of gastric cancer include gastric cancer-related diseases and dysplasia

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of gastric mucosa [16–19]. Gastric mucosal dysplasia is currently recognized as a precancerous lesion, especially moderate to severe dysplasia. Gastric intraepithelial neoplasia (GIN) is synonymous with dysplasia.

LPA is a multifunctional "messenger phospholipid", which can promote cell proliferation and change cell morphology. LPA is a normal component of serum, but its level in normal human plasma is extremely low [20]. As a lipid signaling molecule, LPA can mediate various signal transduction pathways and plays its biological role by activating specific G protein-coupled receptors. There are 6 G protein-coupled receptors (GPCRs) in LPA, namely LPA1-6. Classical LPA receptors, including LPA1, LPA2, and LPA3, belong to the endothelial differentiation gene receptor (EDG) family, namely LPA1/EDG2, LPA2/EDG4, and LPA3/EDG7. LPA2 protein is encoded by the *LPA* gene, which is located in the 19.62–19.62 region of human chromosome 19. LPA2 is a G protein-coupled receptor. LPA2 binding with its ligand can activate LPA signaling pathway, thereafter, promote cell proliferation and malignant transformation [6]. Human LPA2 protein contains 351 amino acid residues with molecular weight of 39 100. There are 3 exons and 2 introns in the coding region of *LPA2* gene. LPA1, LPA2 and LPA3 can bind to Gai/o and Gaq to regulate the signal transduction pathway of LPA.

Studies have shown that LPA2 is closely related to the occurrence of various solid tumors, such as breast cancer, ovarian cancer, colorectal cancer, pancreatic cancer, etc. [21,22]. LPA2 is abnormally expressed in these tumors, and has a certain correlation with the tumor occurrence, invasion, metastasis, and prognosis.

In the present work, we found that the positive rate of LPA2 in gastric cancer tissue was significantly higher than that of GIN and normal gastric mucosa ($P<0.001$), which was in accordance with a precious study [23]. However, LPA2 positive expression was not correlated with age, sex, tumor location, tumor diameter, or histological grade of gastric adenocarcinoma ($P>0.05$), but was significantly correlated with depth of invasion, Lauren classification, vascular invasion, lymph node metastasis, and clinical stage (all $P<0.05$). The expression of LPA2 protein increased with the depth of invasion, regional lymph node metastasis, vascular invasion, Lauren's diffuse type, and clinical stage of gastric adenocarcinoma, which preliminarily indicated that the gastric adenocarcinoma with high expression of LPA2 might be more invasive, and LPA2 might be involved in the development and metastasis of gastric adenocarcinoma, which played a role in the invasion, metastasis, and progression of gastric adenocarcinoma. However, long-rank survival analysis did not find overall and DFS difference between LPA2 positive and negative groups.

The human *KLF5* gene is encoded in the 13q21 region of human chromosome. The KLF5 protein contains 457 amino acids with a molecular weight of 55 kDa. Its CDS coding region contains an activation domain and a DNA binding domain. KLF5 contains many target genes, such as nuclear factor κB (NF-κB), peroxisome proliferator-activated receptor (PPAR), platelet-derived growth factor a (pDGFa) and T cell antigen receptor (TCR), which have been confirmed in different cells. As a zinc finger transcription factor, KLF5 further participates in the regulation of cell proliferation, cell differentiation, cell apoptosis, and individual development by regulating the expression of GC-rich promoter region.

Publications have proven that KLF5 plays an important role in many malignant tumors, such as bladder cancer [24], prostate cancer [25], breast cancer [26], colon cancer, thyroid cancer [27], etc., but the biological behavior of KLF5 is different in different tumors [28]. Nandan et al. [29] found that KLF5 was highly expressed in the proliferative and active crypt epithelium of normal intestinal tissues. By stimulating cyclinB1, cyclinD1 and Cdc2, KLF5 accelerated cell cycle and promoted cell growth. KLF5 can promote the growth of normal cells, while KLF5 can inhibit the growth of some cancer cells, which is incomprehensible. Studies have reported that KLF5 is highly expressed in gastric adenocarcinoma [30], but studies have also shown that the expression of KLF5 in gastric adenocarcinoma is significantly downregulated [31]. In our study, we didn't find any correlation between KLF5 expression and patients' clinicopathological features and prognosis.

Conclusions

LPA2 and KLF5 were different expressed in gastric adenocarcinoma, GIN, and normal gastric tissue. LPA2 protein is highly expressed in gastric adenocarcinoma tissues. Its positive expression is closely related to the depth of invasion, Lauren classification, vascular invasion, regional lymph node metastasis, and clinical stage. This suggests that LPA2 might be involved in the development of gastric adenocarcinoma and could be used as an important biological marker for prognosis and biological behavior of gastric cancer. However, the sample size of our study was small, and the statistical power was limited. The conclusion should be further proven by large sample sized high quality studies.

Conflict of interest

None.

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