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Original contribution

Decreased expression of LKB1 is associated with epithelial-mesenchymal transition and led to an unfavorable prognosis in gastric cancer☆

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Summary Liver kinase B1 (*LKB1*) is a newly discovered tumor suppressor gene that plays a role in tumorigenesis and cancer progression. However, LKB1 expression and its precise impact on gastric cancer (GC) have not yet been elucidated. The aim of this study was to explore the significance of LKB1 expression, as well as its correlation with epithelial-mesenchymal transition (EMT) in GC. In the present study, LKB1 protein was detected in 107 GC tissue samples and adjacent paracancerous tissues by immunohistochemical staining. The relationship of LKB1 expression with clinicopathological features and its correlation with 3 EMT-related markers (E-cadherin, β-catenin, and vimentin) in GC were analyzed. Results revealed that the expression of LKB1 was decreased in GC tissues compared with that in adjacent paracancerous tissues ($P = .005$). GC patients with greater invasion depth ($P = .007$), higher pathological TNM stage ($P = .014$), and lymph node metastasis ($P = .026$) showed lower LKB1 expression; furthermore, E-cadherin and β-catenin expression decreased, whereas vimentin expression increased (all $P < .05$). Kaplan-Meier analysis indicated that the expression of LKB1, E-cadherin, β-catenin, and vimentin, as well as differentiation, invasion, pathological TNM, and lymph node metastasis, was associated with disease-free survival (DFS) (all $P < .05$). Multivariate analysis also showed that LKB1 expression (hazard ratio, 0.578 [0.351-0.950]; $P = .031$) may be an independent factor for DFS. In conclusion, LKB1 expression was decreased in GC, and this positively correlated with EMT and a shorter DFS, suggesting that LKB1 could act as an independent factor in predicting GC progression.

1. Introduction

Gastric cancer (GC) is the fifth most common malignancy and the second leading cause of cancer-related deaths worldwide [1,2]. Surgery resection remains to be the primary course of therapy for GC, with a high rate of success in the early stage

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Table 1 Expression of LKB 1 in gastric cancerous and paracancerous tissue

	LKB1 expression		*P*
	Low, n (%)	High, n (%)	
Gastric cancerous tissue (n = 107)	59 (55.1)	48 (44.9)	.005
Paracancerous tissue (n = 107)	24 (22.4)	83 (77.6)	

of the disease. However, most cases (>75%) are diagnosed at an advanced stage, and the survival rate falls below 20% with local extension or lymph node metastasis [3]. Therefore, it is necessary to discover prognostic markers, as well as new therapeutic targets for GC.

Liver kinase B1 (*LKB1*), also called serine/threonine protein kinase 11 (*STK 11*), is a newly discovered tumor suppressor gene that plays a role in several malignancies, including lung cancer, breast cancer, and cervical cancer [4]. Studies have indicated that the mutation or down-regulation of the *LKB1* gene in several cancers is associated with tumorigenesis and cancer progression [5,6]. However, the expression level of LKB1 and its role in GC has been controversial.

An earlier study by Park et al [7] failed to identify common *LKB1* gene mutations in sporadic GC, whereas Jiang et al [8] found that the expression of LKB1 was reduced in GC tissues but was not associated with the clinicopathological data of those patients. Meanwhile, Sun et al [9] demonstrated that the expression of LKB1 mRNA and protein was inversely related to tumor progression and poor prognosis with a low survival rate in GC. Therefore, the level of LKB1 expression and the mechanism underlying the possible down-regulation of LKB1 expression in GC remain to be elucidated.

Epithelial-mesenchymal transition (EMT) is a developmental process in which epithelial cells lose their epithelial phenotype and acquire a mesenchymal cell phenotype. A substantial number of studies have demonstrated that the development of most human cancers involves the process of EMT [10,11], which has been proven to be a critical phenotypic alteration of cancer cells that triggers invasion and metastasis [12]. Roy et al [13] demonstrated that the inactivation of LKB1 in lung cancer cells induced EMT and promoted lung carcinoma invasiveness and metastasis. Nevertheless, the correlation of LKB1 with EMT in GC has not yet been elucidated.

In the present study, we investigated the expression of LKB1 and its correlation with the clinicopathological features of GC. Furthermore, we explored the correlation of LKB1 with 3 EMT markers, E-cadherin, β-catenin, and vimentin, and analyzed whether the expression level of LKB1 and the presence of EMT correlated with prognosis in GC.

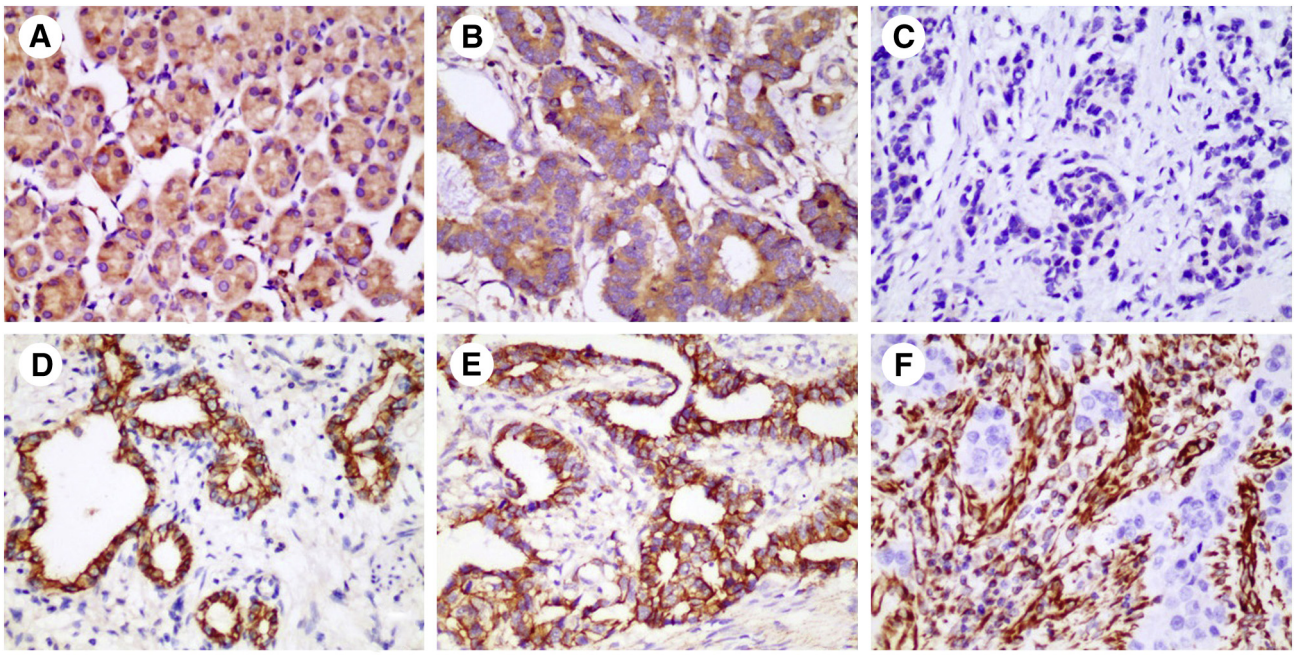

Fig. 1 IHC staining of LKB1, E-cadherin, β-catenin, and vimentin. The positive staining of LKB1 protein was mainly found in the cytoplasm of GC tumor cells and paracancerous normal gastric mucosa: normal gastric mucosa, positive staining (A); high/moderate differentiated GC, positive staining (B); and low differentiated GC, negative staining (C). The positive staining of E-cadherin and β-catenin protein was mainly found in the membrane of GC: intestinal GC, E-cadherin– (D) and β-catenin– (E) positive staining. F, The staining of vimentin protein was mainly found in the cytoplasm of GC tumor stroma: diffused GC, vimentin-positive staining (original magnification ×200).

2. Materials and methods

2.1. Patients

This was a retrospective study of a series of 107 patients who underwent gastrectomy between 2010 and 2017 in the Jingzhou Central Hospital. All specimens were tubular adenocarcinoma. Gastric cancerous and relevant adjacent (≥5 cm) nontumor tissues were obtained, and clinicopathological features of each patient were obtained from the Department of Oncology, Jingzhou Central Hospital, The Second Clinical Medical College, Yangtze University (Table 1). The pathological TNM (pTNM) staging of GC was determined according to the eighth edition American Joint Committee on Cancer TNM system for differentiated gastric carcinoma [14]. The study was approved by the scientific research ethics committee of Jingzhou Central Hospital, and the informed consent for the use of tissues for ex vivo experimentation was obtained from each patient before surgery. Follow-up duration was defined as the time from the diagnosis of GC until the final visit. Disease-free survival (DFS) was defined as the interval from the date of surgery to GC-related recurrence or metastasis, or the final visit.

2.2. Immunohistochemistry

A conventional immunohistochemical (IHC) staining protocol was used in this study. Briefly, paraffin-embedded tumor tissue blocks were cut into 4-μm-thick sections, dried, deparaffinized, and dehydrated in a graded series of ethanol. Tissue sections were treated with 1% hydrogen peroxide for 10 minutes to block endogenous tissue peroxidase activity, followed by treatment with bovine serum for 30 minutes to reduce nonspecific binding. Antigen retrieval was then accomplished using citrate buffer (pH 6.0) as follows: high-heat microwave processing for 5 minutes followed by low-heat microwave processing for 20 minutes. All the slides were incubated with rabbit polyclonal antihuman LKB1 antibody (OM222158, 1:1000; OmnimAbs, Alhambra, CA), mouse monoclonal antihuman β-catenin antibody (Ready-to-use, CAT-5H10; Maixin-Bio, Fuzhou, China), mouse monoclonal antihuman E-cadherin antibody (Ready-to-use, 4A2C7; Maixin-Bio), and mouse monoclonal antihuman vimentin antibody (Ready-to-use, V9; Gene Tech, Shanghai, China) overnight at 4°C, followed by incubation for 30 minutes in Ultra-Sensitive S-P Kit (Maixin-Bio). Slides were rinsed with phosphate-buffered saline before color development using

Table 2 Correlation of LKB1 expression with clinicopathological features and expression of E-cadherin, β-catenin, and vimentin in GC

	n (n = 107)	LKB1 expression		*P*
		Low, n (%)	High, n (%)	
Sex				
Male	81	43 (53.1)	38 (46.9)	.451
Female	26	16 (61.5)	10 (38.5)	
Age (y)				
<57	52	32 (61.5)	20 (38.5)	.196
≥57	55	27 (49.1)	28 (50.9)	
Differentiation				
High/moderate	38	19 (50.0)	19 (50.0)	.428
Low	69	40 (58.0)	29 (42.0)	
Invasion				
T1/T2	23	7 (30.4)	16 (69.6)	.007
T3/T4	84	52 (61.9)	32 (38.1)	
pTNM stage				
I/II	42	17 (40.5)	25 (59.5)	.014
III/IV	65	42 (64.6)	23 (35.4)	
Lymph node metastasis				
No	39	16 (41.0)	23 (59.0)	.026
Yes	68	43 (63.2)	25 (36.8)	
E-cadherin expression				
Low	47	32 (68.1)	15 (31.9)	.017
High	60	27 (45.0)	33 (55.0)	
β-Catenin expression				
Low	46	32 (69.6)	14 (30.4)	.009
High	61	27 (44.3)	34 (55.7)	
Vimentin expression				
Low	40	17 (42.5)	23 (57.5)	.042
High	67	42 (62.7)	25 (37.3)	

3,3′-diaminobenzidine substrate kit and then counterstained with hematoxylin.

2.3. Evaluation of immunohistochemistry

The immunoreactivity of LKB1 and 3 EMT-related markers was examined by 2 senior pathologists who were blinded to the clinicopathological data. Ten areas were randomly selected and counted at a magnification of ×200. LKB1 staining was evaluated semiquantitatively based on staining intensity and percentage of positive cells as follows: 0, no staining or weak staining in less than 10% of cells; 1+, weak immunostaining in more than 10% of cells; 2+, moderate immunostaining in more than 10% of cells; and 3+, strong immunostaining in more than 10% of cells. The staining pattern was either granular or diffuse. Scores of 1+ or lower indicated the absence of a tumor, whereas scores of 2+ or higher were considered positive [9].

IHC staining of E-cadherin, β-catenin, and vimentin proteins was assessed in a semiquantitative manner in terms of staining intensity and percentage of positive cells. The intensity scores were defined as follows: 0 (negative), 1+ (weak staining), 2+ (moderate staining), and 3+ (strong staining). The proportion scores were defined as follows: 0 (negative), 1 (≤10% positive cells), 2 (11%-50% positive cells), 3 (51%-80% positive cells), and 4 (≥80% positive cells). The final score for each slide was represented by the average of 3 representative high-power fields (×400). Scores of 4 or lower were defined as low expression, and scores of higher than 4 were described as high expression [15].

2.4. Statistical analysis

Statistical analysis was performed using SPSS 21.0 software (SPSS, Chicago, IL). The differences in LKB1 expression in gastric cancerous and paracancerous tissues were analyzed by Wilcoxon signed rank tests. Correlations of LKB1 with β-catenin, E-cadherin, and vimentin and with the clinicopathological features of GC patients were compared using the χ^2 and Mann-Whitney *U* tests. Furthermore, the correlations of DFS with LKB1, β-catenin, E-cadherin, and vimentin expression were analyzed using the Kaplan-Meier method and compared with each other using the log-rank test. The Cox proportional hazard regression model was used to identify the prognostic factors that influenced survival.

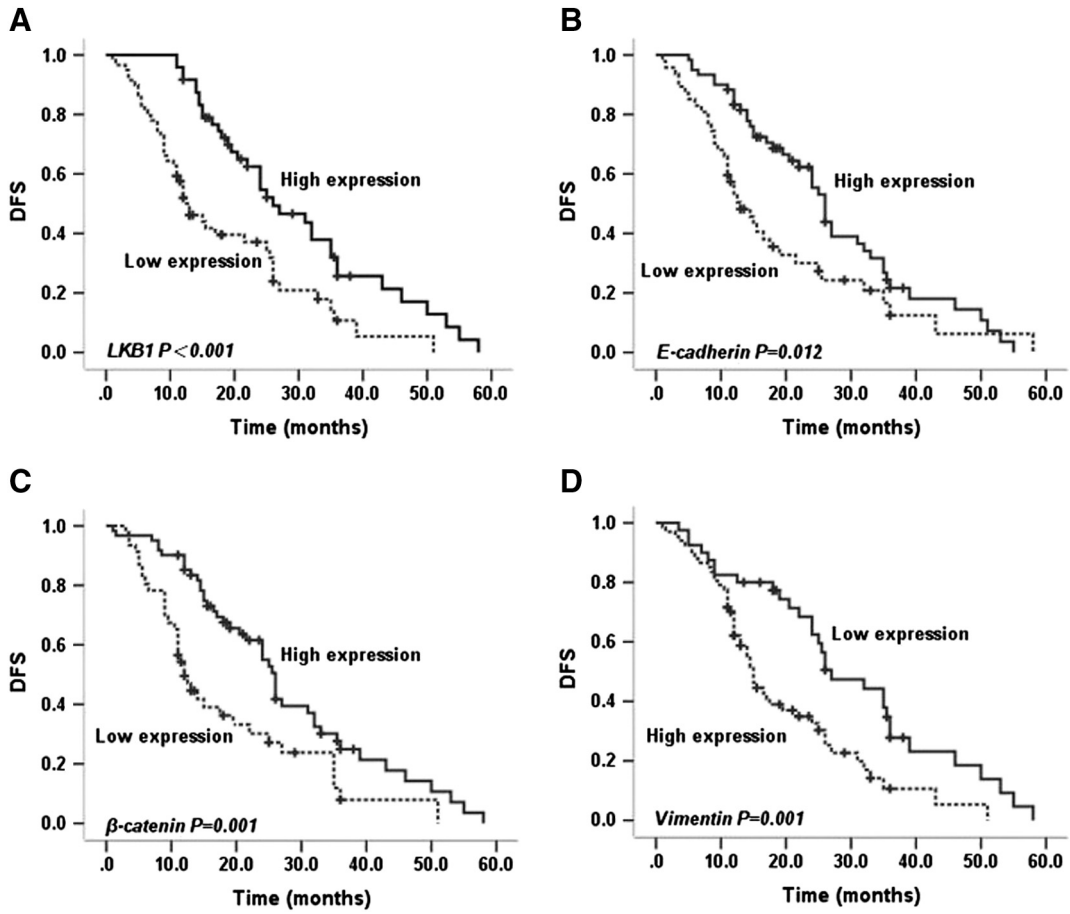

Fig. 2 Kaplan-Meier analysis of DFS according to LKB1 expression (A), E-cadherin expression (B), β-catenin expression (C), and vimentin expression (D). (+), data censored.

3. Results

3.1. Expression of LKB1 in GC and paracancerous tissues

Expression of LKB1 was analyzed by IHC in 107 tissue samples of GC and in corresponding paracancerous tissue samples. According to the LKB1 immunoreactivity, 59 (55.1%) exhibited low LKB1 expression and 48 (44.9%) exhibited high LKB1 expression, whereas among the paracancerous tissues, 24 (22.4%) exhibited low LKB1 expression and 83 (77.6%) exhibited high LKB1 expression.

Positive staining of the LKB1 protein was mainly located in the cytoplasm of both tumor and normal cells (Fig. 1A-C). The results of IHC staining of LKB1 protein are shown in Table 1. LKB1 expression in paracancerous tissues was significantly higher than that in GC tissues ($P = .005$).

3.2. Correlation of LKB1 expression with clinicopathological features and expression of E-cadherin, β-catenin, and vimentin in GC

The correlation of LKB1 expression with the clinicopathological features and expression of E-cadherin, β-catenin, and vimentin in GC is shown in Table 2. It was found that GC patients with greater invasion depth ($P = .007$), higher pTNM stage ($P = .014$), and lymph node metastasis ($P = .026$) exhibited lower LKB1 expression, whereas LKB1 expression was not associated with sex ($P = .451$), age ($P = .196$), and differentiation ($P = .428$).

Expression levels of E-cadherin, β-catenin, and vimentin were also analyzed by IHC in 107 GC tissue samples. Positive staining for the expression of E-cadherin (Fig. 1D) and that for β-catenin (Fig. 1E) were mainly found in the membrane of tumor cells, whereas positive staining of the expression of vimentin was mainly found in the cytoplasm of tumor stroma (Fig. 1F). It was found that, with low LKB1 expression, the expression of E-cadherin and β-catenin decreased, and the expression of vimentin increased ($P = .017$, $P = .009$, and $P = .042$, respectively).

3.3. DFS analysis of GC

The median DFS duration of the patients was 15 months (range, 1-53 months). The Kaplan-Meier and Cox proportional hazard regression methods were used to evaluate the risk factors with the DFS of GC patients. Kaplan-Meier analysis

Table 3 Univariate analysis of predictive factors for DFS in GC patients

	n	n of event	Median DFS (range)	Log-rank test, χ^2	*P*
Sex					
Male	81	65 (80.2)	20.5 (13.5-27.5)	0.096	.757
Female	26	17 (69.2)	21.5 (12.7-30.3)		
Age (y)					
<57	52	44 (84.6)	19.0 (7.7-30.3)	0.133	.715
≥57	55	38 (69.1)	22.0 (15.5-28.5)		
Differentiation					
High/moderate	38	25 (65.8)	24.0 (16.8-31.2)	3.989	.046
Low	69	57 (82.6)	17.5 (10.0-25.1)		
Invasion					
T1/T2	23	15 (65.2)	26.0 (20.1-31.9)	7.679	.006
T3/T4	84	67 (79.8)	16.5 (11.2-21.8)		
pTNM stage					
I/II	42	29 (69.1)	26.0 (24.0-28.0)	5.618	.018
III/IV	65	53 (81.5)	15.0 (11.9-18.1)		
Lymph node metastasis					
No	39	25 (64.1)	26.0 (23.6-28.4)	4.174	.041
Yes	68	57 (83.8)	15.0 (11.3-18.7)		
LKB1 expression					
Low	59	46 (78.0)	13.0 (9.6-16.4)	13.354	<.001
High	48	36 (75.0)	26.0 (18.7-33.3)		
E-cadherin expression					
Low	47	38 (80.9)	13.0 (9.5-16.6)	6.354	.012
High	60	44 (73.3)	26.0 (23.6-28.4)		
β-Catenin expression					
Low	46	37 (80.4)	12.0 (9.6-14.4)	10.374	.001
High	61	45 (73.8)	26.0 (22.9-29.1)		
Vimentin expression					
Low	40	31 (77.5)	27.0 (18.2-35.8)	10.532	.001
High	67	51 (76.1)	15.0 (13.2-16.8)		

Table 4 Multivariate analyses of predictive factors for the DFS in GC patients

	B	Wald	*P*	HR (95% CI)
Differentiation				
High/moderate	0.382	1.979	.160	1.465 (0.860-2.496)
Low				
Invasion				
pT1/T2	0.548	2.027	.155	1.729 (0.814-3.674)
pT3/T4				
pTNM stage				
I/II	−0.329	0.533	.465	0.720 (0.298-1.740)
III/IV				
Lymph node metastasis				
No	0.273	0.450	.502	1.314 (0.592-2.914)
Yes				
LKB1 expression				
Low	−0.549	4.676	.031	0.578 (0.351-0.950)
High				
E-cadherin expression				
Low	−0.370	2.201	.138	0.690 (0.423-1.126)
High				
β-Catenin expression				
Low	−0.449	3.261	.071	0.638 (0.392-1.039)
High				
Vimentin expression				
Low	0.384	2.013	.156	1.468 (0.864-2.497)
High				

Abbreviations: CI, confidence interval; HR, hazard ratio.

revealed that patients with low expression of LKB1 (log-rank test, $P < .001$), E-cadherin (log-rank test, $P = .012$), and β-catenin (log-rank test, $P = .001$), and patients with high expression of vimentin (log-rank test, $P = .001$) had a shorter DFS than did patients with high expression of LKB1, E-cadherin, and β-catenin and low expression of vimentin (Fig. 2). DFS was also significantly correlated with differentiation (log-rank test, $P = .046$), invasion depth (log-rank test, $P = .006$), pTNM stage (log-rank test, $P = .018$), and lymph node metastasis (log-rank test, $P = .041$; Table 3).

The factors affecting DFS in patients with GC were further analyzed using the Cox proportional hazard regression method. Among the variables, LKB1 (hazard ratio, 0.578 [0.351-0.950]; $P = .031$) expression was identified as an independent factor for DFS (Table 4).

4. Discussion

LKB1, also known as serine/threonine protein kinase 11 (*STK 11*), was first found as the causative gene for inherited Peutz-Jeghers syndrome [16]. Subsequently, *LKB1* somatic mutations were also found in some sporadic cancers, such as GC, colorectal cancer, pancreatic cancer, lung cancer, breast cancer, and cervical cancer [4]. *LKB1* functions as a tumor suppressor gene and plays a role in inhibiting the growth and migration of tumor cells via AMP-activated protein kinase/mammalian target of rapamycin signaling [17,18]. However, in most cancers, *LKB1* is mutated or down-regulated and results in tumorigenesis and cancer progression [5,6]. However, the expression level of *LKB1* and its role in GC has been controversial.

An earlier study by Park et al [7] failed to identify common *LKB1* mutations in sporadic GC, whereas Jiang et al [8] found that the expression of *LKB1* was reduced in GC tissues, but was not associated with the clinicopathological data for the patients. Meanwhile, Sun et al [9] demonstrated that the decreased expression of LKB1 mRNA and protein was significantly inversely related to tumor progression and a poor prognosis with a lower survival rate in GC. In the present study, IHC staining was performed, and we observed that the expression of LKB1 was decreased in GC tissues compared with that in adjacent paracancerous tissues, indicating that a loss of LKB1 resulted in tumorigenesis. Evaluation of the correlation of LKB1 expression with the clinicopathological parameters of GC patients revealed that LKB1 expression was inversely correlated with invasion, pTNM stage, and lymph node metastasis. These results were consistent with the findings of Sun et al [9], indicating that LKB1 played a role in GC tumorigenesis and progression.

EMT is a biological process in which epithelial cells lose their polarity and their connection with the basement membrane under the influence various factors, thus losing the epithelial phenotype and acquiring an interstitial phenotype. Cancer-associated EMT is a process wherein cancer cells acquire migration and invasion ability, during which differentiated epithelial

cancer cells reverse to an undifferentiated state [19]. The specific manifestations of EMT include the down-regulation of epithelial cell markers, such as E-cadherin, β-catenin, and cytokeratin, and the up-regulation of interstitial phenotypic markers.

E-cadherin is a calcium-dependent transmembrane glycoprotein that is expressed in most epithelial cells and interacts with β-catenin to promote cell adhesion; vimentin is a type III intermediate filament protein that is normally found in mesenchymal cells and is involved in the invasion and migration of epithelial cells [20]. The loss of E-cadherin expression, together with the up-regulation of vimentin expression, is known to be a phenomenon that is indicative of EMT. Accumulating pieces of evidence indicate that the decreased expression of E-cadherin and the increased expression of vimentin play an important role in cancer invasion and metastasis, and that EMT may predict a relatively poor prognosis [12,21]. A study has demonstrated that the inactivation of LKB1 in lung cancer cells induced EMT and promoted lung carcinoma invasiveness and metastasis [13]. Nevertheless, the correlation of LKB1 with EMT in GC has not yet been elucidated.

In the present study, we explored the correlation of LKB1 with E-cadherin, β-catenin, and vimentin; we found that, with decreased LKB1 expression, the expression of E-cadherin and β-catenin was decreased, whereas the expression of vimentin was increased. Furthermore, Kaplan-Meier and Cox proportional hazard regression methods were used to evaluate the risk factors with the DFS of GC patients. Kaplan-Meier analysis revealed that patients with low expression of LKB1, E-cadherin, and β-catenin, and high expression of vimentin had shorter DFS. Cox proportional hazard regression method revealed LKB1 expression to be an independent factor for DFS. These results indicate that the reduction of LKB1 expression resulted in EMT and promoted invasion and metastasis in GC.

To the best of our knowledge, this is the first report exploring the correlation of LKB1 with EMT in GC, as well as being the first to demonstrate the prognostic role of LKB1 associated with EMT; however, the mechanism underlying how LKB1 influences GC progression requires further investigation. In addition, because of the limited number of patients in this study, a larger study is required, especially that including prolonged follow-up to allow for the analysis of 5-year survival rates.

In conclusion, the current study revealed that the level of LKB1 expression was decreased in GC patients. The decreased expression of LKB1 was associated with invasion and metastasis of GC, which may have resulted from the occurrence of EMT in GC. Therefore, LKB1 is a promising candidate prognostic factor for GC. However, further studies are required to elucidate the mechanism through which LKB1 participates in the progression of GC.

Author contributions

H. Guo and P. Gong designed the research; M. Hu, Z. Zou and Q. Xu performed the research; T. Zhao and J. Liu assessed the results; M. Hu analyzed the data and wrote the manuscript.

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