

# Role of kinesin family member 14 in disease monitoring and prognosis in patients with gastrointestinal cancer

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**Abstract.** Kinesin family member 14 (KIF14) is not only involved in numerous essential biological activities, such as cytokinesis and myelination, but also regulates several malignant behaviors and progression of cancer. However, its role in gastrointestinal cancer is rarely reported. Therefore, the present study aimed to investigate the association of KIF14 expression with disease-free survival (DFS) and overall survival (OS) times in patients with gastrointestinal cancer. A total of 101 patients with gastrointestinal cancer (36 patients with gastric cancer and 65 patients with colorectal cancer) were retrospectively reviewed, and their cancer samples were collected to detect the protein and mRNA expression levels of KIF14 using immunohistochemistry and reverse transcription-quantitative PCR, respectively. KIF14 protein expression was increased in cancer tissues compared with adjacent tissues (all  $P < 0.001$ ). The protein expression levels of KIF14 were positively associated with T stage ( $P < 0.001$ ), distant metastases ( $P = 0.007$ ) and TNM stage ( $P < 0.001$ ), while KIF14 mRNA expression was positively associated with T stage ( $P < 0.001$ ), lymph node metastasis ( $P = 0.004$ ), distant metastases ( $P = 0.001$ ) and TNM stage ( $P < 0.001$ ). High protein and mRNA expression levels of KIF14 were associated with worse DFS ( $P < 0.001$ ) and OS ( $P = 0.016$ ) times. In addition, high KIF14 protein expression independently predicted unfavorable DFS times ( $P = 0.007$ ). Subgroup analysis revealed that in patients with gastric cancer,

KIF14 expression was associated with DFS and OS times, while in patients with colorectal cancer, KIF14 expression was only associated with DFS time, but not with OS time. In conclusion, KIF14 expression was not only associated with advanced pathological differentiation and TNM stage but was also associated with poor survival time in patients with gastrointestinal cancer. These results indicate the potential of KIF14 as a biomarker for gastrointestinal cancer prognosis.

## Introduction

Gastrointestinal cancer is one of the major contributors to global cancer prevalence and cancer-associated mortality (1,2). In addition, gastric and colorectal cancers are the most common gastrointestinal cancers in China (1,2). With respect to gastric cancer, early disease could be eradicated by surgical resection, while the majority of patients with gastric cancer do not recognize any of the clinical symptoms until the disease has progressed to an advanced stage (3-5). This situation largely contributes to the poor prognosis of patients with gastric cancer. It has been reported that the 5-year survival rate is ~60% in patients with non-advanced cancer, while it declines to ~30% in patients with advanced stage cancer (6). In terms of the colorectal cancer, its incidence is raised throughout the past three decades, especially in the young population (7). Furthermore, it is still important to investigate biomarkers or a model that can boost the efficiency of prognosis in colorectal cancer management (8). Therefore, identification of biomarkers that could assist with identifying early disease, guiding treatment and optimizing disease prognosis is essential in these two types of cancer.

Kinesin family member 14 (KIF14), a member of the kinesin-3 family, is a regulator of cell mitosis, which is similar to other kinesins (9). KIF14 is involved in numerous essential biological activities in organisms, such as the regulation of cytokinesis and myelination (10-12). Notably, an increasing number of studies have examined KIF14 and its mechanistic role and potential clinical value in several types of cancer, including cervical, lung and prostate cancer (13-15). In terms of the role of KIF14 expression in gastrointestinal cancer, only a few studies have reported this issue. For instance, Previous studies indicated that KIF14 is positively associated with aggravating disease features and its high expression is associated with worse survival in patients with gastric cancer and

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**Abbreviations:** KIF14, kinesin family member 14; DFS, disease-free survival; OS, overall survival; IHC, immunohistochemistry; RT-qPCR, reverse transcription quantitative PCR; LNM, lymph node metastasis; HCC, hepatocellular carcinoma

**Key words:** gastrointestinal cancer, KIF14, pathological differentiation, TNM stage, survival

pancreatic adenocarcinoma (16,17). Additionally, upregulation of KIF14 has also been found to be associated with the elevated tumor stage and pathological tumor grade of patients with hepatocellular carcinoma (HCC) (18). However, the role of KIF14 in gastrointestinal cancer requires further in-depth investigation.

Therefore, the present study aimed to investigate the association between KIF14 expression and disease-free survival (DFS) and overall survival (OS) times in patients with gastrointestinal cancer.

## Materials and methods

**Patients.** The present study retrospectively reviewed 101 patients with gastrointestinal cancer [36 patients with gastric cancer consisting of 16 (44.4%) males and 20 (55.6%) females and 65 patients with colorectal cancer consisting of 40 (61.5%) males and 25 (38.5%) females] who were treated at the General Hospital of Ningxia Medical University (Ningxia, China) and the First People's Hospital Affiliated to Shanghai Jiaotong University (Shanghai, China) between January 2008 and December 2010. The screening criteria for all patients included: i) Diagnosis of gastrointestinal cancer by surgery and postoperative pathology; ii) had complete clinical characteristics and follow-up information; and iii) had available cancer specimens to perform immunohistochemistry (IHC) and reverse transcription-quantitative PCR (RT-qPCR). Patients were excluded if, according to the medical records, they met the following criteria: i) Had a history of other cancers or malignancies at diagnosis; and ii) received preoperative chemotherapy or radiotherapy. The study was approved by the Internal Review Boards of General Hospital of Ningxia Medical University (Ningxia, China) and the First People's Hospital Affiliated to Shanghai Jiaotong University (approval no. 2011-268; Shanghai, China). All patients or their families provided written informed consent.

**Data collection.** By reviewing the medical documents, the clinical characteristics, including age, sex, current smoking and drinking status, tumor location, tumor size, pathological grade, T stage, lymph node metastasis (LNM), distant metastases and TNM stage, were collected (19,20). Follow-up was conducted every 6 months via either clinic visits, telephone calls or letters, and survival data were collected to calculate DFS and OS times.

**IHC analysis.** Tumor tissue was available in all patients, while adjacent tissue was also available in 49 patients, including 19 patients with gastric cancer and 30 patients with colorectal cancer. IHC analysis was used to evaluate KIF14 protein expression in the cancer and adjacent specimens. The methods used were the same as previously described (21). The slices of cancer and adjacent specimens were incubated with KIF14 polyclonal antibody (1:200 dilution; cat. no. BL358; Bethyl Laboratories, Inc.) at 4°C overnight, then the slices were incubated with biotinylated goat anti-rabbit Envision + System-HRP (1:500 dilution; cat. no. E432; Dako; Agilent Technologies, Inc.) at 37°C for 15 min. Diaminobenzidine and hematoxylin were used for staining and counterstaining, respectively. PBS instead of the primary antibody was used as the negative control. The

results of IHC staining were evaluated with a light microscope and were independently graded by two pathologists who were blinded to the clinical and pathological information of the patients. The staining intensity score and density score were used to assess the KIF14 protein expression in specimens using a semi-quantitative scoring method as described previously (22). Briefly, the intensity score of IHC staining ranged between 0 and 3, and the range of the density score was 0-4. The total IHC score was 12, which was calculated by multiplying the intensity score and the density score, and the final IHC score was the average value of the scores of the two pathologists.

**RT-qPCR.** The mRNA expression levels of KIF14 were determined using RT-qPCR. Total RNA was extracted from fresh tumor tissue with TRIzol® LS (cat. no. A33253; Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol. Then, RNA was reverse transcribed using an ABI P RISM 7900HT thermocycler (cat. no. 4317596; Thermo Fisher Scientific, Inc.) with PrimeScript RT Master Mix (Perfect Real Time) (cat. no. RR036A; Takara Bio, Inc.) according to the manufacturer's instructions. qPCR was performed with cDNA using iTaq Universal SYBR® Green Supermix (cat. no. 1725120; Bio-Rad Laboratories, Inc.). The following PCR primers were used:  $\beta$ -actin (control) forward, 5'-GTGGGGCGCCCC AGGCACCA-3' and reverse, 5'-CTCCTTAATGTACGCAC GATTTC-3' (540-bp fragment); and KIF14 forward, 5'-TGG AACACCCTGACACGA-3' and reverse, 5'-GAGCCAGTC TGACCATAAGC-3'. Quantification of gene expression was performed using a Real Plex RT-PCR System (Eppendorf) and the following thermocycling conditions were used: Initial denaturation at 95°C for 2 min, followed by 40 cycles of denaturation at 95°C for 20 sec, annealing at 54°C for 15 sec and elongation at 72°C for 20 sec, with a final extension at 72°C for 10 min. Relative KIF14 expression was calculated using the  $2^{-\Delta\Delta C_q}$  method (23).

**Definitions.** A final IHC score  $\leq 3$  was classified as low KIF14 protein expression, while an IHC score  $> 3$  was classified as high KIF14 protein expression. The exact value of 1.000 was included in the colorectal cancer patients' group. The median relative mRNA expression levels of KIF14 were used to classify the samples into high ( $> 1.000$ ) and low ( $< 1.000$ ) mRNA expression groups.

**Statistical analysis.** SPSS v21.0 software (IBM Corp.) and GraphPad Prism v7.02 (GraphPad Software, Inc.) were used for statistical analysis and generation of the graphs. Normally distributed quantitative data are presented as the mean  $\pm$  SD. Non-normally distributed quantitative data are presented as the median (25-75th quantiles). Qualitative data are presented as the count (percentage). Associations between clinical characteristics and KIF14 expression were evaluated using a  $\chi^2$  test or the Fisher's exact test. Kaplan-Meier curves and the log-rank test were used to analyze the survival data and KIF14 expression. Prognostic factors were determined using a Cox's proportional hazard regression model. Significant variables ( $P < 0.05$ ) in the univariate analysis were included in multivariate Cox's regression analysis.  $P < 0.05$  was considered to indicate a statistically significant difference. Each experiment was repeated in three duplicates.

Table I. Association of clinical characteristics with KIF14 expression.

Variables	All patients, n (%)	KIF14 protein expression		$\chi^2$	P-value	KIF14 mRNA expression		$\chi^2$	P-value
		Low, n (%)	High, n (%)			Low, n (%)	High, n (%)		
Age				0.590	0.442			0.524	0.469
≤60 years	42 (41.2)	16 (38.1)	26 (61.9)			19 (45.2)	23 (54.8)		
>60 years	59 (57.8)	27 (45.8)	32 (54.2)			31 (52.5)	28 (47.5)		
Sex				0.556	0.456			2.222	0.136
Female	45 (44.1)	21 (46.7)	24 (53.3)			26 (57.8)	19 (42.2)		
Male	56 (54.9)	22 (39.3)	34 (60.7)			24 (42.9)	32 (57.1)		
Current smoking status				0.171	0.679			0.685	0.408
No	73 (71.6)	32 (43.8)	41 (56.2)			38 (52.1)	35 (47.9)		
Yes	28 (27.5)	11 (39.3)	17 (60.7)			12 (42.9)	16 (57.1)		
Current drinking status				0.027	0.870			0.479	0.489
No	62 (60.8)	26 (41.9)	36 (58.1)			29 (46.8)	33 (53.2)		
Yes	39 (38.2)	17 (43.6)	22 (56.4)			21 (53.8)	18 (46.2)		
Tumor location				0.080	0.777			0.819	0.365
Colorectal	65 (63.7)	27 (41.5)	38 (58.5)			30 (46.2)	35 (53.8)		
Gastric	36 (35.3)	16 (44.4)	20 (55.6)			20 (55.6)	16 (44.4)		
Tumor size				0.088	0.766			0.008	0.930
≤5 cm	57 (55.9)	25 (43.9)	32 (56.1)			28 (49.1)	29 (50.9)		
>5 cm	44 (43.1)	18 (40.9)	26 (59.1)			22 (50.0)	22 (50.0)		
Pathological grade				4.359	0.111			4.617	0.105
Grade 1	24 (23.5)	13 (54.2)	11 (45.8)			16 (66.7)	8 (33.3)		
Grade 2	45 (44.1)	21 (46.7)	24 (53.3)			22 (48.9)	23 (51.1)		
Grade 3	32 (31.4)	9 (28.1)	23 (71.9)			12 (37.5)	20 (62.5)		
Distant metastases				7.302	0.007			12.102	0.001
No	90 (88.2)	43 (47.8)	47 (52.2)			50 (55.6)	40 (44.4)		
Yes	11 (10.8)	0 (0.0)	11 (100.0)			0 (0.0)	11 (100.0)		
T stage				22.091	<0.001			25.301	<0.001
T1	15 (14.7)	14 (93.3)	1 (6.7)			15 (100.0)	0 (0.0)		
T2	23 (22.5)	10 (43.5)	13 (56.5)			13 (56.5)	10 (43.5)		
T3	42 (41.2)	15 (35.7)	27 (64.3)			17 (40.5)	25 (59.5)		
T4	21 (20.6)	4 (19.0)	17 (81.0)			5 (23.8)	16 (76.2)		
LNM				3.184	0.076			8.343	0.004
No	46 (45.1)	24 (52.2)	22 (47.8)			30 (65.2)	16 (34.8)		
Yes	55 (53.9)	19 (34.5)	36 (65.5)			20 (36.4)	35 (63.6)		
TNM stage				21.487	<0.001			44.662	<0.001
I	16 (15.7)	13 (81.2)	3 (18.8)			16 (100.0)	0 (0.0)		
II	34 (33.3)	19 (55.9)	15 (44.1)			24 (70.6)	10 (29.4)		
III	35 (34.3)	8 (22.9)	27 (77.1)			8 (22.9)	27 (77.1)		
IV	16 (15.7)	3 (18.8)	13 (81.2)			2 (12.5)	14 (87.5)		

KIF14, kinesin family member 14; mRNA, messenger RNA; LNM, lymph node metastasis.

## Results

*Characteristics of patients with gastrointestinal cancer.* The mean age of the 101 enrolled patients with gastrointestinal cancer was 60.3±6.6 years. There were 45 (44.1%) female patients and 56 (54.9%) male patients. There were 65 (63.7%)

and 36 (35.3%) patients who had colorectal or gastric cancer, respectively. In addition, the numbers of patients with a tumor size ≤5 or >5 cm were 57 (55.9%) and 44 (43.1%), respectively. The numbers of patients with pathological grade 1, 2 and 3 were 24 (23.5%), 45 (44.1%) and 32 (31.4%), respectively. Furthermore, there were 55 (53.9%) patients with LNM and

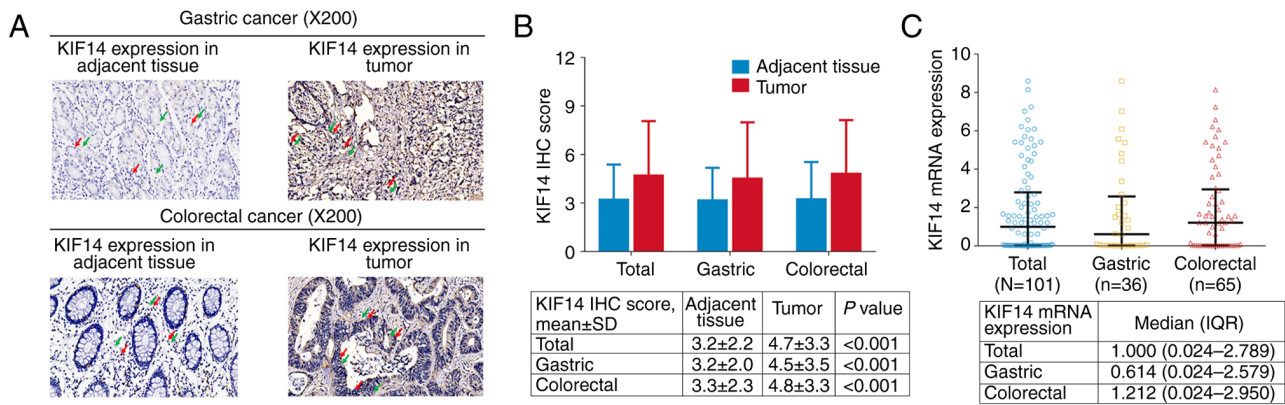


Figure 1. Expression levels of KIF14 in patients with gastrointestinal cancer. (A) Images of KIF14 protein expression in cancer and adjacent tissues from patients with colorectal and gastric cancer. The red arrows indicate KIF14 protein locating in cell nucleus and the green arrow indicates KIF14 protein locating in cell cytoplasm. (B) KIF14 IHC score in patients with gastrointestinal, colorectal and gastric cancer. (C) KIF14 mRNA expression in patients with gastrointestinal, gastric and colorectal cancer. KIF14, kinesin family member 14; IHC, immunohistochemistry; IQR, interquartile range.

46 (45.1%) patients without LNM. The number of patients who had no distant metastases was 90 (88.2%) and the number of patients who had distant metastasis was 11 (10.8%). Other clinical characteristics including: current smoking and drinking status, T stage and TNM stage are shown in Table I.

**KIF14 expression.** The IHC staining of KIF14 in gastric and colorectal cancer tissues and the adjacent tissue is shown in Fig. 1A. KIF14 protein expression was mainly located in the cell nucleus and cytoplasm in both gastric cancer (upper panel) and colorectal cancer (lower panel) tissues. In addition, the KIF14 IHC score was elevated in tumor tissue of all patients ( $4.7 \pm 3.3$  vs.  $3.2 \pm 2.2$ ;  $P < 0.001$ ), patients with gastric cancer ( $4.5 \pm 3.5$  vs.  $3.2 \pm 2.0$ ;  $P < 0.001$ ) and patients with colorectal cancer ( $4.8 \pm 3.3$  vs.  $3.3 \pm 2.3$ ;  $P < 0.001$ ) compared with adjacent tissue (Fig. 1B). The median KIF14 mRNA expression in all patients, patients with gastric cancer and patients with colorectal cancer was 1.000 (0.024–2.789), 0.614 (0.024–2.579) and 1.212 (0.024–2.950), respectively (Fig. 1C).

**Association of KIF14 expression with clinicopathological characteristics.** In all patients with gastrointestinal cancer, KIF14 protein expression was associated with T stage ( $P < 0.001$ ), distant metastases ( $P = 0.007$ ) and TNM stage ( $P < 0.001$ ) (Table I). KIF14 protein expression was not associated with age, sex, current smoking and drinking status, tumor location, tumor size, pathological grade, or LNM (all  $P > 0.05$ ). KIF14 mRNA expression was associated with T stage ( $P < 0.001$ ), LNM ( $P = 0.004$ ), distant metastases ( $P = 0.001$ ) and TNM stage ( $P < 0.001$ ) (Table I). KIF14 mRNA expression was not associated with age, sex, current smoke, current drink, tumor location, tumor size, or pathological grade (All  $P > 0.05$ ).

**Association between KIF14 expression and survival time.** High KIF14 protein expression was associated with worse DFS time in all patients with gastrointestinal cancer ( $P < 0.001$ ; Fig. 2A), patients with gastric cancer ( $P = 0.004$ ; Fig. 2B) and patients with colorectal cancer ( $P = 0.008$ ; Fig. 2C). In addition, high KIF14 mRNA expression was also associated with DFS time in the aforementioned patients (all  $P < 0.01$ ; Fig. 2D–F).

High KIF14 protein expression was associated with worse OS time in all patients with gastrointestinal cancer ( $P = 0.016$ ; Fig. 3A) but not in patients with gastric cancer ( $P = 0.114$ ; Fig. 3B) or patients with colorectal cancer ( $P = 0.066$ ; Fig. 3C). In addition, high KIF14 mRNA expression was associated with worse OS time in all patients with gastrointestinal cancer ( $P = 0.016$ ; Fig. 3D) and patients with gastric cancer ( $P = 0.044$ ; Fig. 3E) but not in patients with colorectal cancer ( $P = 0.145$ ; Fig. 3F).

**Independent prognostic factors.** Multivariate Cox's proportional hazards regression analysis revealed that in all patients with gastrointestinal cancer, high KIF14 protein expression ( $P = 0.007$ ) was an independent prognostic factor for unfavorable DFS time, along with TNM stage (III/IV vs. I/II;  $P = 0.010$ ; Table II). TNM stage (III/IV vs. I/II;  $P = 0.003$ ) could independently predict shorter OS time in all patients with gastrointestinal cancer (Table III).

## Discussion

As a crucial member of the kinesin family, KIF14 has been reported to be a regulator of tumor development and progression in previous studies and could also be a potential biomarker in the management of patients with cancer (24,25). A prior study revealed that KIF14 inhibition using small interfering (si)RNA could repress proliferation and enhance apoptosis in medulloblastoma cells, while KIF14 inhibition using short hairpin RNA could suppress cell viability, colony formation, invasion, migration and tumor sphere formation in medulloblastoma cells (18). Furthermore, KIF14 expression is upregulated in patients with medulloblastoma and is associated with unfavorable progression-free survival and poor OS time (26). Another study identified KIF14 as a tumor enhancer in HCC, since knockdown of KIF14 expression reduced the acquired chemoresistance to sorafenib by decreasing AKT activation and ETS proto-oncogene 1, transcription factor expression in the HCC cells, and siRNA targeting KIF14 reduced tumor growth of sorafenib-resistant HCC cells in a mice model *in vivo* (27). Furthermore, in ovarian cancer cells, upregulated KIF14 expression enhanced proliferation and

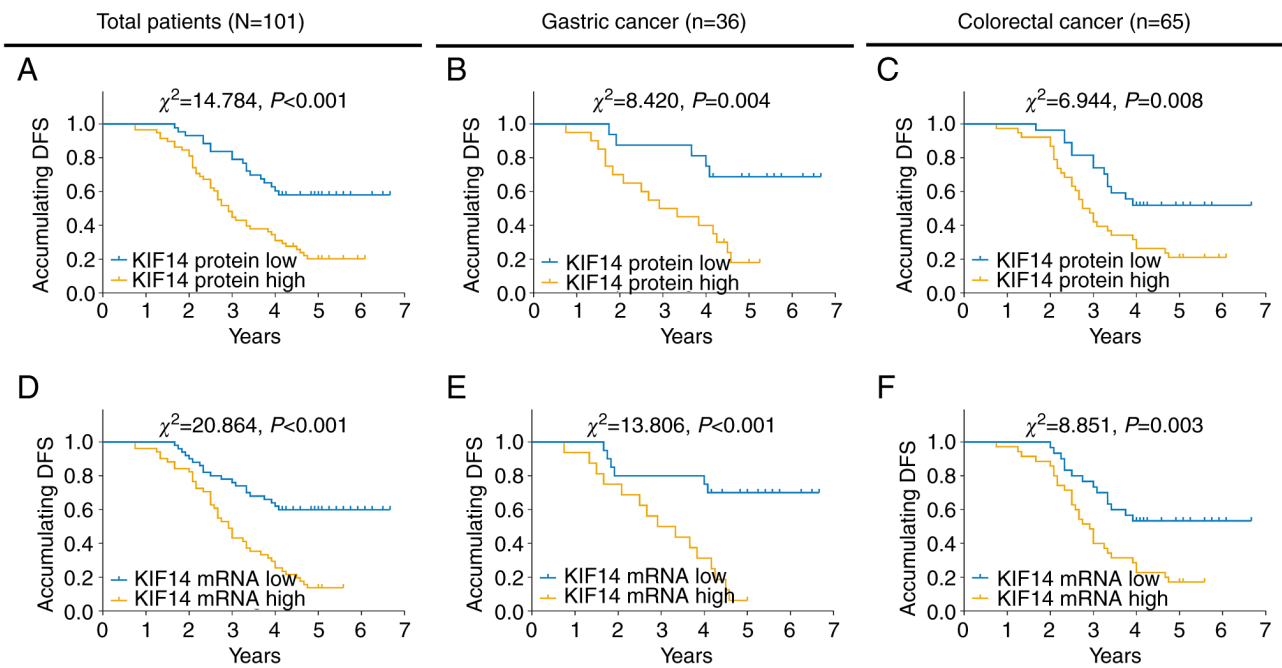


Figure 2. Association between KIF14 expression and DFS time. Association between KIF14 protein expression and DFS in patients with (A) gastrointestinal, (B) gastric and (C) colorectal cancer. Association between KIF14 mRNA expression and DFS time in patients with (D) gastrointestinal, (E) gastric and (F) colorectal cancer. DFS, disease-free survival; KIF14, kinesin family member 14.

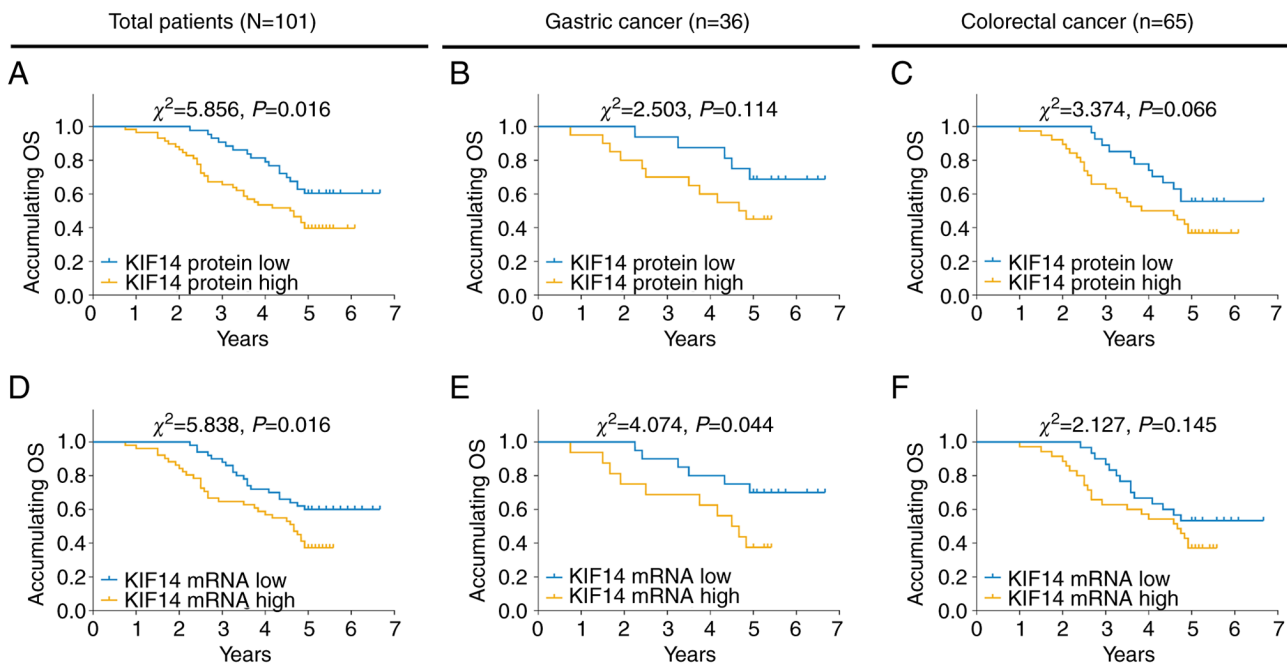


Figure 3. Association between KIF14 expression and OS time. Association between KIF14 protein expression and OS time in patients with (A) gastrointestinal, (B) gastric and (C) colorectal cancer. Association between KIF14 mRNA expression and OS time in patients with (D) gastrointestinal, (E) gastric and (F) colorectal cancer. OS, overall survival; KIF14, kinesin family member 14.

colony formation; however, downregulated KIF14 expression promoted apoptosis and decreased colony formation (28). In addition, KIF14 was upregulated in tumor tissues and could predict unfavorable outcomes in patients with ovarian cancer (29). These aforementioned studies indicated that in numerous types of cancer, KIF14 might be a promoter of cancer progression, and could be a potential biomarker for prognosis (21,24-29).

With respect to the role of KIF14 in gastrointestinal cancer, research is limited. A previous study reported that KIF14 enhanced gastric cancer cell proliferation, migration and invasion by positively regulating the AKT signaling pathway (30). In addition, KIF14 expression was positively associated with tumor stage, TNM stage and tumor metastasis, and its high expression levels could independently predict poor survival in patients with gastric cancer (16). In

Table II. Factors affecting disease-free survival according to Cox's proportional hazards regression analysis.

Variables	P-value	HR	95% CI	
			Lower	Upper
Univariate Cox's regression analysis				
KIF14 protein (high vs. low)	<0.001 <sup>a</sup>	2.770	1.602	4.789
Age (>60 years vs. ≤60 years)	0.122	0.678	0.414	1.109
Sex (male vs. female)	0.904	1.031	0.628	1.694
Current smoking status (yes vs. no)	0.381	1.268	0.746	2.154
Current drinking status (yes vs. no)	0.753	0.923	0.558	1.525
Tumor location (Gastric vs. Colorectal)	0.415	0.804	0.476	1.358
Tumor size (>5 cm vs. ≤5 cm)	0.732	0.917	0.558	1.506
Pathological grade (Grade 3 vs. Grade 1/Grade 2)	0.277	0.742	0.434	1.270
Distant metastases (yes vs. no)	<0.001 <sup>a</sup>	6.696	3.190	14.054
T stage (T3/T4 vs. T1/T2)	0.035 <sup>a</sup>	1.801	1.042	3.111
LNM (yes vs. no)	0.679	0.902	0.552	1.473
TNM stage (III/IV vs. I/II)	<0.001 <sup>a</sup>	1.702	1.274	2.275
Multivariate Cox's regression analysis				
KIF14 protein (high vs. low)	0.007 <sup>a</sup>	2.189	1.240	3.864
TNM stage (III/IV vs. I/II)	0.010 <sup>a</sup>	1.519	1.104	2.091

<sup>a</sup>P<0.05 was considered to indicate a statistically significant difference. DFS, disease free survival; HR, hazard ratio; CI, confidence interval; KIF14, kinesin family member 14; LNM, lymph node metastasis.

Table III. Factors affecting overall survival according to Cox's proportional hazards regression analysis.

Variables	P-value	HR	95% CI	
			Lower	Upper
Univariate Cox's regression analysis				
KIF14 protein (high vs. low)	0.018 <sup>a</sup>	2.010	1.125	3.591
Age (>60 years vs. ≤60 years)	0.623	0.871	0.504	1.507
Sex (male vs. female)	0.699	0.898	0.521	1.549
Smoke (yes vs. no)	0.305	1.355	0.758	2.420
Drink (yes vs. no)	0.403	0.784	0.443	1.388
Tumor location (Gastric vs. Colorectal)	0.332	0.747	0.414	1.347
Tumor size (>5 cm vs. ≤5 cm)	0.638	0.876	0.505	1.519
Pathological grade (Grade 3 vs. Grade 1/Grade 2)	0.110	0.599	0.320	1.122
Distant metastases (yes vs. no)	<0.001 <sup>a</sup>	19.843	8.014	49.136
T stage (T3/T4 vs. T1/T2)	0.250	1.406	0.787	2.510
LNM (yes vs. no)	0.413	0.797	0.462	1.373
TNM stage (III/IV vs. I/II)	0.001 <sup>a</sup>	1.805	1.289	2.528
Multivariate Cox's regression analysis				
TNM stage (III/IV vs. I/II)	0.003 <sup>a</sup>	1.711	1.195	2.451

<sup>a</sup>P<0.05 was considered to indicate a statistically significant difference. OS, overall survival; HR, hazard ratio; CI, confidence interval; KIF14, kinesin family member 14; LNM, lymph node metastasis.

colorectal cancer, a previous study found that KIF14 enhanced colorectal cancer cell proliferation via the activation of AKT signaling, and was also targeted by miR-200c (30). In addition, in pancreatic adenocarcinoma, KIF14 was highly

expressed in tumor tissues compared with normal tissues, and this coincided with unfavorable prognosis (17). Furthermore, elevated KIF14 expression has also been observed in tumor tissues of patients with esophageal squamous cell carcinoma



compared with in normal tissues (31). Additionally, upregulation of KIF14 has been found to be associated with the tumor stage and pathological tumor grade of patients with HCC (18). Notably, to the best of our knowledge, the role of KIF14 in patients with gastrointestinal cancer has not been investigated; therefore, the present study investigated the role of KIF14 in patients with this type of cancer. It was found that KIF14 expression was associated with advanced pathological differentiation and tumor stages, and also predicted worse survival time. It was hypothesized that these results could be attributed to the following reasons: i) As a carcinogenesis gene, KIF14 reflected the proliferation speed of cells, while the proliferation speed of tumor cells was higher than that of the normal cells, thus, the KIF14 expression was elevated in tumor tissues compared with adjacent tissues (17,18,31); ii) KIF14 can promote malignant behavior in cancer cells, such as enhancement of cancer cell proliferation, by interacting with related factors (30). This might explain the association between KIF14 expression and clinicopathological characteristics in patients with gastrointestinal cancer and the association with unfavorable survival times (16,26,27,29,30,32); and iii) in addition, KIF14 expression was associated with DFS time, but not OS time, suggesting that OS time could be affected by additional factors, such as treatment after disease relapse. Thus, this finding might imply that after determining the KIF14 expression in tumor tissues of patients with gastrointestinal cancer, the treatment strategy might be adjusted accordingly. For example, if a patient with gastric cancer exhibits high KIF14 expression, then a more intensive treatment regimen should be considered for their subsequent treatment.

The present study had several limitations. First, only 101 patients with gastrointestinal were recruited, which made that sample size was too small to investigate the clinical value of KIF14. Second, there may be some confounding factors affecting the effect of KIF14; therefore, multivariate Cox's proportional hazard analysis was performed to decrease this effect. Third, the patients enrolled in the present study were from Northwest China, which might cause patient selection bias.

In conclusion, KIF14 expression was associated with advanced pathological differentiation and TNM stage, and also predicted worse survival time in patients with gastrointestinal cancer. This indicates its potential as a biomarker for gastrointestinal cancer prognosis.

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#### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

#### Authors' contributions

PC and WF contributed to the study design. PC, WF, YH, FW and NL reviewed the medical documents and collected the clinical characteristics of patients. PC, WF, YH, FW and NL contributed to the data acquisition and analysis. PC, WF, YH, FW and NL wrote the manuscript, and PC and WF critically revised the manuscript for important intellectual content. PC agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. PC and WF confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

#### Ethics approval and consent to participate

The study was approved by the Internal Review Boards of General Hospital of Ningxia Medical University (Ningxia, China) and the First People's Hospital Affiliated to Shanghai Jiaotong University (Shanghai, China). All patients or their families provided written informed consent.

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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