

# Association between IL-6 and prognosis of gastric cancer: a retrospective study

Panping Liang\*, Yuexin Zhang\*, Tianyuchen Jiang, Tao Jin, Zhengwen Chen, Zedong Li, Zehua Chen, Fengjun He, Jiankun Hu and Kun Yang 

Ther Adv Gastroenterol

2023, Vol. 16: 1–14

DOI: 10.1177/  
17562848231211543

© The Author(s), 2023.  
Article reuse guidelines:  
sagepub.com/journals-  
permissions

## Abstract

**Background:** Gastric cancer (GC) is one of the common and fatal cancers. Even though the Tumor, Node, Metastasis (TNM) staging system is the most classical staging system recognized worldwide, it has been controversial because there are various factors affecting the prognosis of GC patients.

**Objectives:** The study aims to evaluate the relationship between interleukin-6 (IL-6) and several clinical indicators and construct a prognostic model to better predict the prognosis of GC.

**Design:** A retrospective study.

**Methods:** Data of 249 patients with GC diagnosed in GC center of West China Hospital were collected. Clinicopathological characteristics were analyzed to determine whether there were differences between IL-6 HIGH group and IL-6 LOW group. Besides, the association between the two groups and tumor marker levels was clarified. The K-M curves of 3- and 5-year were plotted with log-rank test. Afterward, we conducted univariate and multivariate analysis and a predicting nomogram. Significantly, C-index, and calibration were used to evaluate the value of nomogram in predicting prognosis.

**Results:** The overall survival of GC in the IL-6 HIGH and IL-6 LOW groups were 47.8 months (95% CI: 42.1–53.4) and 57.9 months (95% CI: 54.1–61.7), respectively, with significant differences ( $p=0.0046$ ). Average tumor size of GC ( $p=0.000$ ) and nerve invasion ( $p=0.018$ ) were statistically significant between two groups. Multivariate analysis revealed that the factors affecting prognosis were IL-6 ( $<5.51$  and  $\geq 5.51$  pg/ml) (Hazard Ratio(HR): 1.665, 95% CI: 1.026–2.703,  $p=0.039$ ), N stage (HR: 1.336, 95% CI: 1.106–1.615,  $p=0.003$ ), and T stage (HR: 1.268, 95% CI: 0.998–1.611,  $p=0.052$ ), which were included in the nomogram with a C-index of 0.71. The current data calculated TNM staging C-index was 0.68, and the  $p$ -value for the difference between the two models was 0.08. Internal validation revealed that the predicted overall survival did not differ significantly from the actual observed patient survival.

**Conclusion:** The differential expression of IL-6 has a tendency to differentiate the prognosis of GC patients. IL-6, N stage, and T stage are independent prognostic factors, and the new survival prognostic model consisting of the above three indicators is better than the classical TNM staging system.

**Trial registration:** This study is a retrospective study, which does not require clinical registration.

**Keywords:** cancer multidrug resistance, gastric cancer, IL-6, nomogram, prognosis

Correspondence to:

**Kun Yang**  
Gastric Center and  
Laboratory of Gastric  
Cancer, State Key  
Laboratory of Biotherapy,  
West China Hospital,  
Sichuan University, No.  
37 Guo Xue Xiang Street,  
Chengdu, Sichuan 610041,  
China

Gastric Cancer Center,  
West China Hospital,  
Sichuan University,  
Chengdu, Sichuan, China  
[yangkun068@163.com](mailto:yangkun068@163.com)

**Panping Liang**  
**Tianyuchen Jiang**  
**Tao Jin**  
**Zhengwen Chen**  
**Zedong Li**  
**Zehua Chen**  
**Fengjun He**  
**Jiankun Hu**

Department of General  
Surgery and Laboratory of  
Gastric Cancer, State Key  
Laboratory of Biotherapy/  
Collaborative Innovation  
Center of Biotherapy  
and Cancer Center, West  
China Hospital, Sichuan  
University, Chengdu,  
Sichuan, China

Gastric Cancer Center,  
West China Hospital,  
Sichuan University,  
Chengdu, Sichuan, China

**Yuexin Zhang**  
Colorectal Cancer  
Center, Department of  
General Surgery, West  
China Hospital, Sichuan  
University, Chengdu,  
Sichuan, China

\*These authors have  
contributed equally to  
this work and share first  
authorship.

Received: 27 June 2023; revised manuscript accepted: 13 October 2023.

## Introduction

### Background

Gastric cancer (GC) is one of the common and fatal cancers. With the continuous improvement of screening technology, more and more patients with early GC are detected in time.<sup>1</sup> Compared to early GC patients, the prognosis of advanced GC is poor.<sup>2</sup> GC has become a serious global health economic burden.<sup>3</sup> The TNM staging system is commonly used to assess the prognosis of patients with GC, which is the most classic staging system recognized worldwide. However, the determination of TNM staging relies on the experience of pathologists, and the retrieving of lymph nodes is also influenced by the sorting level of physicians; in addition, the distant metastases of some patients are difficult to be determined by imaging.<sup>4</sup> All these have limited the clinical use of TNM staging. The inclusion of clinical indicators that can provide more accurate prognostic information of GC on the basis of TNM staging has been longed for by the academic community. Serum indicators are easier to quantify and assess than tumor lymph node or distant metastasis. Therefore, a prognostic model of GC with the participation of serum indicators may be more convenient for clinical use.

Interleukin-6 (IL-6), a 21–28 kDa 4-helix bundle glycoprotein consisting of 184 amino acids, is a cytokine produced by a variety of normal cells such as monocytes, macrophages, and epithelial cells and plays an extremely important role in normal physiological activities such as inflammation, immunity, reproduction, metabolism, and angiogenesis.<sup>5–8</sup> Tumor cells can either produce IL-6 or interact with IL-6 in the microenvironment by expressing IL-6 complex receptors,<sup>9</sup> thus contributing to tumor cell occurrence, migration and invasion, cell cycle arrest, evasion of apoptosis, and cell death.<sup>9</sup>

Current studies on IL-6 have focused on colorectal cancer, breast cancer, myeloma, and so on. Eldesoky *et al.*<sup>10</sup> found that IL-6 were closely associated with stage and metastasis in patients with colorectal carcinomatosis. Shinriki *et al.*<sup>11</sup> found that IL-6 promotes lymph node metastasis in oral mucosal squamous cell carcinoma.

In GC, it has been demonstrated that sustained high level of IL-6 expression is associated with the maintenance of a state of chronic inflammation of

the digestive tract, gastritis associated with *Helicobacter pylori* infection and gastric carcinogenesis.<sup>12–15</sup> Su *et al.*<sup>16</sup> found that IL-6 may activate and enrich macrophages and promote proliferation and invasion of GC.<sup>17,18</sup> Meanwhile, IL-6 secreted by tumor-associated fibroblasts may activate the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathway or activate the Phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway by inducing Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform (PIK3-R3) expression after downregulating miR-152, thus promoting proliferation, migration, invasion, Epithelial-Mesenchymal Transition (EMT) transformation, and metastasis of GC.<sup>19,20</sup> Ham *et al.*<sup>21</sup> found that GC resistance to chemotherapeutic agents was also associated with high levels of IL-6 by cancer-associated fibroblasts. Laurino *et al.*<sup>22</sup> found that high levels of IL-6 are closely associated with the development of cisplatin resistance. IL-6 can promote the survival, proliferation, and invasive capabilities of GC cells by activating the STAT3 signaling pathway. The IL-6/STAT3 axis affects the sensitivity of GC cells to cisplatin through molecular mechanisms such as suppressing the expression of apoptosis-regulating factors, promoting the expression of DNA repair-related genes, altering the expression of cell cycle-related genes, and regulating changes in stem cell markers.

### Objectives

Although experiments have confirmed the possible role of IL-6 in gastric carcinogenesis and development, the value of IL-6 in predicting patient prognosis remains unclear, because no studies have included IL-6 into the clinical prognostic model of GC. The clinical application potential of IL-6 has not been fully evaluated and exploited. We aimed to construct a prognostic model with high calibration and better distinction than classical TNM staging. First, clinicopathological characteristics recorded in the database were analyzed to determine whether there were differences between IL-6 HIGH group and IL-6 LOW group. Then, the association between the two groups and tumor marker levels was clarified, and the K-M curves of 3- and 5-year were plotted with log-rank test. Afterward, we conducted univariate and multivariate analysis and a predicting nomogram. Significantly, C-index and calibration were used to evaluate the value of nomogram in predicting prognosis of GC patients.

## Methods

### *Study design and data selection*

The reporting of this study conforms to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.<sup>23</sup> Patients with GC who were admitted and treated at the Department of Gastrointestinal Surgery, West China Hospital of Sichuan University from 1 January 2013 to 31 December 2017, were included in this study. Data included in this study are kept in the registration database of the Center of Gastrointestinal Surgery.

### *Inclusion and exclusion criteria*

Patients with GC who were admitted and treated at the Department of Gastrointestinal Surgery, West China Hospital of Sichuan University from 1 January 2013 to 31 December 2017, were included in this study. Inclusion criteria: (1) 18 years  $\leq$  age  $\leq$  80 years; (2) ECOG 0–2 points; (3) no neoadjuvant treatment before operation; (4) postoperative pathology confirmed as GC or adenocarcinoma of the esophagogastric junction; (5) radical laparoscopic or open surgery; (6) distal, proximal or total gastrectomy; and (7) the relevant data were complete and followed up.

Exclusion criteria: complicated with (1) other malignant tumors; (2) chronic inflammatory diseases; (3) infectious diseases; (4) autoimmune diseases; (5) receiving hormone or immunosuppressive therapy in the near future; and (6) incomplete survival data.

### *Data collection and outcomes*

The indicators included sex, age, differentiation, Lauren's classification, TNM stage, tumor maximum diameter, Her2 expression, tumor deposits, vascular invasion, nerve invasion, lymphatic invasion, and IL-6 levels.

Determination of inflammatory factors and tumor markers in serum: Fasting blood (3 ml) was collected at 7:00 on the second day after admission. Serum samples were prepared by differential centrifugation, and the levels of CA724, CA125, CA199, CA153, carcinoembryonic antigen (CEA), Alpha-fetoprotein (AFP), and IL-6 in serum samples were measured by

electrochemiluminescence immunoassay. This was measured by the Department of Laboratory, West China Hospital, Sichuan University.

The pathological features (differentiation, Lauren's classification, TNM stage, tumor maximum diameter, Her2 expression, tumor deposits, vascular invasion, nerve invasion, and lymphatic invasion) were determined according to the post-operative pathological report. This was determined by the Department of Pathology, West China Hospital, Sichuan University, in accordance with the 15th edition of the Japanese Gastric Cancer Management Protocol.

The follow-up information of the patients was collected by the gastroenterologist and volunteers of Sichuan University in a variety of ways twice a year.

### *Statistical analysis*

This is a retrospective study to investigate the correlation between IL-6 and other clinicopathological data and to assess whether IL-6 can be used as an independent prognostic factor for patients with GC. The next was to construct a new clinical prognostic evaluation model for guiding the clinical diagnosis and treatment of GC.

First, we analyzed the correlation between IL-6 and tumor markers. The cutoff values of IL-6 were determined by the maximum selected rank statistic to divide patients into two groups with high and low IL-6 expression, and then, the 3- and 5-year survival rates were calculated and K-M curves were plotted for the two groups. SPSS software developed by IBM Corporation was used to analyze the relationship between the expression of serum IL-6 and other related clinicopathological data in patients with GC. The included clinicopathological data were subjected to univariate analysis, and then, the statistically significant clinical indicators were subjected to multivariate analysis. Nomographs of the 3- and 5-year survival of patients with GC were drawn, and the internal verification of the model was carried out by the bootstrap self-sampling method. Finally, the C-index of the new prognostic model was calculated using R to determine the differentiation of the model and to compare with the TNM staging system to evaluate the clinical predictive value of the new prediction model.

For the quantitative data, if it conformed to a normal distribution, the mean  $\pm$  standard deviation was used for description and the Pearson test was used for correlation analysis; otherwise, the median (interquartile range) and the Spearman test was used. The Chi-square test was used for the comparison. For count data, the *t* test was used for intergroup comparisons conforming to a normal distribution; otherwise, the nonparametric test (independent samples Mann–Whitney *U* test) was used. Differences were considered statistically significant if the two-sided *p* value was less than 0.05.

The statistical process is completed by SPSS Statistics 21 developed by IBM Corporation or R 4.0.3 statistical software which is an open-source statistical software, in which the description of baseline information is completed by SPSS, and the cutoff value of continuous data is determined by the *surv\_cutpoint* function in the *survminer* package, which determines the cutoff value according to the maximum selection rank statistics. The survival analysis of the Cox proportional risk model adopted the *coxph* function. Nomograph and the calibration diagram were drawn using the *rms* package. The model was compared using the *surv-comp* package.

## Results

### *The relationship between the IL-6 and tumor markers*

The serum levels of CA724, CA125, CA199, CA153, CEA, AFP, and IL-6 in all patients were tested for normality. The above data were not in

accordance with a normal distribution. Therefore, the Spearman correlation coefficient between IL-6 and other tumor markers was calculated. It was found that only the level of CEA in serum was positively correlated with the level of IL-6 (Spearman correlation coefficient = 0.132, *p* = 0.037). Serum IL-6 levels were not correlated with CA724 (Spearman correlation coefficient = 0.057, *p* = 0.370), CA125 (Spearman correlation coefficient = -0.043, *p* = 0.501), CA199 (Spearman correlation coefficient = -0.016, *p* = 0.796), CA153 (Spearman correlation coefficient = 0.093, *p* = 0.142), or AFP (Spearman correlation coefficient = 0.014, *p* = 0.820) (Table 1).

### *The cutoff value of serum IL-6*

Using the *surv\_cutpoint* function, the cutoff value of the serum IL-6 level was 5.51 pg/ml (Figure 1 for details).

### *The relationship between IL-6 and other pathological data*

The average tumor size of GC was 4.00 (2.00–5.00 cm) in the IL-6 low expression group and 5.00 (4.00–6.00 cm) in the IL-6 high expression group (*p* = 0.000). There was no difference in the distribution of other continuous variables between the two groups of low and high expression of IL-6 (Table 2).

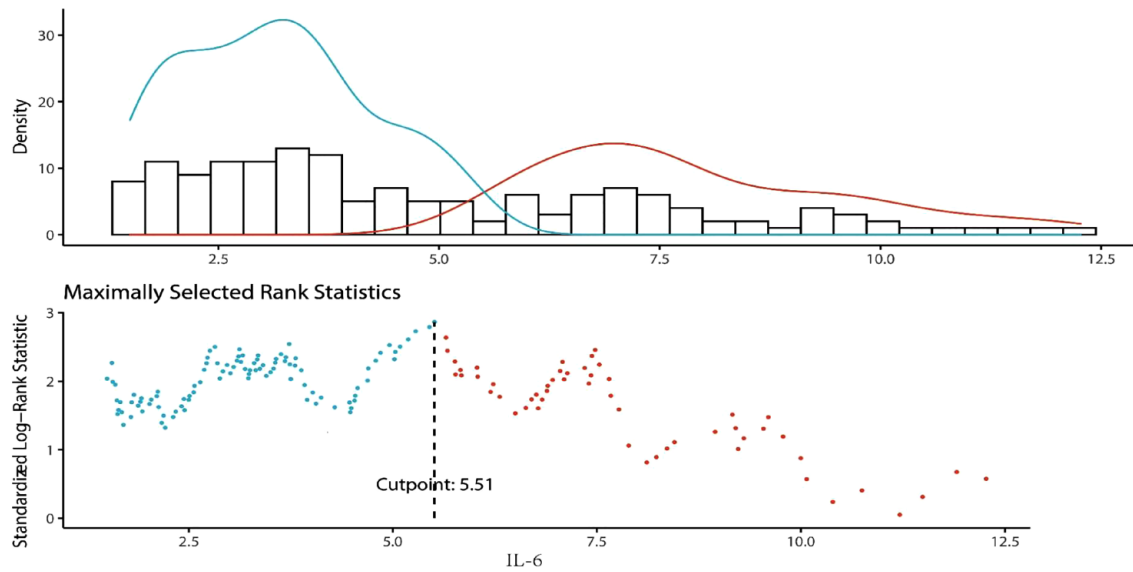
Among the categorical variables, only average tumor size of GC (*p* = 0.000) and nerve invasion (*p* = 0.018) were statistically significant. In the IL-6 low expression group, 93 cases were nerve invasion positive and 72 cases were negative. In

**Table 1.** Analysis of the correlation between IL-6 and other tumor markers.

Variable	Tumor markers	Spearman correlation coefficient	<i>p</i> Value
IL-6	CA724	0.057	0.370
	CA125	-0.043	0.501
	CA199	-0.016	0.796
	CA153	0.093	0.142
	CEA	0.132	<b>0.037</b>
	AFP	0.014	0.820

CEA, carcinoembryonic antigen; IL-6, interleukin-6.

The *p* value less than 0.05 indicates the difference is statistically significant and should be marked in bold.



**Figure 1.** Cutoff value of IL-6 in 249 GC patients.  
GC, Gastric cancer; IL-6, interleukin-6.

**Table 2.** Differences in continuous variables between patients in the IL-6 high group and IL-6 low group.

Variable	Overall	IL-6 low expression group	IL-6 high expression group	<i>p</i> Value
Age (year)	60.00 (50.50–66.00)	58.00 (49.00–65.50)	61.00 (52.25–66.00)	0.16
Height (cm)	162.00 (158.00–167.00)	161.00 (158.00–167.00)	162.00 (159.25–168.00)	0.287
Body weight (kg)	59.00 (53.00–65.00)	58.50 (53.50–65.00)	60.00 (51.25–65.75)	0.86
BMI	23.00 (20.00–25.00)	23.00 (20.00–25.00)	23.00 (19.25–25.00)	0.717
Tumor maximum diameter (cm) <sup>w</sup>	4.00 (3.00–5.00)	4.00 (2.00–5.00)	5.00 (4.00–6.00)	<b>0.00</b>
Number of positive lymph nodes	2.00 (0.00–6.00)	1.00 (0.00–5.00)	2.00 (0.00–8.00)	0.481

IL-6, interleukin-6.  
The *p* value less than 0.05 indicates the difference is statistically significant and should be marked in bold.

the IL-6 high expression group, 34 cases were positive and 50 cases were negative (Table 3).

#### *Survival prognosis of patients with high IL-6 expression and low IL-6 expression*

5.51 pg/ml was used to divide the patients into an IL-6 high group and an IL-6 low group. The mean survival time was 54.9 months (95% CI: 51.7–58.2 months), 84 patients in the IL-6 high expression group had an average survival time of

47.8 months (95% CI: 42.1–53.4 months), and 165 patients in the IL-6 low expression group had an average survival time of 57.9 months (95% CI: 54.1–61.7 months). The 3- and 5-year survival rates of patients with low expression of IL-6 were 85.4% and 84.0%, respectively. The 3- and 5-year survival rates of patients with high expression of IL-6 were 65.4% and 55.2%, respectively. The survival prognosis of the two groups was calculated by a K-M curve ( $p=0.0046$ ) (Figure 2).

**Table 3.** Differences in categorical variables between patients in the IL-6 high group and IL-6 low group.

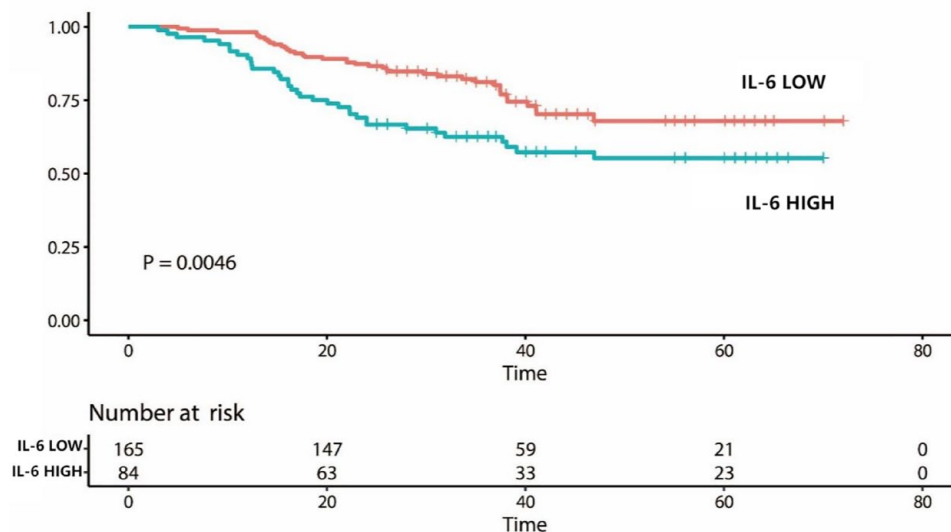
Variable	IL-6 low expression group (165 cases)	IL-6 high expression group (84 cases)	p Value
Gender			
Male	108	65	0.053
Female	57	19	
Age			
<60	87	37	0.195
≥60	78	47	
Differentiation			
High	3	0	0.457
Middle	24	13	
Low	138	71	
Lauren's classification			
Intestinal	44	25	0.467
Diffusion	78	43	
Mixed	43	16	
T stage			
T1	44	18	0.590
T2	28	18	
T3	43	17	
T4a	46	28	
T4b	4	3	
N stage			
N0	65	26	0.734
N1	24	14	
N2	31	16	
N3a	27	15	
N3b	18	9	
M stage			
M0	162	80	0.184
M1	3	4	

(Continued)

**Table 3.** (Continued)

Variable	IL-6 low expression group (165 cases)	IL-6 high expression group (84 cases)	<i>p</i> Value
Tumor maximum diameter			
<5 cm	114	34	<b>0.000</b>
≥5 cm	51	50	
pTNM stage			
I A	30	13	0.704
I B	19	8	
II A	26	11	
II B	22	12	
III A	19	10	
III B	17	14	
III C	29	12	
IV	3	4	
Her2 expression			
Negative	96	51	0.135
+	48	15	
++	17	15	
+++	4	3	
Tumor deposits			
No	150	75	0.682
Yes	15	9	
Vascular invasion			
No	148	75	0.920
Yes	17	9	
Nerve invasion			
No	72	50	<b>0.018</b>
Yes	93	34	
Lymphatic invasion			
No	124	71	0.090
Yes	41	13	

The *p* value less than 0.05 indicates the difference is statistically significant and should be marked in bold.



**Figure 2.** Prognosis in the IL-6 high group and IL-6 low group. IL-6, interleukin-6.

#### Univariate analysis and multivariate analysis

Univariate analysis showed that IL-6 (<5.51 and  $\geq 5.51$  pg/ml,  $p = 0.005$ ), maximum diameter of GC (<5 and  $\geq 5$  cm,  $p = 0.006$ ), T stage ( $p = 0.000$ ), N stage ( $p = 0.000$ ), M stage ( $p = 0.015$ ), TNM stage ( $p = 0.000$ ), and GC nodules ( $p \leq 0.014$ ) were correlated with survival (Table 4).

The statistically significant variables in univariate analysis were included in the multivariate analysis. Although there was a statistical correlation between TNM stage and T stage, N stage, and M stage single substages and prognosis of patients with GC, because of the repetition of the information they covered, we only included T stage, N stage, and M stage single substages in the multivariate analysis. The differences in IL-6 (<5.51 and  $\geq 5.51$  pg/ml) (HR: 1.665, 95% CI: 1.026–2.703,  $p = 0.039$ ), N stage (HR: 1.336, 95% CI: 1.106–1.615,  $p = 0.003$ ), and T stage (HR: 1.268, 95% CI: 0.998–1.611,  $p = 0.052$ ) were statistically significant (Table 4).

#### Evaluation of model differentiation and drawing of line diagram

According to the results of multivariate analysis, clinical model diagrams of IL-6, T stage, and N stage were drawn. The total score of the line chart was 220 points. Compared with the low-level

expression of IL-6, the IL-6 score of high level expression was higher (Figure 3).

The C-index of clinical models of IL-6, T stage and N stage was calculated by the coxph function in R language survival, which was equal to 0.71.

#### Drawing of model calibration diagram

To evaluate the internal validity of the new line diagram, the bootstrap method is used to complete the internal verification. The calibration diagram is drawn by 1000 repeated bootstrap sample corrections in the dataset. The transverse coordinates represent the 3- and 5-year survival probabilities predicted by 1000 resampled bootstrap samples, and the vertical coordinates represent the actual 3- and 5-year survival rates of the patients obtained by Cox proportional risk analysis. The ideal reference line, that is, the perfect match between the prediction probability and the observation probability, is represented by the diagonal line of the dotted line. These six points represent the predicted and observed survival probabilities, and each of the six groups is internally verified. Because the intersection line and the dotted line reference line basically coincide, this study can draw the conclusion that the predicted overall survival rate is not significantly different from that of the observed patients, and the IL-6, T stage, and N stage models evaluate the survival performance of the patients for 3 and 5 years (Figures 4 and 5).



**Table 4.** Univariate and multivariate analysis of clinicopathological data in patients with GC.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> Value	HR	95% CI	<i>p</i> Value
Gender	0.921	0.559–1.516	0.745			
Age (<60 and ≥60 years)	1.521	0.958–2.414	0.075			
Smoking	0.878	0.549–1.405	0.589			
Drinking alcohol	0.828	0.476–1.442	0.506			
BMI	1.015	0.949–1.086	0.656			
IL-6 (<5.51 and ≥5.51 ng/ml)	1.919	1.214–3.033	<b>0.006</b>	1.665	1.026–2.703	<b>0.039</b>
Maximum diameter of tumor (<5 and ≤5 cm)	2.555	1.602–4.076	<b>0.000</b>	1.545	0.925–2.581	0.096
Tumor differentiation degree	1.141	0.622–2.096	0.670			
Lauren typing	1.030	0.754–1.406	0.855			
T stage	1.604	1.300–1.978	<b>0.000</b>	1.268	0.998–1.611	<b>0.052</b>
N stage	1.543	1.308–1.820	<b>0.000</b>	1.336	1.106–1.615	<b>0.003</b>
M stage	3.075	1.240–7.624	<b>0.015</b>	1.733	0.687–4.371	0.244
TNM stage	1.369	1.219–1.536	<b>0.000</b>			
Tumor Her2 expression level	1.094	0.831–1.442	0.522			
Cancer node	2.170	1.168–4.031	<b>0.014</b>	1.376	0.792–2.581	0.325
Vascular invasion	1.650	0.846–3.220	0.142			
Lymphatic invasion	1.127	0.624–2.034	0.692			
Nerve invasion	1.219	0.763–1.948	0.408			

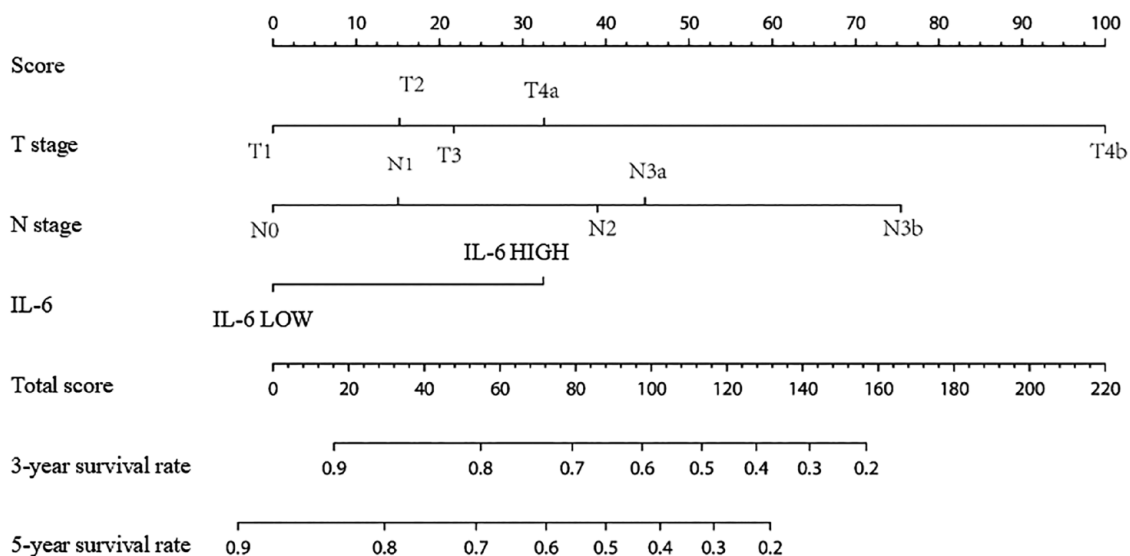
GC, gastric cancer; IL-6, interleukin-6.  
The *p* value less than 0.05 indicates the difference is statistically significant and should be marked in bold.

### Comparison between new model and classical TNM staging

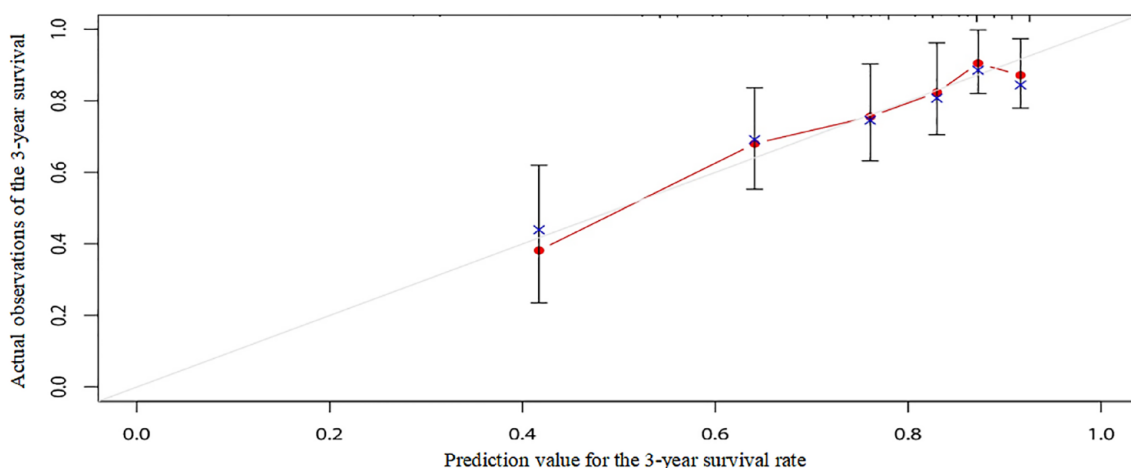
In this study, T staging, N staging, and M staging were used for multivariate analysis, and the C-index of classical TNM staging was calculated. It was found that the C-index of TNM staging was equal to 0.68. The difference between the new model and the classical TNM staging was compared by using *survcomp* in R. The results showed that the *p* value of the two models was equal to 0.08.

### Discussion

IL-6 is a kind of multieffect cytokine that is not only indispensable in many important normal physiological activities but is also considered to be closely related to the occurrence and development of inflammation and cancer. IL-6 mainly plays a role through the IL-6/STAT3 signaling pathway, activating the signaling pathway to trigger cascade reactions at multiple downstream targets.



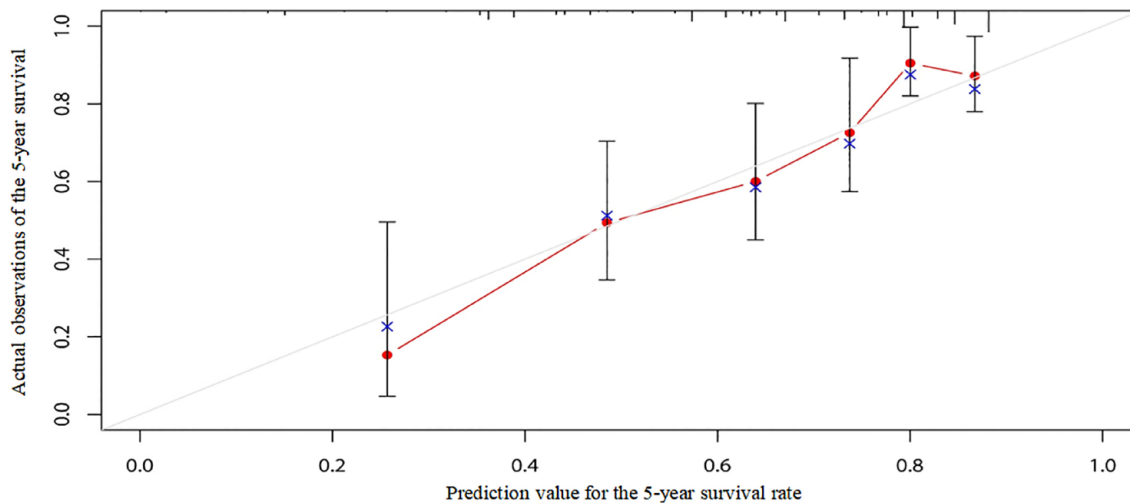
**Figure 3.** Nomograph of the model composed of T stage, N stage, and IL-6. IL-6, interleukin-6.



**Figure 4.** Calibration for predicting the 3-year survival rate of patients with GC by a newly constructed model. GC, gastric cancer.

CEA is a classical tumor marker. The preoperative CEA in patients with GC can better predict the prognosis of patients.<sup>24</sup> In addition, a recently published large cohort study confirmed that elevated CEA levels are independent prognostic factors for the recurrence of GC.<sup>25</sup> In their study, it was found that IL-6 and CEA in the serum of patients with GC increased synchronously. For the relationship between IL-6 and CEA, this has not been confirmed in GC patients, but similar results have now been obtained in the colorectal cancer population. Nakagoe *et al.*<sup>26</sup> published a

study stating that there was a significant correlation between the high level of serum IL-6 and the high expression of serum CEA in patients with colorectal cancer before surgery. In addition, Belluco *et al.*<sup>27</sup> confirmed that the expression of IL-6 and CEA in serum was related to the stage of colorectal cancer, and the high expression of IL-6 and CEA levels indicated that the stage was late. Although the possible molecular mechanism between CEA and IL-6 is unknown, considering that CEA is a recognized classical tumor marker of digestive tract tumors, the findings of this study



**Figure 5.** Calibration for predicting the 5-year survival rate of patients with GC by a newly constructed model. GC, gastric cancer.

may confirm the role of IL-6 in GC, and IL-6 may become an important index to evaluate the prognosis of patients with GC.

This study did not serve as the cutoff of serum IL-6 in GC patients according to the laboratory-recommended standard, as there is still controversy about the truncation of IL-6 levels in patients with GC. A study published in 2005 reported that the cutoff value of IL-6 in the serum of patients with GC was 1.97 pg/ml, where sensitivity is 81.8% and specificity is 66.7%. Another study from South Korea whose sensitivity is 85.7% reported that the best diagnostic threshold of serum IL-6 in patients with GC was 6.77 pg/ml.<sup>28</sup> In this study, the cutoff value of IL-6 was calculated as 5.51 pg/ml, and all GC patients were divided into an IL-6 high expression group and an IL-6 low expression group. The K-M curve showed that there was almost no overlap between two groups, and the survival difference between the two groups was significant ( $p < 0.05$ ). Because the prognosis of patients with different stages of GC is quite different, to evaluate more accurately whether IL-6 can play a good role in distinguishing prognosis for patients with GC of each stage, the data of patients with GC of each stage are distinguished. The study found that IL-6 levels may correspond to prognosis for the two groups of patients, and the prognosis of patients with high IL-6 expression levels was poor. For IIIA and IIIB patients, although there was no significant difference in the prognosis of patients with different IL-6 expression levels after drawing the K-M curves, the

two curves had no obvious intersection in the early and middle phases of the study and showed that the survival of patients in the low IL-6 group was better than that in the high IL-6 group. The survival of the two groups did not show a significant difference, which may be due to the small sample size. For stage IIIC GC, the prognosis of patients with high levels of IL-6 was significantly worse than patients with low levels of IL-6 expression. As the study continues and more cases are included, the prognostic value of IL-6 may be more accurately assessed. In univariate analysis, it was found that the prognosis of patients was related to IL-6 level, maximum diameter of tumor, T stage, N stage, M stage, TNM stage, and so on. Further multivariate analysis showed that only T stage, N stage, and IL-6 level were related to the survival of patients with GC, indicating that these three indexes are independent prognostic factors in patients with GC and have an important impact on the survival and prognosis of patients with GC. Existing basic studies have proven that a high level of IL-6 expression is closely related to the poor prognosis of patients with GC. Although there are few studies on IL-6 and GC, it is not difficult to see that IL-6 is closely related to the occurrence, proliferation, and migration of GC from the perspective of both basic experiments and clinical practice.

In this study, T stage, N stage, and serum IL-6 level, which were statistically significant in multivariate analysis, were used to evaluate the prognosis of patients with GC. After internal

verification, it was found that the C-index of the model was 0.71, indicating that the model had good discrimination in the current data set. Next, the study continued to use the bootstrap resampling method to draw calibration maps and found that the predicted value of the model was basically consistent with the actual survival value of the patients, indicating that the new model could truly reflect the true prognosis of patients with GC, regardless of whether the 3-year survival rate or the 5-year survival rate was predicted.

In this study, M stage, referring to distant metastasis of GC cells, was not an independent prognostic factor in patients with GC. In TNM stage, M stage is the most important factor affecting the prognosis of patients with GC. Once distant metastasis of GC is found, the clinical stage directly rises to stage IV regardless of the level of T stage and N stage. The reason why M stage was excluded after multivariate Cox survival analysis may be due to the small number of distant metastases of GC in all patients. It is believed that with the expansion of the study sample, the status of M staging in evaluating the prognosis of GC patients will be reflected.

It is sometimes very difficult to determine whether patients have distant metastasis in the clinical diagnose. For early abdominal metastasis or liver metastasis, it is often difficult to find in simple imaging. Some patients need surgical exploration to determine the staging of GC. More easily quantitative serum IL-6 level can be included in the prognosis model of GC, which reduces the difficulty of staging GC and may make patients free from exploratory surgery. Through calculation, it is found that the C-index of the new model constructed with the IL-6 index is 0.71, while that of the classical TNM stage C-index is 0.68. Then, using survcomp in R to compare the discrimination degree between the new model and the classical TNM stage, it is found that the *p* value of the two models is equal to 0.08. Although there is no significant difference, the division degree of the new model has shown a trend better than that of the classical TNM stage. There was no significant difference in the *p* value, which may be due to the small sample size. More patients will be included in the follow-up study to further evaluate the prognostic effectiveness of the serum IL-6 level.

This study has some limitations. First, the study was a retrospective study, which is easily affected by many confounding factors. Second, the number of cases included in the study was too small. Finally, the IL-6 included in the study was preoperative measured and postoperative dynamic measurement data were missing for analysis.

### Conclusion

Collectively, our study found that there was a positive correlation between IL-6 and serum CEA levels. Further, N stage, M stage, and IL-6 were identified as independent factors affecting the overall survival of patients with GC. Based on these factors, we built a nomogram that can be used to assess the prognosis of individual patients with GC at different sites. Our model has better predictive efficacy than the classical TNM staging system and can help medical workers to individualize the care of patients with GC.

### Declarations

#### *Ethics approval and consent to participate*

The study was reviewed and approved by the Research Ethics Committee of West China Hospital and Surgical Gastric Cancer Patient Registry. As the study was performed retrospectively, the Research Ethics Committee of West China Hospital permitted a waiver of informed consent [IRB No. 2014(215)].

#### *Consent for publication*

Not applicable.

#### *Author contributions*

**Panping Liang:** Methodology; Software; Visualization; Writing – original draft; Writing – review & editing.

**Yuexin Zhang:** Data curation.

**Tianyuchen Jiang:** Data curation.

**Tao Jin:** Data curation.

**Zhengwen Chen:** Data curation.

**Zedong Li:** Resources.

**Zehua Chen:** Data curation; Investigation.

**Fengjun He:** Data curation.

**Jiankun Hu:** Funding acquisition.

**Kun Yang:** Funding acquisition; Methodology; Supervision; Validation.

### Acknowledgements

None.

### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Domestic support from (1) Foundation of Science and Technology Department of Sichuan Province (2023YFS0060); (2) 1. 3. 5 projects for disciplines of excellence, West China Hospital, Sichuan University (No. ZYJC21006).


### Competing interests

The authors declare that there is no conflict of interest.

### Availability of data and materials

The data and materials of this article could be available by contacting the corresponding author.

### ORCID iD

Kun Yang  <https://orcid.org/0000-0002-8891-5736>

### References

- Chen X-Z, Zhang W-H and Hu J-K. A difficulty in improving population survival outcome of gastric cancer in mainland China: low proportion of early diseases. *Med Oncol* 2014; 31: 315.
- Digkila A and Wagner AD. Advanced gastric cancer: current treatment landscape and future perspectives. *World J Gastroenterol* 2016; 22: 2403–2414.
- Wei W, Zeng H, Zheng R, *et al.* Cancer registration in China and its role in cancer prevention and control. *Lancet Oncol* 2020; 21: e342–e349.
- Wittekind C. The development of the TNM classification of gastric cancer. *Pathol Int* 2015; 65: 399–403.
- Tanaka T, Narazaki M and Kishimoto T. IL-6 in Inflammation, immunity, and disease. *Cold Spring Harbor Perspect Biol* 2014; 6: a016295.
- Eskiler GG, Bezdegumeli E, Ozman Z, *et al.* IL-6 mediated JAK/STAT3 signaling pathway in cancer patients with cachexia. *Bratisl Lek Listy* 2019; 120: 819–826.
- Guo Y, Xu F, Lu T, *et al.* Interleukin-6 signaling pathway in targeted therapy for cancer. *Cancer Treat Rev* 2012; 38: 904–910.
- Vainer N, Dehlendorff C and Johansen JS. Systematic literature review of IL-6 as a biomarker or treatment target in patients with gastric, bile duct, pancreatic and colorectal cancer. *Oncotarget* 2018; 9: 29820–29841.
- Barre B, Vigneron A, Perkins N, *et al.* The STAT3 oncogene as a predictive marker of drug resistance. *Trends Mol Med* 2007; 13: 4–11.
- Eldesoky A, Shouma A, Mosaad Y, *et al.* Clinical relevance of serum vascular endothelial growth factor and interleukin-6 in patients with colorectal cancer. *Saudi J Gastroenterol* 2011; 17: 170–173.
- Shinriki S, Jono H, Ueda M, *et al.* Interleukin-6 signalling regulates vascular endothelial growth factor-C synthesis and lymphangiogenesis in human oral squamous cell carcinoma. *J Pathol* 2011; 225: 142–150.
- Atreya R, Mudter J, Finotto S, *et al.* Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn disease and experimental colitis in vivo. *Nat Med* 2000; 6: 583–588.
- Xu S, Wu X, Zhang X, *et al.* CagA orchestrates eEF1A1 and PKC delta to induce interleukin-6 expression in *Helicobacter pylori*-infected gastric epithelial cells. *Gut Pathog* 2020; 12: 31.
- Piao J-Y, Lee HG, Kim S-J, *et al.* Helicobacter pylori activates IL-6-STAT3 signaling in human gastric cancer cells: potential roles for reactive oxygen species. *Helicobacter* 2016; 21: 405–416.
- Crabtree JE, Shallcross TM, Heatley RV, *et al.* Mucosal tumor-necrosis-factor-alpha and interleukin-6 in patients with *Helicobacter pylori*-associated gastritis. *Gut* 1991; 32: 1473–1477.
- Su C-Y, Fu X-L, Duan W, *et al.* High density of CD68<sup>+</sup> tumor-associated macrophages predicts a poor prognosis in gastric cancer mediated by IL-6 expression. *Oncol Lett* 2018; 15: 6217–6224.
- Fu X-L, Duan W, Su C-Y, *et al.* Interleukin 6 induces M2 macrophage differentiation by STAT3 activation that correlates with gastric cancer progression. *Cancer Immunol Immunother* 2017; 66: 1597–1608.
- Kawada M, Inoue H, Ohba S-I, *et al.* Stromal cells positively and negatively modulate the growth of cancer cells: stimulation via the PGE2-TNF alpha-IL-6 pathway and inhibition via secreted GAPDH-E-cadherin interaction. *PLoS One* 2015; 10: e0119415.

19. Sun J and Fu L. IL-6 promotes gastric cancer cell proliferation and EMT through regulating miR-152/PIK3R3 pathway. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2017; 42: 1241–1247.
20. Wu X, Tao P, Zhou Q, *et al.* IL-6 secreted by cancer-associated fibroblasts promotes epithelial-mesenchymal transition and metastasis of gastric cancer via JAK2/STAT3 signaling pathway. *Oncotarget* 2017; 8: 20741–20750.
21. Ham I-H, Oh HJ, Jin H, *et al.* Targeting interleukin-6 as a strategy to overcome stroma-induced resistance to chemotherapy in gastric cancer. *Mol Cancer* 2019; 18: 68.
22. Laurino S, Brancaccio M, Angrisano T, *et al.* Role of IL-6/STAT3 axis in resistance to cisplatin in gastric cancers. *Biomedicines* 2023; 11: 694.
23. Collins GS, Reitsma JB, Altman DG, *et al.* Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med* 2015; 162: 55–63.
24. Nakane Y, Okamura S, Akehira K, *et al.* Correlation of preoperative carcinoembryonic antigen levels and prognosis of gastric-cancer patients. *Cancer* 1994; 73: 2703–2708.
25. Cai Q, Zhou W and Li J, *et al.* Association of preoperative serum carcinoembryonic antigen and gastric cancer recurrence: a large cohort study. *J Cancer* 2021; 12: 397–403.
26. Nakagoe T, Tsuji T, Sawai T, *et al.* The relationship between circulating interleukin-6 and carcinoembryonic antigen in patients with colorectal cancer. *Anticancer Res* 2003; 23: 3561–3564.
27. Belluco C, Nitti D, Frantz M, *et al.* Interleukin-6 blood level is associated with circulating carcinoembryonic antigen and prognosis in patients with colorectal cancer. *Ann Surg Oncol* 2000; 7: 133–138.
28. Monastero RN and Pentylala S. Cytokines as biomarkers and their respective clinical cutoff levels. *Int J Inflamm* 2017; 2017: 1–11.