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Prognostic Performance of High Expression of KIF23 and Loss of c-CBL in Gastric Cancer Patients: An Immunohistochemical Study

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Abstract

Background: Kinesin family member 23 (KIF23) has an important role in mitosis of cytoplasmic separation process. Casitas B-lineage lymphoma (c-Cbl) is a protein ligase E3 ubiquitin in tyrosine kinase pathways, involved in numerous cell types.

The current study aimed to evaluate the tissue expression of KIF23 and c-Cbl in gastric cancer (GC) tissues and normal gastric mucosa using immunohistochemistry and to investigate the correlation among their expressions, clinicopathological parameters, and the prognosis of patients in order to detect their role in the progression of GC and patientsí prognosis.

Method: We conducted this prospective study on 120 samples retrieved from 120 patients; 80 samples were taken from GC patients and 40 from normal gastric mucosa. We assed tissue protein expression of KIF23 and c-Cbl using immunohistochemistry. We evaluated the correlations between KIF23 and C-Cbl expression with clinicopathological and prognostic parameters of patients.

Results: KIF23 expression level in GC tissues was positively correlated with high pTNM stage ($P = 0.001$), larger tumor size ($P = 0.010$), high tumor grade ($P = 0.006$), poor overall survival ($P < 0.001$), disease-free survival rates ($P = 0.003$), and tumor recurrence after therapy ($P = 0.004$). c-Cbl expression level in GC tissues was positively correlated with early pTNM stage ($P = 0.003$), lower tumor grade ($P = 0.005$), the absence of lymph node metastasis ($P = 0.023$), good response to therapy ($P = 0.002$), and the absence of tumor recurrence after the therapy ($P = 0.004$).

Conclusion: The high KIF23 expression and low c-Cbl expression in GC tissues were attributed to progression and poor prognosis in gastric cancer patients.

Keywords: Stomach neoplasms, KIF23, C-Cbl, Immunohistochemistry, Prognosis

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Introduction

Gastric cancer (GC) is believed to be the 4th commonest recorded cancer, with a great incidence and high mortality rate.[1] High proportions of relapse and metastasis are the leading difficulties faced in improving patients' long-term survival;[2] therefore, new prognostic markers and therapeutic targets are needed so that the clinical outcome for patients with this disease would be ameliorated.

Kinesin 23 (KIF23) is a member of kinesin motor protein family involved in the regulation of cytokinesis, which has been found to play a critical role in the process of cytoplasm separation in mitosis.[3, 4] Research has recently shown the overexpression of KIF23 in cancers of many organs.[2, 5, 6] Casitas B-lineage lymphoma (c-Cbl) is an E3 ubiquitin-protein ligase in tyrosine kinase signaling pathways, involved in several cell types.[7] The c -Cbl may play an important role as a tumor suppressor in pathogenesis of human cancer. Moreover, the c-Cbl-dependent negative regulation is considered to have a role in tumorigenesis,[8] but its role in GC has not been profoundly studied. The role of expression of both KIF23 and c-Cbl in gastric adenocarcinoma has not been previously investigated.

We conducted the present work to evaluate the tissue expression of KIF23 and C-Cbl in GC tissues and in normal gastric mucosa using immunohistochemistry (IHC), and to study the correlation among their expressions, clinicopathological parameters, and the prognosis of patients in order to detect their role in the progression of GC and patients' prognosis.

Patients and Methods

This retrospective randomized cohort study was done on 120 samples retrieved from 120 patients; 80 samples were taken from GC patients and 40 from normal non-neoplastic mucosa of the stomach, which we had obtained from gastrectomy specimens in patients with other non-neoplastic lesions of the stomach. All the cases had been previously surgically managed in the Department of General Surgery, Faculty of Medicine, Zagazig University hospitals, from December 2013 to December 2017. None of the included patients received treatments prior to the surgery. Surgical specimens from all the subjects were sent to Pathology Department, Faculty of Medicine, Zagazig University, for routine processing, diagnosis, and immunohistochemistry. All the samples were clinically evaluated and confirmed by two independent pathologists. The histopathological subtype of GC was classified according to the World Health Organization (WHO) histological classification and Lauren classification.[9, 10] The final stage of the samples was confirmed according to the International Cancer Control League (UICC) classification system.[11]

All the tissue samples were obtained after the patients had signed informed written consent, and the research protocol was approved by the Human Research Ethics Committee of Faculty of Medicine, Zagazig University (ethics code: Zag2017GC). The subjects were followed up for a median period of 35 month (ranging from 15 to 60 months). The patients' follow-up, recurrence, and survival data were obtained from their files in Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University.

IHC

We performed IHC for assessment of tissue protein expression of KIF23 and C-Cbl as mentioned previously.[12]

The sections were incubated with Rabbit polyclonal anti-KIF23 antibody (LS-B1543, aa32-81) and anti-c-Cbl antibody (LS C358440, 1:50) at 4ºC overnight. The sections from breast cancer and normal mucosa of the colon were used as the positive control for KIF23 and C-Cbl, respectively. For the negative control, we replaced the included antibodies with saline.

Evaluation of KIF23 and c-Cbl expression

The KIF23 protein is mainly located in the cytoplasm and the nucleus of tumor cells and c-Cbl protein is mainly found in the cytoplasm of tumor cells.

The stained tumor cells were assessed and evaluated according to the degree of stain intensity and stain extent. The extent was assessed as follows: Zero (if the stained tumor cells were <

Table 1. Distribution of the studied patients according to histopathological examination

Histopathological examination	N =120%	Intestinal type of gastric cancer
Diffuse type of gastric cancer	70	58.3
Normal gastric mucosa	10	33.3
	40	8.4

10), 1 (if the stained tumor cells were from 10% to 30%), 2 (if the stained tumor cells were from 31% to 70%), and 3 (if the stained tumor cells were > 70%). The intensity was assessed as follows: 0 (for negative stain), 1 (for weakly positive faint stain), 2 (for moderately positive stain), and 3 (for strongly positive stain). The final scores of the stains were obtained by multiplication of the extent and intensity of the stain. Finally, we divided KIF23 and c-Cbl expression into the high (>3) and low (0-3) expression in order to facilitate statistical analysis.[1, 12]

Statistical analysis

Quantitative variables were described based on their means and standard deviations. Categorical variables were described using the frequencies and were compared via Chi square test. We utilized independent sample t test to compare the means of the two groups for normally distributed data, and Mann Whitney test once the data were not normally distributed. We also employed Kaplan Meier plot for measuring the survival rates. The level of statistical significance was set at 5% ($P < 0.05$). A highly significant difference was present if $P \leq 0.001$.

Results

Tables 1 to 3 along with figures 1 to 3 represent the patients' demographics, histopathological subtype, pathological findings, and both markers expression in the included samples.

KIF23 immunohistochemical expression in stained tissues (Figures 2 and 4)

KIF23 expression in the GC tissues was significantly higher than that in the normal gastric mucosa ($P < 0.001$).

KIF23 expression level in the GC tissues was positively correlated with advanced pTNM stage ($P = 0.001$), larger tumor size ($P = 0.010$), high tumor grade ($P = 0.006$), the presence of lymph node metastasis ($P = 0.04$), as well as the presence of distant metastases ($P = 0.029$).

We found no associations among KIF23 expression, age or sex of the patient, the initial site or histopathological subtype of the tumor.

Based on our observations, the high expression of KIF23 was inversely associated with the favorable overall survival (OS) ($P < 0.001$) and disease-free survival (DFS) rates ($P < 0.003$). The patients with a high expression of KIF23 had shorter OS and DFS time. KIF23 was positively correlated with poor response to the therapy ($P = 0.002$) and tumor recurrence after the therapy ($P = 0.004$) (Table 4).

c-Cbl immunohistochemical expression in the stained tissues (Figures 3 and 4)

c-Cbl expression in the GC tissues was significantly lower than that in the non-neoplastic normal gastric tissues ($P <0.001$).

The level of c-Cbl expression in the GC tissues was positively correlated with early pTNM stage ($P = 0.003$), smaller tumor size ($P = 0.049$), lower tumor grade ($P = 0.005$), the absence of lymph node metastasis ($P = 0.023$), and the absence of distant metastases ($P = 0.021$).

There were no significant associations among c-Cbl expression, age or sex of the patient, the initial site, or histopathological subtype of the tumor.

We found that the high expression of c-Cbl was positively associated with favorable OS ($P < 0.001$) and DFS rates ($P < 0.003$). The patients with a low expression of c-Cbl had shorter OS and DFS time. c-Cbl was positively correlated with good response to the therapy ($P = 0.002$) and the absence of tumor recurrence following the therapy ($P = 0.004$) (Table 4).

Expression of KIF23 was negatively associated with c-Cbl expression in the GC tissues and non-neoplastic gastric mucosa phi correlation coefficient = - 0.456.

Table 2. Distribution of the studied patients according to the levels of KIF23 and c-Cbl

	Gastric cancer N (%)	Normal gastric mucosa N (%)	*p*
KIF23			
Low	31 (38.8)	34 (85)	<0.001**
High	49 (61.2)	6 (15)	
c-Cbl			
Low	48 (60)	10 (25)	0.019*
High	32 (40)	30 (75)	

*$P < 0.05$ is statistically significant; **$P \leq 0.001$ is statistically highly significant; KIF23: Kinesin family member 23; c-Cbl: Casitas B-lineage lymphoma type c

Discussion

In this study, we investigated the expression level of KIF23 and c-Cbl to assess its prognostic value in GC. They were studied separately in many cancer types, yet their expressions and roles in GC have not been studied together.

Our results revealed that the KIF23 expression was further elevated in the GC tissues compared with that in the normal gastric mucosa, highlighting its role in pathogenesis of GC. KIF23 expression in the GC cells was found to be associated with a high grade, advanced pTNM stage, the existence of lymph node, and distant metastasis; this indicates its role in progression of GC. In line with various previous studies, we showed that KIF23 may play an impending role in proliferation of cancer cells.[13-15] Liu et al.[15] revealed that KIF23 stimulated proliferation of GC cells by triggering the signaling of Wnt/β-catenin pathway. Through mitosis, KIF23 was

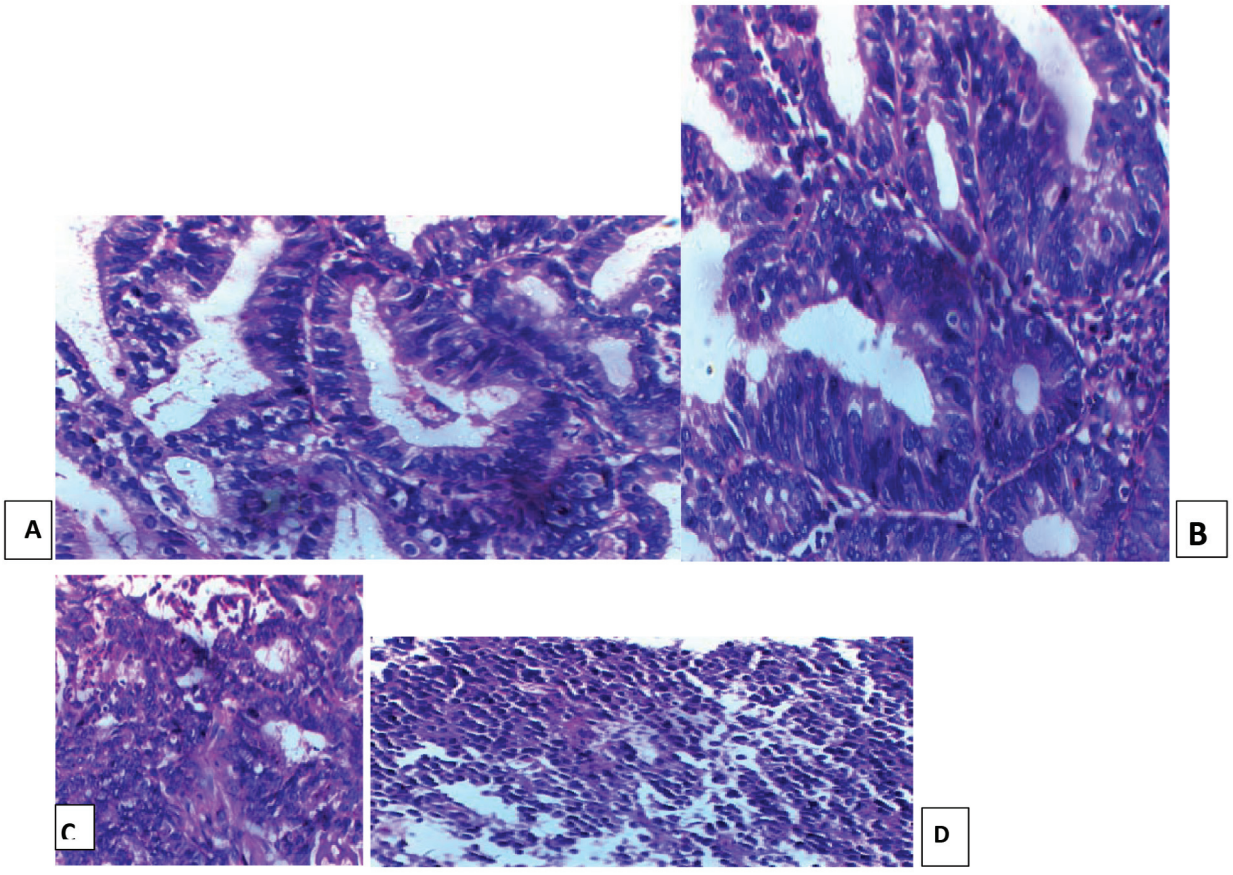

Figure 1. Hematoxylin and eosin (H&E) stained sections of gastric carcinoma cells: (A) Well-differentiated low-grade intestinal type gastric carcinoma (Immunohistochemistry, ×400); (B) Moderately-differentiated intermediate-grade intestinal type gastric carcinoma (Immunohistochemistry, ×400); (C) Poorly-differentiated high-grade intestinal type gastric carcinoma (Immunohistochemistry, ×400); (D) Poorly-differentiated high-grade diffuse gastric carcinoma (Immunohistochemistry, ×400).

Table 3. Correlations among KIF23 and c-Cbl and the patients' clinicopathological findings and demographics

	KIF23 level			c-Cbl		
	Low N=31 (38.8%)	High N=49 (61.2%)	*P*#	Low N=48 (60%)	High N=32 (40%)	*P*#
Gender						
Male	20 (64.5)	32 (65.3)	0.724	31 (64.6)	21 (65.6)	0.856
Female	11 (38.5)	17 (34.7)		17 (35.4)	11(34.4)	
Age group						
<60 years old	10 (32.3)	18 (36.7)	0.432	18 (37.5)	12(37.5)	0.558
≥60 years old	21 (67.7)	31 (63.3)		30 (62.5)	20 (62.5)	
Initial site						
Proximal	20 (64.5)	21 (42.9)	0.074	21 (43.8)	20 (62.5)	0.084
Distal	11 (35.5)	21 (42.9)		20 (41.6)	12 (37.5)	
Diffuse	0 (0)	7 (14.2)		7 (14.6)	0 (0)	
Histopathology						
Intestinal	31 (100)	42 (85.8)	0.066	41 (85.4)	32 (100)	0.059
Diffuse	0 (0)	7 (14.2)		7(14.6)	0 (0)	
Size						
<5 cm	17 (42.9)	21 (42.9)	0.010	21 (43.8)	16 (50)	0.049
≥5 cm	14 (45.2)	28 (57.1)		27 (56.2)	16 (50)	
Grade						
Poor	0 (0)	20 (40.9)	0.006*	20 (41.6)	0 (0)	0.005*
Moderate	16 (51.6)	23 (46.9)		22 (45.9)	19 (59.4)	
Well	15 (48.4)	6 (12.2)		6 (12.5)	13 (40.6)	
T						
T1b	9 (29.2)	2 (4.1)	0.001**	2 (4.1)	8 (25)	0.005*
T2	9 (29.2)	1 (2.1)		1 (2)	7 (21.9)	
T3	5 (16)	14 (28.6)		14 (29.1)	7 (21.9)	
T4a	7(22.5)	9 (18.3)		19 (39.5)	7 (21.9)	
T4b	1 (3.1)	23 (46.9)		12 (25)	3 (9.3)	
N						
N0	10 (32.3)	14 (28.6)	0.04	3 (6.2)	12(37.5)	0.023*
N1	10 (32.3)	16 (32.6)		16 (33.3)	8 (25)	
N2	6 (19.4)	8 (16.4)		18 (37.5)	8 (25)	
N3	5 (16)	11 (22.4)		11(23)	4 (12.5)	
M						
Absent	31 (100)	25 (51)	0.029	34 (70.8)	32 (100)	0.021
Present	0 (0)	24 (49)		14 (29.2)	0 (0)	
Stage						
1A	6 (19)	0 (0)	0.001**	0 (0)	6 (18.7)	0.003*
1B	6 (19)	3 (6.1)		2 (4.1)	6 (18.7)	
IIA	6 (19)	2 (4.1)		1 (2)	6 (18.7	
IIB	8 (25.8)	12 (24.4)		1 (2)	8 (25)	
IIIA	1 (3.2)	13 (26.5)		14 (29.2)	4 (12.5)	
IIIB	2 (6.4)	7 (14.3)		9 (18.8)	3 (9.3)	
IIIC	2 (6.4)	20 (40.1)		17 (35.4)	1 (3.1)	
IV	0 (0)	4 (8.1)		4 (8.3)	0(0)	

*$P < 0.05$ is statistically significant; #Chi square test; ** $P \leq 0.001$ is statistically highly significant; T: Tumor; N: Node; M: Metastases; KIF23: Kinesin family member 23; c-Cbl: Casitas B-lineage lymphoma type c

convoluted in the mid-body formation and it had additional effects during cytokinesis through engaging regulatory factors; these effects were observed in cell division.[3, 16] Additionally, the process of cell proliferation was stimulated by KIF23 through several related transcription factors.[17] KIF23 was found to play an essential role in the occurrence and development of several tumors, mainly through controlling the invasion, proliferation, and apoptosis of tumor cells.[4, 18] In the hepatocellular carcinoma, KIF23 was found to increase and was associated with poor prognosis.[2] Moreover, KIF23 was described to be over-expressed in non-small cell lung cancer, and patients with low KIF23 expression were found to have a better prognosis.[19] Our results regarding survival analysis of GC patients implied that the OS and DFS rates of patients with high expression of KIF23 were significantly worse than those of patients with low expression, which is in agreement with the findings by Liu[15] who reported that high KIF23 levels were associated with poor prognosis. Therefore, we speculated that KIF23 can be used as a biomarker to guide

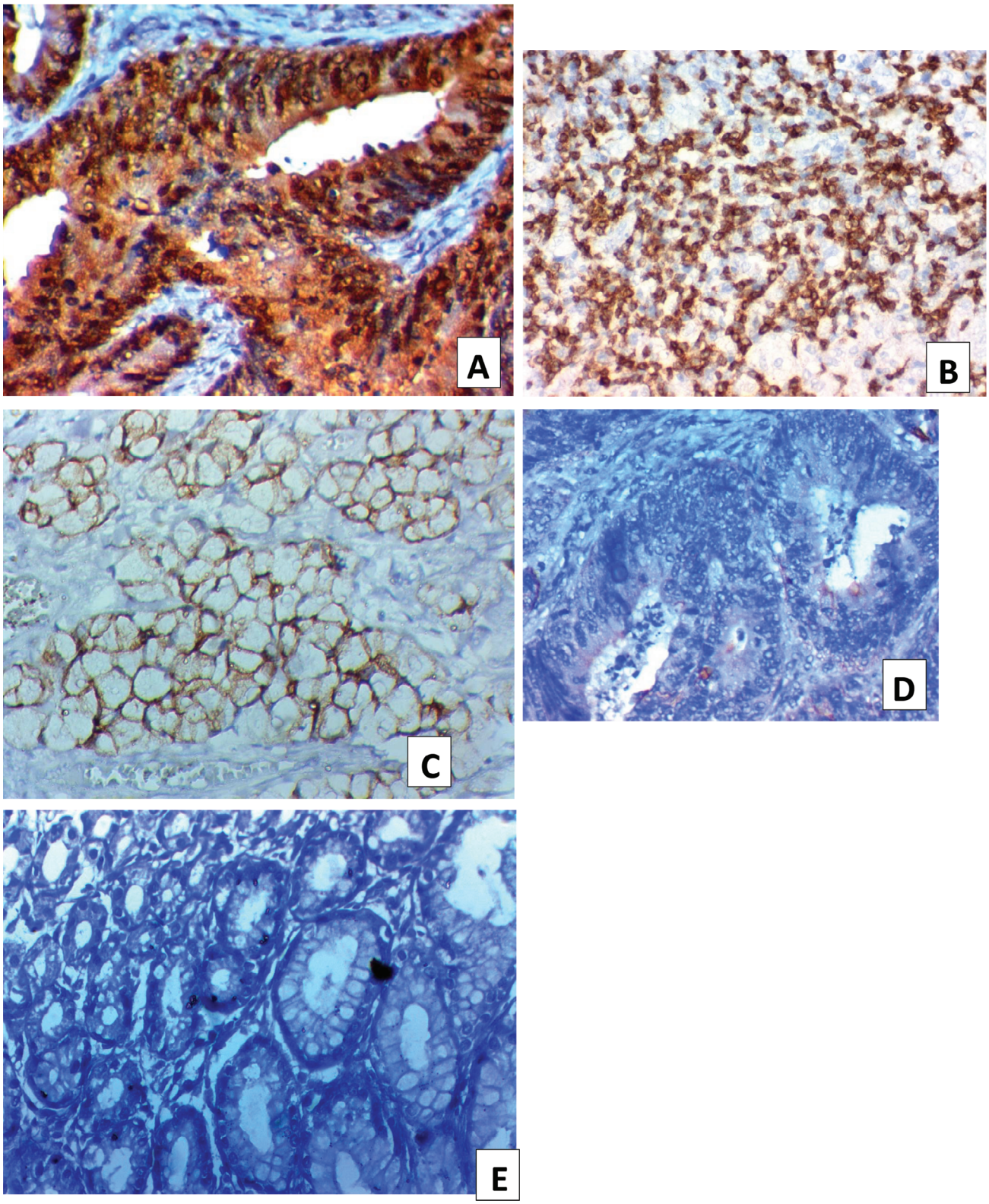

Figure 2. KIF23 expression in gastric carcinoma cells and normal gastric mucosa: (A) KIF23 increased nuclear and cytoplasmic expression in high-grade intestinal type gastric carcinoma (Immunohistochemistry, ×400); (B) KIF23 increased nuclear and cytoplasmic expression in high-grade diffuse gastric carcinoma (Immunohistochemistry, ×400); (C) KIF23 increased nuclear and cytoplasmic expression in high-grade signet ring cell gastric carcinoma (Immunohistochemistry, ×400); (D) KIF23 decreased nuclear and cytoplasmic expression in well-differentiated intestinal type of gastric carcinoma (Immunohistochemistry, ×400); (E) negative KIF23 nuclear and cytoplasmic expression in normal gastric mucosa (Immunohistochemistry, ×400).
KIF23: Kinesin family member 23

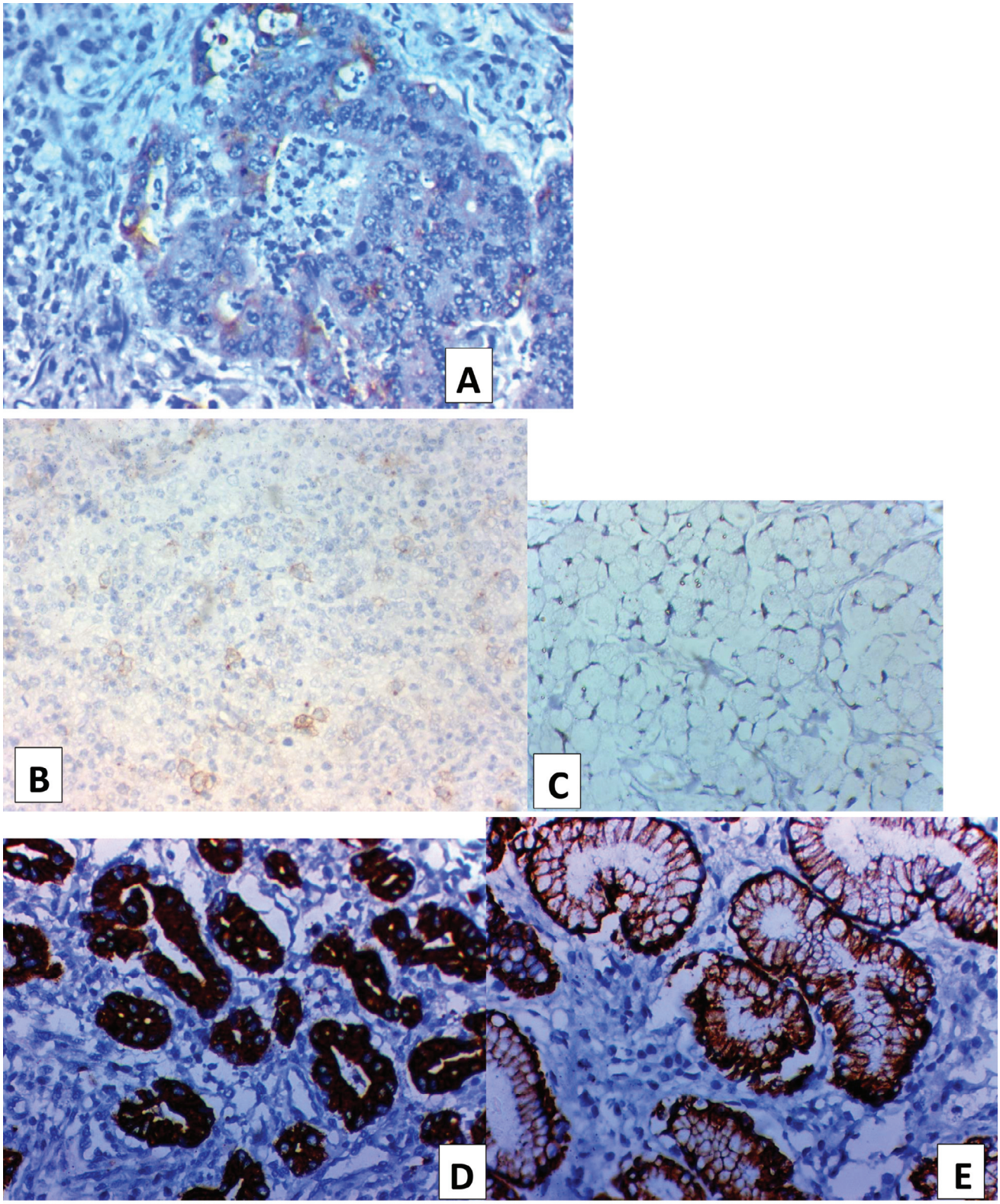

Figure 3. c-Cbl expression in gastric carcinoma cells and normal gastric mucosa: (A) c-Cbl decreased cytoplasmic expression in high-grade intestinal type of gastric carcinoma (Immunohistochemistry, ×400); (B) c-Cbl decreased cytoplasmic expression in high-grade diffuse gastric carcinoma (Immunohistochemistry, ×400); (C) c-Cbl decreased cytoplasmic expression in high-grade signet ring cell carcinoma (Immunohistochemistry, ×400); (D) c-Cbl increased cytoplasmic expression in well-differentiated intestinal type of gastric carcinoma (Immunohistochemistry, ×400); (E) c-Cbl high cytoplasmic expression in normal gastric mucosa (Immunohistochemistry, ×400).

c-Cbl: Casitas B-lineage lymphoma type c

the prognosis and progression of GC patients.

Murakami et al.[20] sequestered KIF23 from GC cell lines paclitaxel resistant through microarray analysis, demonstrating that KIF23 may be indicated in the paclitaxel resistance process in cases with gastric tumor peritoneal metastasis. Chemotherapy resistance in GC may be associated with expression of KIF23. Thus, KIF23 can be considered as a hopeful treatment strategy for GC patients.[14] Li et al.[13] showed that the knock-down of KIF23 resulted in marked inhibition of cell proliferation of GC with significant downregulation of Ki67 and PCNA expression.

Our findings, in addition to the results reported by previous studies, demonstrated the potential of KIF23 a novel prognostic biomarker and a therapeutic target for GC treatment. To prove our findings, we assessed expression of c-Cbl with KIF23 and determined whether both markers were important in determination of the clinical

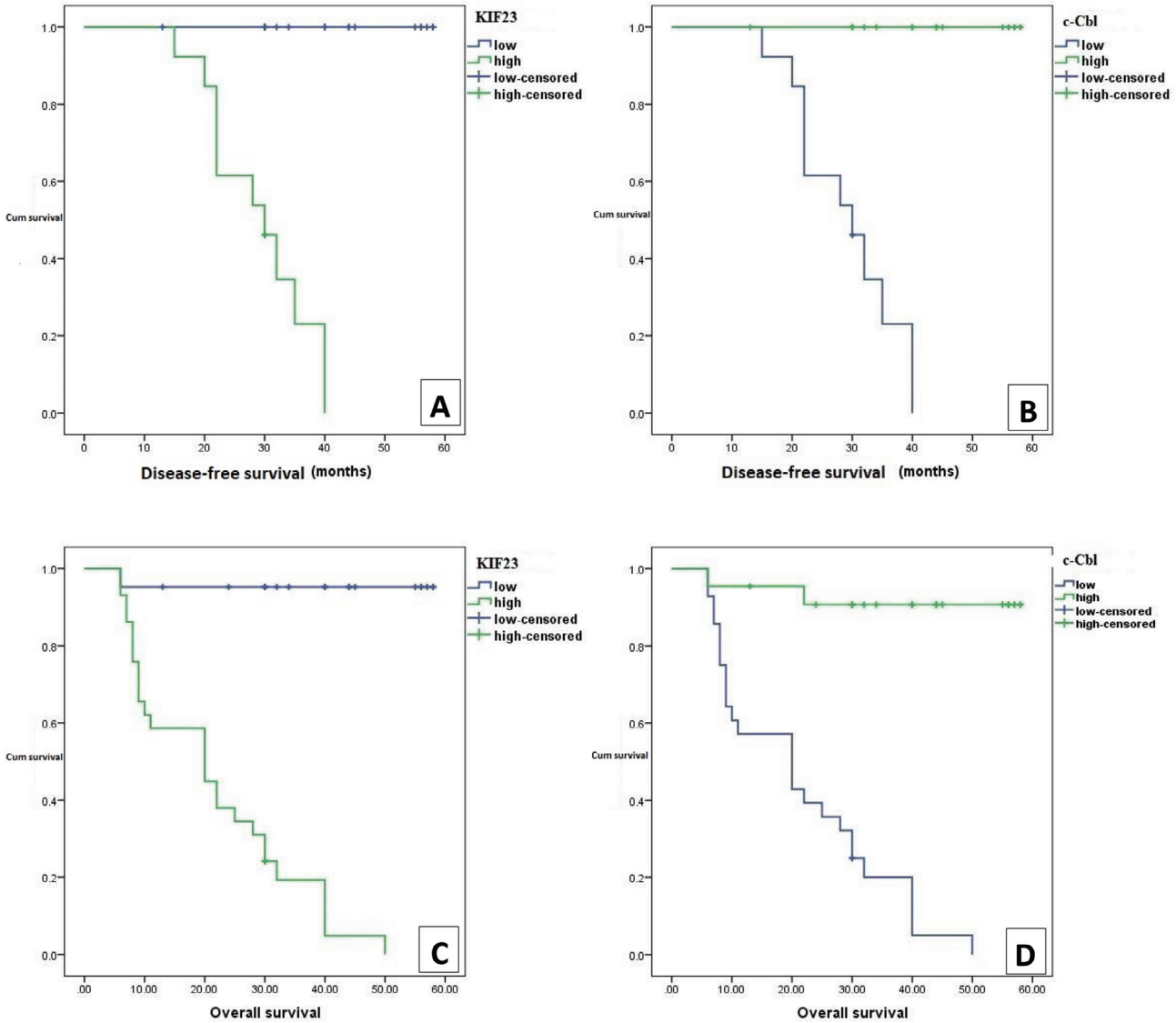

Figure 4. Kaplan Meir survival curves of DFS and OS rate of the included patients with gastric carcinoma: A) and B) DFS survival rates categorized according to KIF23 and c-Cbl expression, respectively; C) and D) OS rates of the included patients with gastric carcinoma categorized according to KIF23 and c-Cbl expression, respectively.

DFS: Disease-free survival; OS: Overall survival; KIF23: Kinesin family member 23; c-Cbl: Casitas B-lineage lymphoma type c

Table 4. Correlations among KIF23 and c-Cbl, patients' outcome, and prognostic findings

	KIF23 level			c-Cbl		
	Low N=31 (38.8%)	High N=49 (61.2%)	*P*#	Low N=48 (60%)	High N=32 (40%)	*P*#
Response						
PD	0 (0)	9 (18.4)	0.002*	9 (18.7)	0 (0)	0.003*
SD	0 (0)	4 (8.1)		4 (8.3)	0 (0)	
PR	1 (3.2)	13 (26.5)		12 (25)	12 (37.5)	
CR	30 (96.8)	23 (46.9)		23 (48)	20 (62.5)	
Relapse						
Free	12 (38.7)	17 (34.7)	0.004*	16 (33.3)	12(37.5)	0.004*
Present	19 (61.3)	32 (65.3)		32 (66.6)	20(62.5)	
Outcome						
Alive	25 (80.6)	12 (24.5)	<0.001**	12 (25)	27 (84.4)	<0.001**
Dead	6 (19.4)	37 (75.5)		36 (75)	5 (15.6)	
Disease-free survival						
Median	40	30	<0.003*¥	30	40	0.003*¥
Range	13 - 58	15 - 40		15 - 40	13 - 58	
Overall survival						
Mean ± SD	40.8 ± 12.98	31.92 ± 8.68	<0.001**∞	31.92 ± 8.68	40.8 ±12.98	<0.001**∞
Range	13- 58	20 -50		20 - 50	13 - 58	

¥Z Mann-Whitney test; * $P < 0.05$ is statistically significant; #Chi square test; ** $P \leq 0.001$ is statistically highly significant; ∞Independent sample test; KIF23: Kinesin family member 23; c-Cbl: Casitas B-lineage lymphoma type c; PD: Progressive disease; SD: Stable disease; PR: Progressive disease; CR: Complete response

outcome. We also identified their prognostic behaviors in GC patients.

Based on our research, expression of c-Cbl was further reduced in the GC tissues compared with that in the normal gastric tissue. Accordingly, the loss of c-Cbl has a role in pathogenesis and tumor development in GC; this finding is in agreement with previous investigations, which found c-CbL expression decreased in GC.[1] The c-Cbl expression was reported to downregulate EGFR signaling and reduce cell proliferation and migration in breast cancer cell lines.[21] Furthermore, c-Cbl-mediated ubiquitination led to down-regulation of EGFR to promote tumor initiation and progression in colorectal cancer.[22] Wei et al.[23] reported that growth inhibition and apoptosis are induced by expression of c-Cbl, approving the tumor-suppressing role of c-Cbl. In addition, c-Cbl played an important role in adverse regulation of receptor tyrosine kinase (RTK), signifying that c-Cbl may be a tumor suppressor factor.[2]

Herein, we observed that c-Cbl with low expressions were related to a high grade of GC, advanced pTNM stage, existence of lymph nodes, and distant metastases, which showed that c-Cbl attributed to tumor suppression of GC. Similarly, the results of a previous study confirmed that high c-Cbl has a protective role against tumor progression.[2] c-Cbl may downregulate signaling molecules, limiting the migration and invasion of tumor cells, which results in the decreased motility of cancer cells.[24] These findings explained the high rate of lymphatic invasion and metastasis in GC tissues with low c-Cbl expression. Moreover, c-Cbl was found to inhibit cell migration activity in melanoma[25] and breast cancer.[21] Hence, evaluation of KIF23 expression with c-Cbl in GC might contribute to prediction invasion and metastatic performance of GC patients. We found that c-Cbl loss was associated with high KIF23 expression, both of which were related to GC progression. Therefore, novel drugs that enhance the activity of c-Cbl may provide new strategies for cancer therapy. Ma et al.[26] reported that the knock-down of c-Cbl decreased lapatinib resistance through HER2 degradation in GC cells; accordingly, the low level of c-Cbl may be a predictive marker of lapatinib sensitivity and patients with c-Cbl low expression may benefit from lapatinib treatment in GC. Therefore, c-Cbl and KIF23 might be considered as hopeful markers for advanced GC patients. Our results also suggested that c-Cbl could be used as a potential source for prospect treatment of GC; however, the causal mechanisms of c-Cbl and KIF23 in GC need additional investigations. According to the survival analysis herein, survival rates of the patients with low expression of c-CBL were significantly worse than that those of

the cases with its high expression, indicating prognostic value in patients with GC.

In the present study, we used only immunohistochemical method for evaluation of the markers. Regarding the points of strengths, we could mention that it is the first study to evaluate the expression of both KIF23 and c-Cbl in GC, which proved its prognostic value in GC. We could recommend further investigations using molecular studies for exploring the mechanism of KIF23 and c-Cbl in GC.

Conclusion

In conclusion, KIF23 was found to be highly expressed in GC, which was associated with low c-Cbl expression. Additionally, its expressions indicated poor prognosis. KIF23 and c-Cbl can be utilized as independent markers to predict the prognosis of patients with GC. Both could be regarded as candidates for the treatment of GC. The management of metastatic cases necessitates exploring the functions of c-Cbl and KIF23 in molecular levels and investigation of their pathways in metastatic GC.

Conflict of Interest

None declared.

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