

World Journal of *Gastrointestinal Oncology*

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MINIREVIEWS

- 1080** Contemporary treatment approaches for metastatic colorectal cancer driven by BRAF V600 mutations
Kanat O, Ertas H, Caner B

ORIGINAL ARTICLE

Basic Study

- 1091** Synergistic anti-liver cancer effects of curcumin and total ginsenosides
Deng Z, Xu XY, Yunita F, Zhou Q, Wu YR, Hu YX, Wang ZQ, Tian XF
- 1104** Prognostic significance of KIF23 expression in gastric cancer
Liang WT, Liu XF, Huang HB, Gao ZM, Li K

Retrospective Cohort Study

- 1119** Changing trends of clinicopathologic features and survival duration after surgery for gastric cancer in Northeast China
Zhai Z, Zhu ZY, Cong XL, Han BL, Gao JL, Yin X, Zhang Y, Lou SH, Fang TY, Wang YM, Li CF, Yu XF, Ma Y, Xue YW

Retrospective Study

- 1133** Minimally invasive *vs* open pancreatectomy for nonfunctioning pancreatic neuroendocrine tumors
Kim J, Hwang HK, Lee WJ, Kang CM
- 1146** Comparison of prognostic factors in different age groups and prognostic significance of neutrophil-lymphocyte ratio in patients with gastric cancer
Li Q, Huang LY, Xue HP
- 1167** Diagnostic value of serum human epididymis protein 4 in esophageal squamous cell carcinoma
Liu SY, Ahsan Bilal M, Zhu JH, Li SM
- 1177** Prognostic factors and therapeutic effects of different treatment modalities for colorectal cancer liver metastases
Ma ZH, Wang YP, Zheng WH, Ma J, Bai X, Zhang Y, Wang YH, Chi D, Fu XB, Hua XD

Observational Study

- 1195** Blood exosomal micro ribonucleic acid profiling reveals the complexity of hepatocellular carcinoma and identifies potential biomarkers for differential diagnosis
Sheng LQ, Li JR, Qin H, Liu L, Zhang DD, Zhang Q, Huang ML, Li XL, Xu XY, Wei YN, Chen ZS, Luo H, Zhang JY, Zhou CH, Chen H, Chen ZG, Li FG, Li NF

CASE REPORT

- 1209** Achievement of complete response to nivolumab in a patient with advanced sarcomatoid hepatocellular carcinoma: A case report

Zhu SG, Li HB, Yuan ZN, Liu W, Yang Q, Cheng Y, Wang WJ, Wang GY, Li H

ABOUT COVER

Editorial board member of *World Journal of Gastrointestinal Oncology*, Adriana Ciocalteu, MD, PhD, is a Researcher at the Research Center of Gastroenterology and Hepatology and a Teaching Assistant in the Department of Gastroenterology of the University of Medicine and Pharmacy, Craiova (Romania). Having received her Bachelor's degree from University of Medicine and Pharmacy of Craiova in 2011, she undertook her postgraduate training at the Clinical Emergency County Hospital Craiova in the Gastroenterology Unit, Copenhagen University Hospital, Herlev and at Aarhus University Hospital (Denmark), receiving her PhD in 2016. Upon return to Craiova, she began her practice as Specialist in Gastroenterology and Teaching Assistant in the Department of Gastroenterology at the University of Medicine and Pharmacy. Her ongoing research interests involve studying malignant pathology of the digestive system using state-of-the-art techniques. (L-Editor: Filipodia)

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Basic Study

Prognostic significance of KIF23 expression in gastric cancer

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Author contributions: Liang WT and Li K designed and performed the experiments; Gao ZM analyzed the data; Liu XF and Huang HB helped perform the analysis with constructive discussions; Liang WT and Li K wrote the paper.

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Abstract

BACKGROUND

Kinesin super family 23 (KIF23) is a member of the KIF family, and it plays an important role in mitosis and cytokinesis. Loss of expression can cause mitotic arrest. The Oncomine database is one of the largest oncogene chip databases in the world, and is an integrated data mining platform for cancer gene information. By querying the database, differences in expression between tumor tissue and normal tissue can be determined.

AIM

To study the expression and prognostic significance of KIF23 in gastric cancer (GC).

METHODS

We used immunohistochemistry to compare the expression of KIF23 in GC and normal gastric tissues. We mined the data on the expression and prognosis of KIF23 in GC using Oncomine and Kaplan-Meier plotter database.

RESULTS

Compared with normal gastric tissues, KIF23 expression was increased in GC tissues, and correlated with T, N, and tumor-node-metastasis stages. Survival analysis showed that patients with high expression of KIF23 had a poor overall survival. There were five studies in the Oncomine database in which expression of KIF23 was significantly higher in GC tissues than in normal gastric tissues ($P < 0.05$). Kaplan-Meier plotter database analysis showed that recurrence-free survival, overall survival, distant metastasis free survival, and post progression survival of patients with high expression of KIF23 were lower than those of patients with low expression. Further stratified analysis found that prognostic survival indicators worsened in patients with T2 and T3 poorly differentiated adenocarcinoma with high expression of KIF23.

CONCLUSION

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KIF23 is highly expressed in GC and is associated with a poor prognosis of patients. It may be of great significance in the diagnosis, treatment, and prognostic evaluation of GC.

Key Words: Gastric cancer; Kinesin super family 23; Immunohistochemistry; Oncomine; Prognosis; Kaplan–Meier plotter

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Core Tip: This study investigated the role of the kinesin super family 23 (KIF23) in the gastric cancer (GC), including its expression and prognosis significance in GC. We found that KIF23 is highly expressed in GC and is associated with a poor prognosis of patients. It may be of great significance in the diagnosis, treatment, and prognostic evaluation of GC. We believe that our study makes a significant contribution to the literature as it revealed a novel relationship between KIF23 and GC and may provide a new therapeutic target for treating GC.

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignant tumors, with a high mortality rate, ranking third among cancer-related deaths, and bringing a huge economic burden to society^[1]. GC is characterized by insidious onset and lack of early clinical symptoms. However, most patients are diagnosed in the middle and advanced stages, which misses the best surgical treatment window and greatly affects prognosis. Surgical resection combined with radiotherapy and chemotherapy is the main treatment method for GC, but due to the characteristics of postoperative recurrence, high metastasis rate, and frequent drug resistance, the 5-year survival rate for GC is only 40%^[2,3]. Therefore, for patients with GC, seeking effective diagnosis and treatment is the only way to improve prognosis. Exploration of specific and sensitive biomarkers may help clinicians predict prognosis and clarify the mechanism underlying gastric tumorigenesis.

The kinesin family members (KIFs) are microtubule-associated movement proteins that mediate multiple functions. Their abnormal expression plays an important role in tumorigenesis and development^[4,5]. KIF23 is a member of the KIF family, and it plays an important role in mitosis and cytokinesis. Loss of KIF23 expression can cause mitotic arrest^[6]. In recent years, research on the role of KIFs in tumors has received increasing attention^[7,8]. Wang *et al*^[9] found that KIF15 can promote the proliferation, invasion, and metastasis of pancreatic cancer cells through the MEK-ERK signaling pathway. Zhang *et al*^[10] reported that KIF26B promoted the development of GC by activating the vascular endothelial growth factor pathway. Chen *et al*^[10] confirmed that KIF4B is an independent prognostic factor for hepatocellular carcinoma. KIF23 is a candidate target gene for paclitaxel resistance in GC cells^[12].

The Oncomine database is one of the largest oncogene chip databases in the world, and is an integrated data mining platform for cancer gene information. To date, the database has collected 715 gene expression data sets and sample data from 86733 cancerous and normal tissues. By querying the database, differences in expression between tumor tissue and normal tissue can be determined. Clinicopathological factors can also be analyzed to find differentially expressed genes in certain cancers and guide research.

In this study, we used immunohistochemistry to detect the expression level of KIF23 protein in GC and adjacent normal tissues, and analyzed the association between KIF23 protein expression and clinicopathological factors. The Oncomine database and high-throughput prognostic analysis (Kaplan–Meier plotter database) were used to analyze the association between expression of KIF23 mRNA and prognosis in GC, which may provide evidence for further research on the role of KIF23 in GC.

MATERIALS AND METHODS

Patients and specimens

We collected 174 GC specimen tissues and 174 paired non-tumor tissues (> 5 cm from the edge of the primary tumor) at the First Affiliated Hospital of China Medical University from January 2011 to December 2012. Written informed consent was obtained from all patients, and the study was approved by the institutional ethics committee of China Medical University. All specimens were obtained during surgical resection from patients who had not received chemotherapy or radiotherapy prior to surgery. All the patients were classified according to the 8th edition of the tumor-node-metastasis (TNM) classification of the International Union Against Cancer, and there were 18 patients with stage I, 53 with stage II, and 103 with stage III cancer. Among 174 patients, 94 had a tumor size > 4 cm. Patients were followed every 3 mo during the first year and every 6 mo thereafter. The patient or his relatives was called according to the follow-up guidelines of the National Comprehensive Cancer Network. The follow-up ended after December 2017. Overall survival (OS) was defined as the time from surgery to death from any cause or last follow-up.

Immunohistochemistry

All tissue pieces were cut into 4- μ m slices, deparaffinized, rehydrated, stained using the Ultrasensitive TM S-P system (KIT-9710; MaiXin, Fuzhou, China), and incubated with anti-KIF23 antibody (1:300, #ab235955; Abcam, Cambridge, MA, USA) overnight at 4 °C. The tissue slices were incubated with secondary antibody labeled with biotin at room temperature for 30 min (Ultrasensitive TM S-P; MaiXin). Diaminobenzidine tetrahydrochloride substrate (MaiXin) was used as the chromogen. The intensity of KIF23 staining was scored as follows: 0 (no staining), 1 (weak), 2 (moderate), and 3 (high). Percentage scores were assigned as follows: 0 (< 10%), 1 (10%-25%), 2 (26%-50%), 3 (51%-75%), and 4 (76%-100%). The score of each tumor sample was multiplied to obtain a final score of 0-12, and the staining results were categorized into negative (0; -), low (1-4; +), moderate (5-8; ++), and high (9-12; +++). The images were viewed with a microscope (Nikon, Tokyo, Japan). The tissue sections from each patient were observed within eight fields of view, and two experienced pathologists read the sections without knowing the pathological grade and clinical data. The result was judged by the double blind method.

Oncomine analysis

Oncomine is a cancer microarray database and web-based data-mining platform that was used to analyze the mRNA levels of KIF23 in GC. We set the screening criteria as: (1) "Cancer Type: Gastric cancer"; (2) "Gene: KIF23"; (3) "Data Type: mRNA"; (4) "Analysis Type: Cancer vs Normal Analysis"; and (5) "Critical value setting condition: $P < 10^{-4}$, fold change > 2, gene rank = top 10%". The results are displayed by histogram.

Kaplan–Meier plotter analysis

Online survival analysis was performed using the GC data set of Kaplan Meier (KM) plotter database (<http://kmplot.com/analysis/>). The screening criteria were as follows: (1) "Cancer: Gastric Cancer"; (2) "Gene: KIF23"; (3) "Survival: OS"; and (4) "Exclude: GES62254". This was because the KM database showed that GES62254 had distinct characteristics compared with other datasets (longer survival time and expression transformation). The database recommends excluding datasets when all samples are used together.

Statistical analysis

The χ^2 test was used to evaluate the association between KIF23 expression and clinicopathological features in GC tissues. The relationship between KIF23 expression and prognosis of GC was analyzed using a Kaplan–Meier model. In order to determine the independent prognostic factors, we used Cox proportional hazards models for univariate and multivariate analyses. Statistical analyses were performed on all data using SPSS version 25.0. $P < 0.05$ showed statistical significance.

RESULTS

KIF23 expression in GC and relationship between KIF23 expression and clinicopathological characteristics

KIF23 protein expression was examined in GC and normal gastric tissues using immunohistochemistry. We detected KIF23 expression in 174 GC samples, and KIF23 was mainly expressed in the cytoplasm (Figure 1). For statistical analysis, - and + were considered low expression of KIF23, while ++ and +++ were considered high expression. We confirmed that the ratio of high KIF23 expression in GC was significantly higher than in normal gastric tissues (Table 1). We evaluated the association between KIF23 expression and the clinicopathological characteristics of GC using a chi-square test. As shown in (Table 2), high expression of KIF23 in GC was significantly related to lymph node metastasis ($P = 0.047$) and poor TNM stage ($P = 0.022$). However, there was no significant difference between KIF23 expression and other clinicopathological characteristics (such as age, gender, histological differentiation, and Borrmann type).

Transcription levels of KIF23 in GC using Oncomine analysis

In Oncomine, we found that, since 2003, there were five studies involving expression of KIF23 in GC and normal tissues (Figure 2). A total of 478 samples including diffuse gastric adenocarcinoma, gastric adenocarcinoma, gastric intestinal type adenocarcinoma, gastric mixed adenocarcinoma, and gastrointestinal stromal tumors were compared with normal tissues^[13-17]. Analysis of these studies showed that compared with the control group, the KIF23 gene ranked 183.0 among all differentially expressed genes ($P = 2.88\text{E-}12$), indicating that KIF23 was highly expressed in GC. Figure 3 shows the expression of KIF23 in the Oncomine database in different GC research chips. All these studies showed that expression of KIF23 in GC was higher than that in normal tissue ($P < 0.05$).

Prognostic value of KIF23 in GC

Kaplan–Meier survival analysis showed that the OS rate of the KIF23-positive group was significantly lower than that of the KIF23-negative group, suggesting that the high level of KIF23 was associated with a poor prognosis ($P = 0.0063$) (Figure 4A). Univariate analysis revealed that differentiation type, Borrmann type, T stage, N stage, TNM stage, and KIF23 expression might be associated with the prognosis of GC patients ($P < 0.05$). Multivariate Cox analysis, using categorical variables, showed that TNM stage [hazard ratio (HR) = 1.869, 95%CI: 1.356-2.575, $P = 0.000$] and KIF23 expression (HR = 1.069, 95%CI: 1.006–1.135, $P = 0.030$) were independent prognostic factors for OS (Table 3). According to KIF23 expression and involved clinicopathological characteristics, we performed survival analysis in different subgroups. The OS of patients with high KIF23 expression was significantly lower than that of patients with T4, N1–N3, IIB–IIIC, or poorly differentiated GC with low KIF23 expression. However, there were no prognostic differences between high and low KIF expression in patients with T1–T3, N0, I–IIA, and well differentiated GC (Figure 4B–I).

Prognostic analysis of KIF23 in GC using Kaplan–Meier survival information

Kaplan–Meier survival information for KIF23 can be found at <https://www.kmplot.com>. We examined the prognostic value of KIF23 mRNA expression in the database. Affymetrix ID is valid: 204709_s_at (KIF23). In all of the GC patients who were followed, KIF23 mRNA overexpression was found to be associated with worsening OS (HR = 1.64, 95%CI: 1.32-2.02, $P = 3.9\text{e-}06$). We then examined the correlation between KIF23 expression and OS in GC patients with different clinicopathological characteristics. High expression of KIF23 mRNA was associated with a poor OS in men, and patients with T3, M0, GDA, and poorly differentiated GC (Table 4). However, there were no significant differences in survival analysis in patients with other clinicopathological characteristics. As the sample size of patients with T1 and T4 GC was too small, no analysis was performed in these patients. Regarding the time span of involved KM survival, the guidelines for TNM staging were changed, so TNM stage was not included in the analysis^[18-22].

Table 1 KIF 23 expression in gastric cancer and normal tissues, *n* (%)

	Cases	KIF23 expression		P value
		Low	High	
Cancer	174	30 (17.2)	144 (82.8)	< 0.001
Normal	174	169 (97.1)	5 (2.9)	

Table 2 Correlation between KIF23 expression and clinicopathological features in gastric cancer

	<i>n</i> = 174	KIF23 expression		P value
		Low (<i>n</i> = 130)	High (<i>n</i> = 44)	
Age (yr)				0.539
≤ 60	90	69	21	
> 60	84	61	23	
Gender				0.583
Male	129	95	34	
Female	45	35	10	
Diameter (cm)				0.667
≤ 4	80	61	19	
> 4	94	69	25	
Differentiation type				0.188
Poor	104	74	30	
Non-poor	70	56	14	
Borrmann type				0.453
I-II	15	10	5	
III-IV	159	120	39	
T stage				0.05 ¹
T1-T3	56	47	9	
T4	118	83	35	
N stage				0.047 ¹
N0	61	51	10	
N1-N3	113	79	34	
TNM stage				0.022 ¹
I-IIA	37	33	4	
IIB-IIIC	137	97	40	

¹Significant difference.

DISCUSSION

GC is one of the malignant tumors with the highest incidence and mortality worldwide. The prognosis of GC has been poor^[23]. Therefore, it is of clinical importance to find the key molecules or targets for the treatment of GC. In this study, we discussed the prognostic value of KIF23 in GC. We examined the expression of KIF32 in GC cases from our hospital and analyzed the data from the Oncomine and Kaplan-Meier databases. Our results suggested that increased KIF23 expression in GC tissues predicted worse prognosis, and KIF23 might be a potential target for GC treatment.

Forty-five different functional KIFs have been found in humans^[18-20]. They all share a

Table 3 Prognostic factors in Cox's proportional hazards model in gastric cancer (n = 174)

Variable	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age (yr): > 60 <i>vs</i> ≤ 60	0.822	0.555-1.217	0.328			
Gender: Male <i>vs</i> female	1.297	0.838-2.008	0.243			
Diameter: > 4 cm <i>vs</i> ≤ 4 cm	0.616	0.350-1.084	0.093			
Differentiation type: Poor <i>vs</i> non-poor	0.552	0.336-0.906	0.019 ¹	0.840	0.502-1.404	0.505
Borrmann type: I-IV	1.703	1.109-2.617	0.015 ¹	1.410	0.916-2.169	0.119
T stage: T1-T4	1.546	1.141-2.095	0.005 ¹	1.310	0.858-2.000	0.210
N stage: N0-N3	1.693	1.424-2.013	0.000 ¹	1.869	1.356-2.575	0.000 ¹
TNM stage: I-IIIC	2.410	1.637-3.547	0.000 ¹	0.595	0.259-1.366	0.221
KIF23 expression: High-level <i>vs</i> low-level	1.064	1.006-1.126	0.029 ¹	1.069	1.006-1.135	0.030 ¹

¹Significant difference.

highly conserved motor area, providing motion with microtubules. KIFs are divided into three types according to which area carries the sports field, including N-kinin, M-kinin, and C-kinin. KIF23 belongs to N-kinin, is located in the cytoplasm and nucleus, and is related to cell differentiation and proliferation^[21]. KIF23 overexpression is a common event seen in various tumors, such as glioma^[22], breast cancer^[5], and lung cancer^[24]. Overexpression of KIF23 in breast cancer is significantly associated with tumor grade, invasion, and prognosis^[5]. *In vivo* and *in vitro* experiments have shown that knockdown of KIF23 significantly inhibits proliferation of glioma cells^[22]. Murakami *et al*^[12] found that KIF23 expression was significantly increased in GC cell lines. Previous evidence supported the role of KIF23 not in vesicular transport but in the bundling and transport of microtubules in specific locations and times in different cell types^[25-28]. In our immunohistochemical study, KIF23 staining was observed mainly in the cytoplasm. It may be that overexpression of the kinesin family can affect normal mitosis, lead to aneuploidy and eventually tumor development.

We previously found that KIF23 is highly expressed in GC tissues by GSE63089 high-throughput microarray analysis, and its expression level is about 3.89 times that of adjacent tissues. The Cancer Genome Atlas database also confirmed that KIF23 is highly expressed in GC. Our study showed that KIF23 overexpression is a valuable independent prognostic factor in GC, particularly in T4, N1-N3, IIB-IIIC, and poorly differentiated cancer. Kaplan-Meier survival analysis suggested that high expression of KIF23 mRNA was associated with a poor OS in male patients, and patients with T3, M0, Lauren differentiation GDA, and poorly differentiated GC. Our data came from clinical cases and gene chips. The research methods were consistent and included a large sample size, which eliminated errors caused by sample size problems and increased the credibility of our conclusions. These findings lead us to believe that KIF23 overexpression represents an important transformation factor associated with a more malignant phenotype and hence poor prognosis, although further investigation is needed to validate this result.

The present study had some limitations. First, some information was obtained from open databases, and the medical parameters were not complete. Therefore, we were not able to perform a far-reaching survival analysis of KIF genes, considering each latent prognostic variable of GC in the multivariate Cox proportional hazards regression model. Second, because of the varied origin of GC patients, together with the number of elements affecting GC prognosis, we were not able to construct a comprehensive hazard score model. Third, for correlation with past research, the constraint of our present investigation suggested that it just studied the relationship between KIF23 expression and GC prognosis.

CONCLUSION

In summary, through in-depth exploration of KIF23-related information in GC tissues, we found that KIF23 overexpression in GC tissues is related to prognosis. Use of a

Table 4 Correlation between KIF23 mRNA expression and gastric cancer patients in Kaplan–Meier database

Variable	Cases	HR (95%CI)	P value
Overall patients	593	1.64 (1.32-2.02)	3.9e-06 ¹
T stage			
T2	66	2.05 (0.98-4.26)	0.050 ¹
T3	117	1.83 (1.14-2.94)	0.012 ¹
N stage			
N0	38	2.78 (0.88-8.73)	0.069
N1 + N2 + N3	175	1.33 (0.92-1.94)	0.130
M stage			
M0	186	1.74 (1.17-2.59)	0.0053 ¹
M1	31	0.49 (0.19-1.23)	0.120
Gender			
Male	360	2.07 (1.60-2.69)	1.9e-08 ¹
Female	138	1.50 (0.95-2.37)	0.078
Differentiation			
Well	32	0.41 (0.16-1.08)	0.062
Moderate	67	0.75 (0.38-1.48)	0.400
Poor	165	1.67 (1.12-2.49)	0.012 ¹
Lauren classification			
GITA	179	0.76 (0.52-1.11)	0.15
GDA	106	2.05 (1.23-3.39)	0.0047 ¹
GMA	25	0.22 (0.03-1.68)	0.11

¹Significant difference.

database for large sample analysis can avoid errors caused by a small sample size and provide an important theoretical basis for clinical treatment. The specific mechanism of KIF23 in the development of GC needs further study.

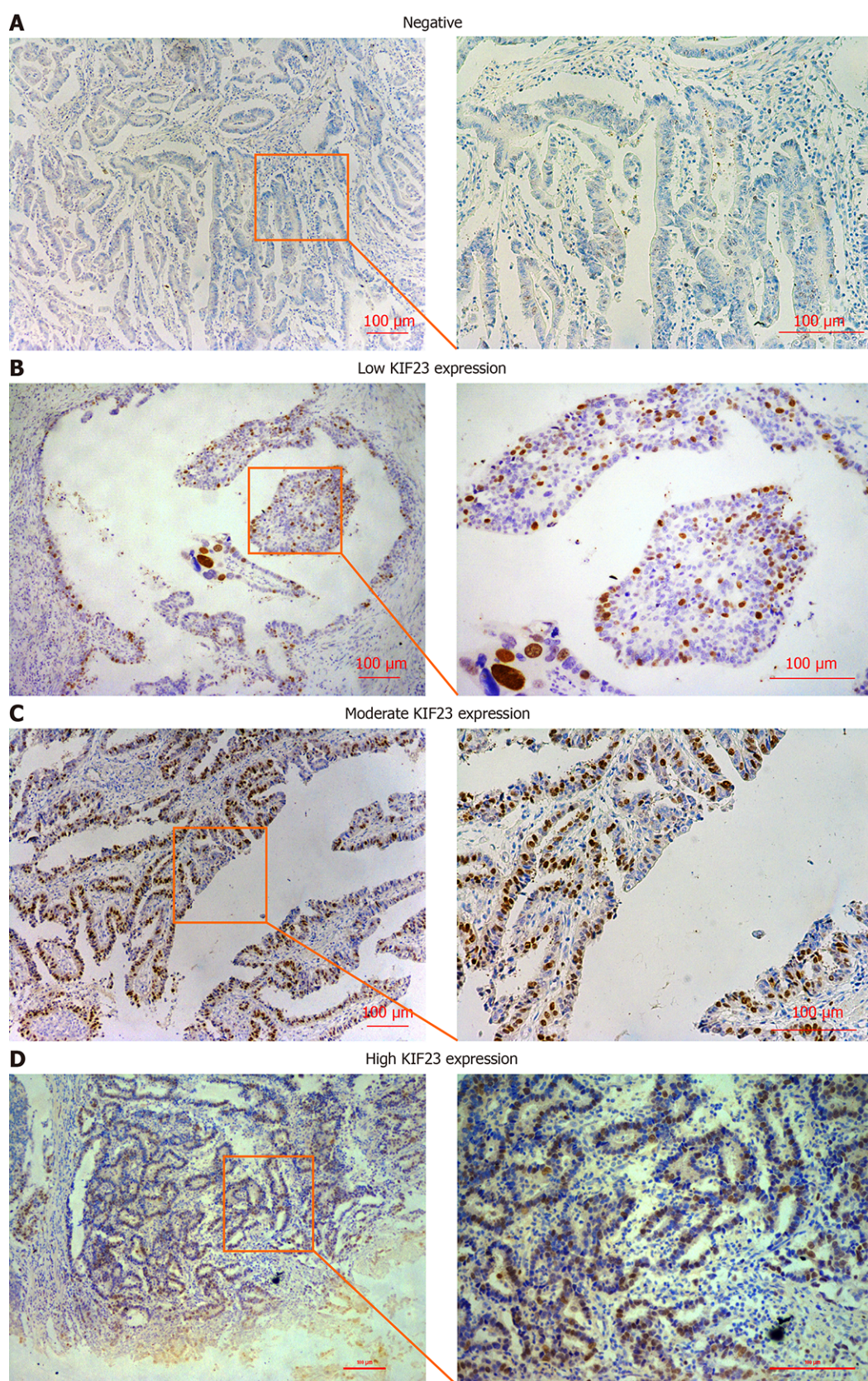


Figure 1 Immunohistochemical staining for KIF23 protein in gastric cancer. A: Negative; B: Low expression; C: Medium expression; D: High expression.

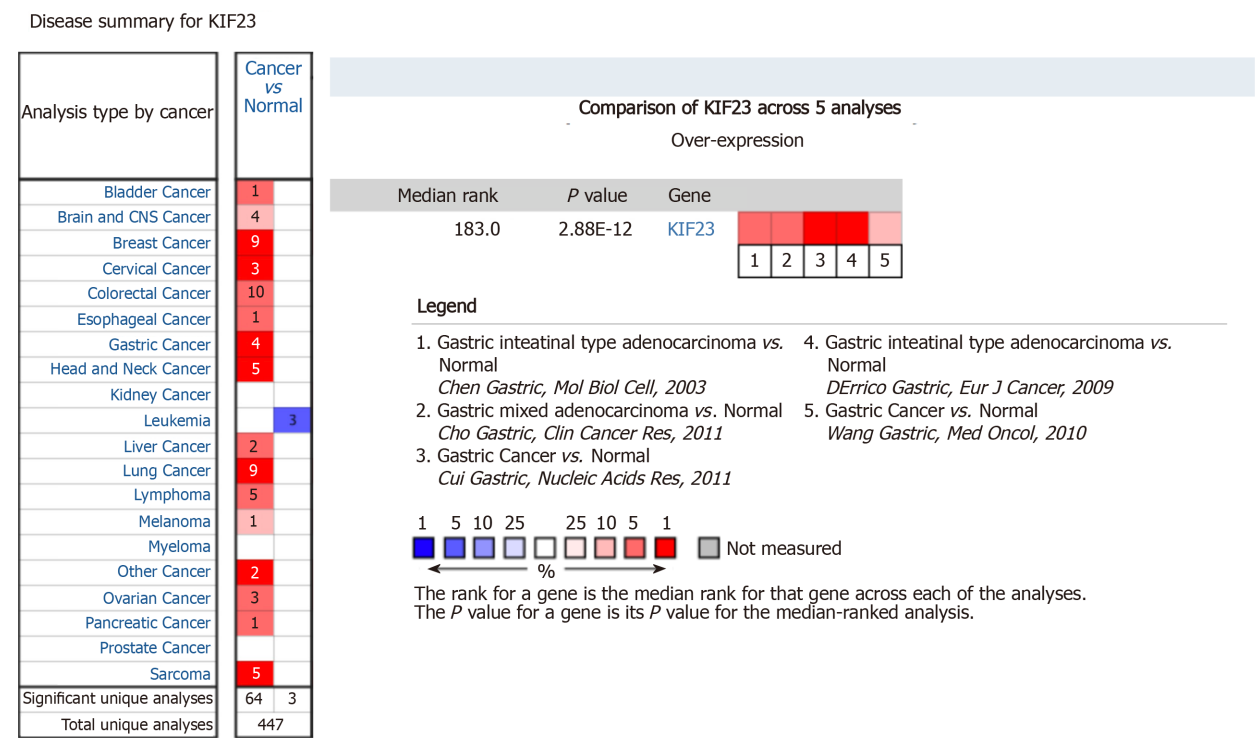
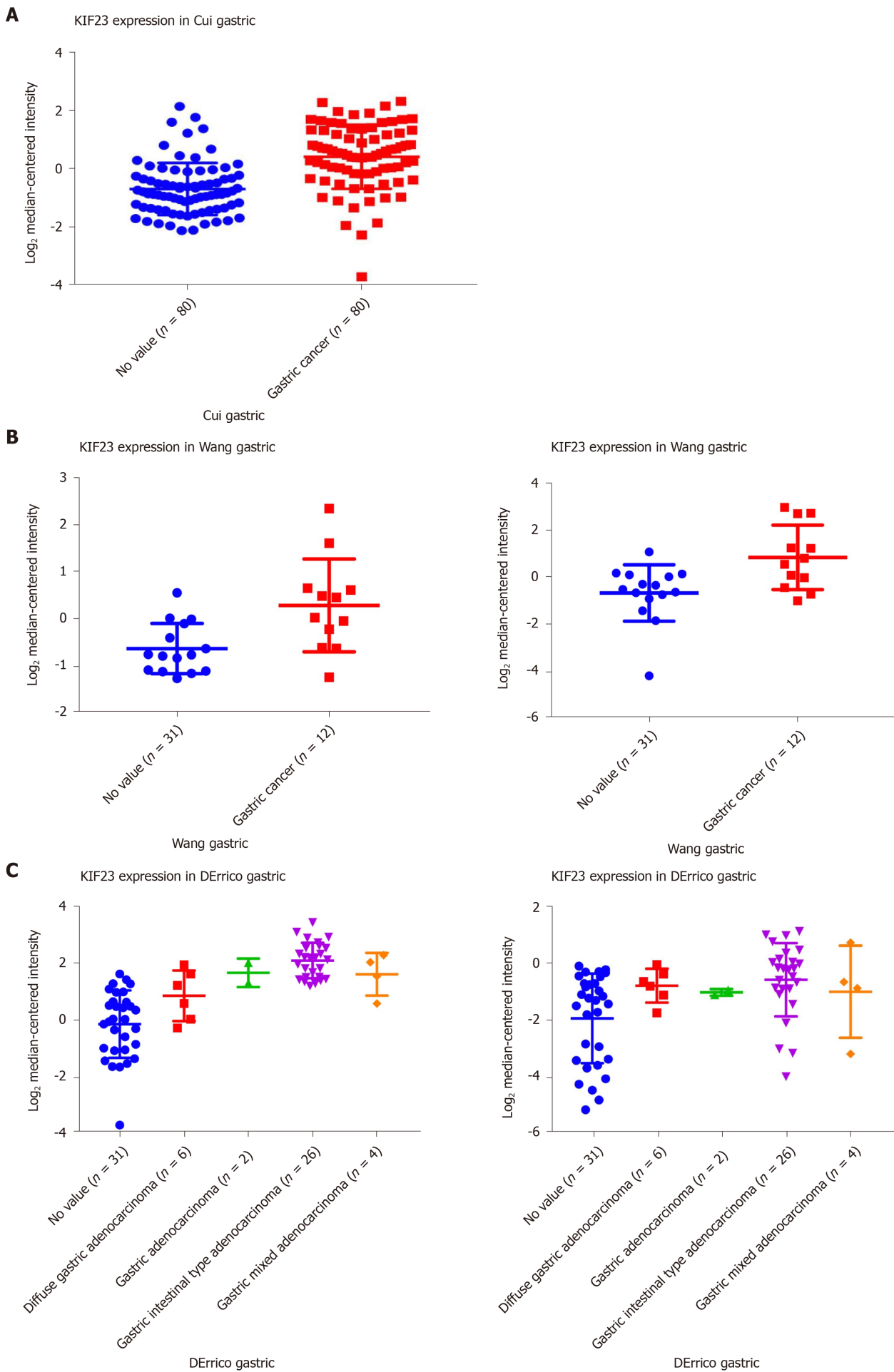


Figure 2 KIF23 mRNA expression in tumors according to Oncomine database. A statistically significant dataset of high (red) or low (blue) *KIF23* gene expression (cancer vs normal).



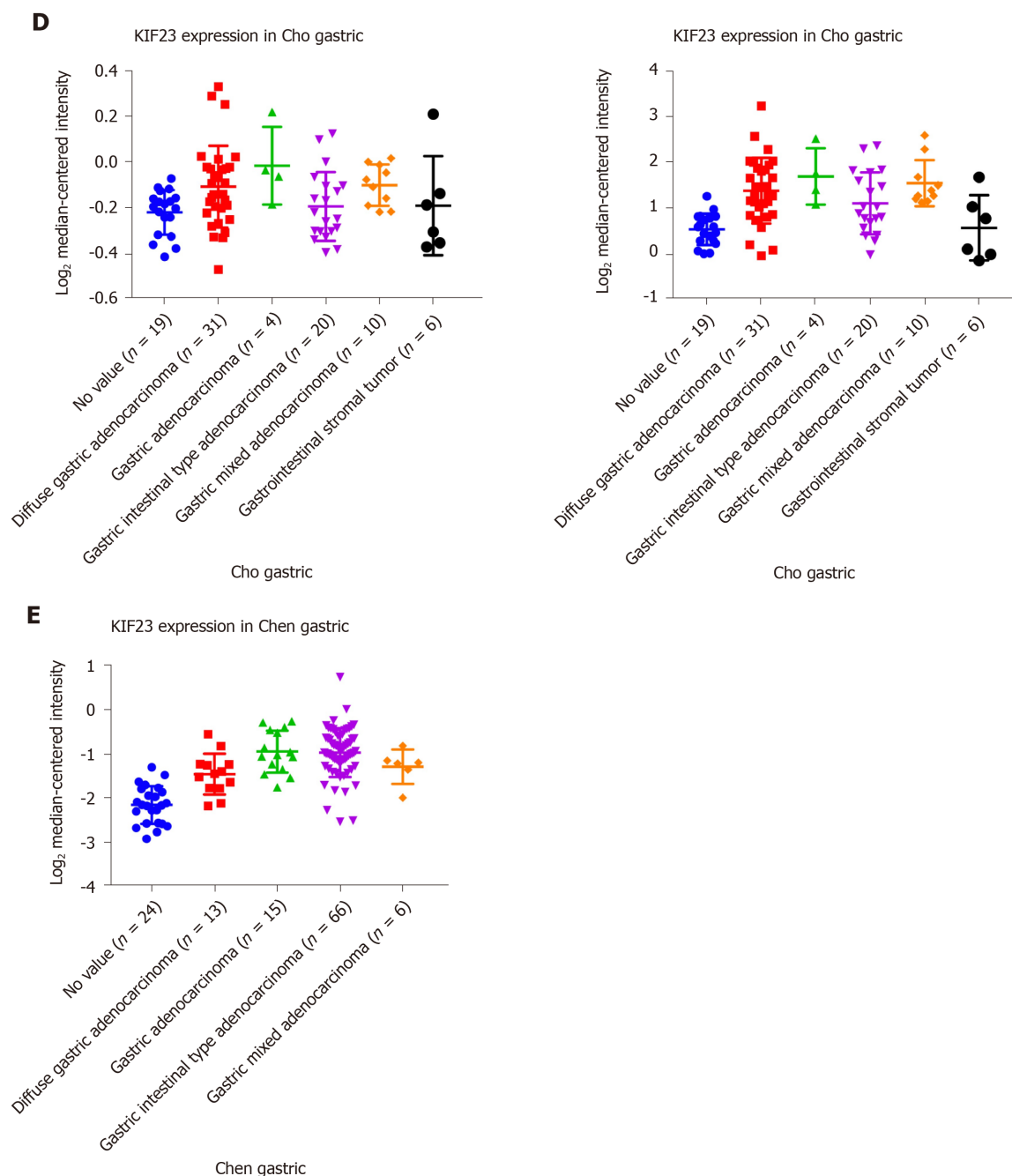
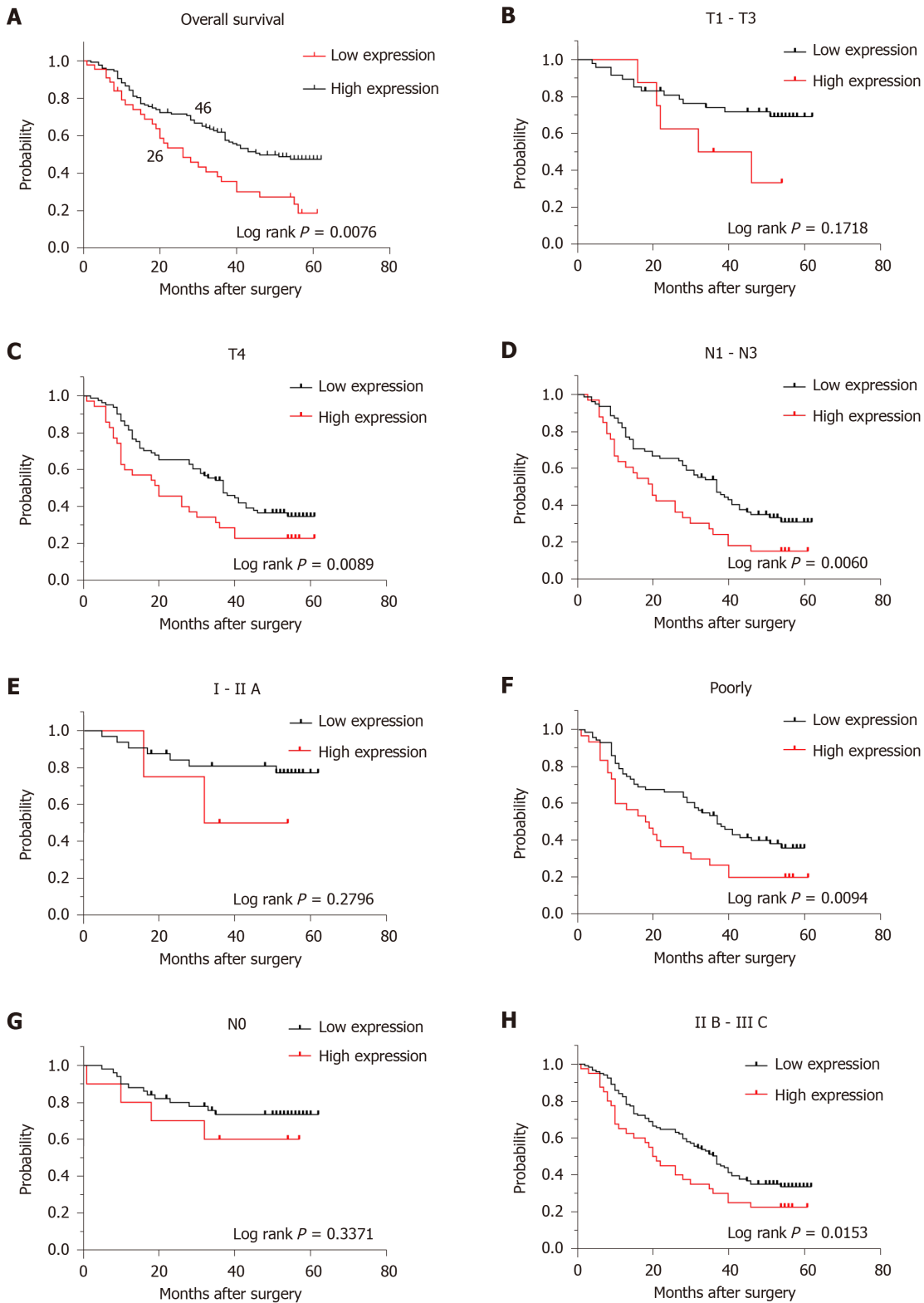


Figure 3 Expression of KIF23 in gastric cancer in Oncomine database. A-E: The results of the five studies involved. The darker the red, the higher the expression of KIF23 in the chip.



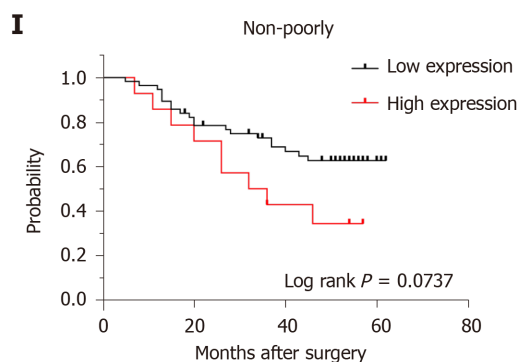


Figure 4 Prognostic effect of KIF23 expression in subgroups with different clinicopathological characteristics. A: Kaplan–Meier analysis of the overall survival (OS) rate between the low- and high-KIF23 expression groups. Median OS in the low- and high-KIF23 expression groups was 41 and 26 mo, respectively; B–I: Kaplan–Meier analysis of OS rate between the low- and high-KIF23 expression groups in GC patients with different T, N, and tumor–node–metastasis stages, and differentiation types.

ARTICLE HIGHLIGHTS

Research background

Kinesin super family 23 (KIF23) is a member of the KIF family, and it plays an important role in mitosis and cytokinesis. Loss of KIF23 expression can cause mitotic arrest. By querying the Oncomine database, differences in expression between tumor and normal tissues can be determined.

Research motivation

We detected the expression level of KIF23 protein in gastric cancer (GC) and adjacent normal tissues, and analyzed the association between KIF23 protein expression and clinicopathological factors.

Research objectives

This study aimed to study the expression and prognostic significance of KIF23 in GC.

Research methods

Immunohistochemistry was used to compare the expression of KIF23 in GC and normal gastric tissues. The data on the expression and prognosis of KIF23 in GC were mined using Oncomine and Kaplan–Meier plotter database.

Research results

Compared with normal gastric tissues, KIF23 expression was increased in GC tissues, and correlated with T, N, and tumor–node–metastasis stages. Survival analysis showed that patients with high expression of KIF23 had a poor overall survival. The prognostic survival indicators worsened in patients with T2 and T3 poorly differentiated adenocarcinoma with high expression of KIF23.

Research conclusions

KIF23 is highly expressed in GC, and it is associated with a poor prognosis of GC patients.

Research perspectives

We found that KIF23 overexpression in gastric cancer tissues is related to prognosis. Use of a database for large sample analysis can avoid errors caused by a small sample size and provide an important theoretical basis for clinical treatment. The specific mechanism of KIF23 in the development of gastric cancer needs further study.

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