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**Research article** 

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# A novel prognostic model to predict OS and DFS of stage II/III gastric adenocarcinoma patients in China



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### ARTICLE INFO

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### ABSTRACT

*Background:* The prognosis of advanced gastric adenocarcinoma (GAC) after radical gastrectomy varies greatly. We aimed to build and validate a novel individualized nomogram based on inflammation index and tumor markers for patients with stage II/III GAC. *Methods:* A total of 755 individuals with stage II/III GAC who had undergone radical gastrectomy at the First Affiliated Hospital of Zhengzhou University between 2012 and 2017 were included in this retrospective study.

The patients were randomly divided into a training cohort (n = 503) and a validation cohort (n = 252). Univariate and multivariate analyses were used to determine independent prognostic factors of overall survival (OS) and disease-free survival (DFS). A nomogram was developed based on these independent factors. The concordance index (C-index) and calibration curves were used to evaluate the predictive accuracy of the nomogram.

**Results:** Univariate and multivariate analyses demonstrated that older age, poor differentiation, advanced stage, elevated neutrophil-to-lymphocyte ratio (NLR), lower hemoglobin, and high carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were significantly associated with lower OS and DFS and were independent prognostic factors in stage II/III GAC. The nomogram developed based on these factors in the training cohort showed excellent calibration and discrimination (OS: C-index = 0.739, 95% CI = 0.706–0.772; DFS: C-index = 0.735, 95% CI = 0.702–0.769). In the internal validation cohort, the nomogram was also well-calibrated for the prediction of OS and DFS; it was superior to the 8th edition UICC/AJCC TNM staging system (for OS: C-index = 0.746 vs. 0.679, respectively; for DFS: C-index = 0.736 vs. 0.675, respectively; P < 0.001). *Conclusion*: The nomogram model could reliably predict OS and DFS in stage II/III gastric cancer patients with radical gastrectomy. It may help physicians make better treatment decisions.

### 1. Introduction

In spite of its declining morbidity and mortality in recent decades, gastric adenocarcinoma (GAC) remains an aggressive cancer with a large number of new cases and deaths worldwide annually [1,2]. In China, GAC, as the most common histological type of gastric cancer (GC), is the second most commonly cancer and the third cause of mortality among all cancer types [3,4]. Currently, gastrectomy with regional lymphadenectomy is the most effective treatment for resectable GAC [5]. However, most patients receive the diagnosis at an advanced stage, and prognosis is dismal, with about 20% patients experiencing early recurrence [6,7].

The tumor–node–metastasis (TNM) staging system by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) is the global standard used for GAC staging. The 8th edition of the staging manual was published in 2016; although the new version has been superior to the 7th edition of the TNM staging system for GAC patients in China, it still has some limitations [8,9]. For example, clinical reality shows that the prognosis may be different even among patients with the same TNM stage. Therefore, it is necessary to integrate multiple prognostic factors to help clinicians with prognostic prediction and individualized treatment decisions [10].

In recent years, the use of nomogram-based clinical models has become increasingly widespread in oncology investigations [11-13].

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Figure 1. Flow diagram of the selected stage II/III GAC patients. GAC, gastric adenocarcinoma.

Owing to its visual and mathematical advantages, this statistical method promotes the probability calculation based on predictor variables and other risk factors. Most previous nomogram models have incorporated tumor depth, histology, differentiation, lymph node metastasis, and other pathologic features [15], but few studies have focused on the combination of pathologic factors, inflammatory indexes, and tumor markers to predict the prognosis and relapse in patients with GAC.

In this study, we developed and validated a novel nomogram that merged multiple risk factors to facilitate the prognosis prediction in stage II/III GAC patients with radical surgical treatment.

### 2. Methods

### 2.1. Patients

In this study, we retrospectively collected information of 876 GAC patients treated with standard curative surgery (R0 resection plus D2 lymphadenectomy) at the First Affiliated Hospital of Zhengzhou University from January 2012 to December 2017. Although 5-fluorouracilbased (5-FU) adjuvant chemotherapy had been routinely recommended by multidisciplinary discussion, some of the patients refused postoperative chemotherapy for various reasons. Staging in all of the patients was performed in accordance with the 8th edition of the UICC/AJCC TNM classification system. The inclusion criteria were as follows: (1) stage II/III gastric adenocarcinoma confirmed by histopathology; (2) R0 resection with D2 lymphadenectomy; (3) no preoperative anticancer treatments; (4) complete clinicopathologic data; (5) no parenteral nutrition, acute inflammation, or significant organ injury within 1 week before surgery. We excluded 58 patients with missing clinicopathologic data, 41 patients undergoing other antitumor treatments, and 22 patients that could not be followed up. Eventually, 755 patients were included in this study and randomly divided into a training cohort and a validation cohort (Figure 1).

All patients provided written informed consent. This study has been reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, which is guided by the international and national ethical requirements for biomedical research.

### 2.2. Hematology examination

In this study, all patients received 1–2 times of hematological examination within one week before surgery. These patients' venous blood under fasting state was collected to detect hematological indicators, such as inflammatory indicators and tumor markers. We collected this data as the baseline data of this study and converted the inflammatory indicators into ratios.

### 2.3. Follow-up

Follow-up data were obtained from inpatient medical records, telephone inquiries, and outpatient visits. The patients were followed up every 3 months during the first 2 years and every 6 months thereafter, or until death. The last follow-up date for all the available patients was October 15, 2020. Local recurrence or distant metastases was diagnosed based on contrast-enhanced computed tomography (CT) scan, gastrofiberscopy with biopsy, bone scan, magnetic response imaging (MRI), or positron emission tomography-computed tomography (PET-CT).

### 2.4. Statistical analysis

Statistical analyses were performed using SPSS Statistics 26.0 (IBM Corporation, USA) and R 4.0.2 (R Core Team, Austria) software. The following end points were assessed: overall survival (OS) and disease-free survival (DFS). OS was defined as the time from the diagnosis to the date of death from any cause or date of the last follow-up. DFS was defined as the time between the date of diagnosis and the date of recorded events of

### Table 1. Characteristics of the training cohort and validation cohort.

Variables	Training cohort $(n = 503)$	Validation cohort $(n = 252)$	P-value	
	No. of patients (%)	No. of patients (%)		
Age (years)			0.815	
$\leq 60$	233 (46.3%)	119 (47.2%)		
> 60	270 (53.7%)	133 (52.3%)		
Gender			0.458	
Female	129 (25.6%)	71 (28.2%)		
Male	374 (74.4%)	181 (71.8%)		
Tumor size (cm)			0.290	
$\leq$ 4.0	270 (53.7%)	125 (49.6%)		
> 4.0	233 (46.3%)	127 (50.4%)		
Tumor location			0.606	
Upper	256 (50.9%)	129 (51.2%)		
Middle	101 (20.1%)	57 (22.6%)		
Lower	146 (29.0%)	66 (26.2%)		
Grade			0.342	
G1–2	138 (27.4%)	61 (24.2%)		
G3	365 (72.6%)	191 (75.8%)		
T stage			0.255	
T1-2	42 (8.4%)	29 (11.5%)		
T3-4	461 (91.6%)	223 (88.5%)		
N stage			0.939	
N0-1	260 (51.7%)	138 (54.8%)		
N2-3	243 (48.3%)	114 (45.2%)		
TNM stage (AJCC, 8th)			0.259	
II (IIA, IIB)	200 (39.8%)	111 (44.0%)		
III (IIIA, IIIB, IIIC)	303 (60.2%)	141 (56.0%)		
Adjuvant chemotherapy			0.421	
Yes	344 (68.4%)	165 (65.5%)		
No	159 (31.6%)	87 (34.5%)		
Leucocytes ( $ imes 10^9$ /L)	5.8 (4.7, 6.9)	5.6 (4.6, 6.8)	0.968	
Monocytes ( $ imes$ 10 <sup>9</sup> /L)	0.48 (0.37, 0.58)	0.46 (0.36, 0.58)	0.280	
Neutrophils ( $ imes$ 10 <sup>9</sup> /L)	3.4 (2.7, 4.3)	3.3 (2.5, 4.2)	0.499	
Lymphocytes ( $ imes$ 10 <sup>9</sup> /L)	1.6 (1.3, 2.0)	1.6 (1.2, 2.0)	0.167	
Platelets ( $ imes 10^9$ /L)	205 (164, 259)	198 (154, 243)	0.097	
Hemoglobin (g/L)	124 (104, 137)	125 (105, 136)	0.529	

Variables are expressed as n (%) or median (upper quartile, lower quartile).

loco-regional recurrence and/or metastasis or the date of the last followup. Receiver operating characteristic (ROC) curves were created to show the nomograms' clinical utility. Variables between two groups were compared using chi-square test or Mann-Whitney *U* test. The end points were analyzed and compared using the Kaplan–Meier method and the log-rank test. Prognostic factors were analyzed by univariate and multivariate Cox proportional-hazards regression analysis. All variables with statistical significance in the univariate analysis by enter method were included in the multivariate analysis and selected by forward stepwise procedure. Nomograms were established based on the selected independent prognostic factors. Discrimination and calibration were evaluated by calibration curves and Harrell's concordance index (C-index). A two-tailed *P*-value <0.05 was considered statistically significant.

### 3. Results

### 3.1. Baseline clinicopathological characteristics and follow-up data

The patients' characteristics in the training cohort and validation cohort are summarized in Table 1. The median age of the patients in both the training and validation cohorts was 60 years (range: 23–80 years), and there were 74.4% and 71.8% men in the training and

Table 2. Univariate and multivariate analyses of prognostic factors for OS.

Variables	Univariate analysis	P-value	Multivariate analysis	P-value	
	HR (95% CI)		HR (95% CI)		
Age (years)					
≤60	reference		reference		
> 60	1.676 (1.241-2.263)	0.001	1.346 (0.985–1.838)	0.048	
Gender					
Female	reference				
Male	0.879 (0.635–1.217)	0.438			
Tumor size (	cm)				
<4.0	reference		reference		
> 4.0	1.446 (1.082–1.932)	0.013	1.072 (0.787-1.460)	0.658	
Grade					
G1-2	reference		reference		
G3	2.452 (1.649-3.648)	< 0.001	2.497 (1.670-3.734)	< 0.001	
T stage					
T1-2	reference		reference		
T2-3	3 948 (1 623–9 603)	0.002	4 043 (1 653–9 890)	0.002	
N stage	01010 (11020 01000)	0.002		0.002	
N0-1	reference		reference		
N2-3	2 816 (2 066–3 839)	< 0.001	2 544 (1 850–3 497)	< 0.001	
Adjuvant che	emotherany	(01001	21011(11000 011)/)	(01001	
Vec	reference				
No	1 005 (0 805 1 400)	0.564			
Hemoglobin	(a/L)	0.304			
<146 5	reference		roforonco		
>146.5	0 326 (0 153_0 694)	0.004	0.370 (0.173_0.791)	0.010	
MIR	0.320 (0.133-0.034)	0.004	0.370 (0.173-0.791)	0.010	
<0.26	reference				
> 0.20	0.002 (0.661, 1.100)	0.401			
> 0.20	0.885 (0.001-1.180)	0.401			
NLR <2.1					
≥3.1 > 2.1	1 (07 (1 205 - 2 262)	0.000	1 458 (1 024 2 056)	0.022	
> 3.1	1.087 (1.205–2.303)	0.002	1.458 (1.034–2.056)	0.032	
WLR	<i>c</i>		C		
<u>≤</u> 4.4	reference	0.01.4	reference	0.440	
> 4.4	1.494 (1.084–2.060)	0.014	0.740 (0.341–1.609)	0.448	
PLR	<u>,</u>				
≤106.3	reference				
>106.3	1.276 (0.933–1.7	0.127			
CA12-5 (U/n	ıL)				
$\leq 13.3$	reference		reference		
> 13.3	1.687 (1.255–2.267)	0.001	1.212 (0.884–1.661)	0.233	
CA 19-9 (U/1	nL)				
$\leq$ 13.9	reference		reference		
>13.9	1.665 (1.246-2.224)	0.001	1.362 (1.012–1.833)	0.041	
CEA (ng/mL)	)				
$\leq$ 5.1	reference		reference		
> 5.1	2.041 (1.498-2.779)	< 0.001	1.678 (1.208–2.330)	0.002	
IID Hanand	notio CI Confidence int	amual .			

validation cohorts, respectively. According to the 8th edition of the UICC/AJCC staging system, in the training cohort, 303 patients were at stage III and 200 patients were at stage II; in the validation cohort, 141 patients were at stage III and 111 patients were at stage II. Most of the patients had poorly differentiated GC (n = 365, 72.6% in the training cohort; n = 191, 75.8% in the validation cohort). A total of 344 (68.4%) patients in the training cohort and 165 (65.5%) patients in the validation cohort received 5-FU-based chemotherapy. The median follow-up duration was 40.0 months (range: 2–100 months). By the last follow-up, 289 patients died, 39 patients developed loco-regional recurrence, 275 patients developed distant metastases, and 19 patients developed both distant metastases and loco-regional recurrence.

Heliyon 8	(2023)	e12403
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Table	3	Univariate	and	multivariate	analyses	of	prognostic	factors	for	DFS
Table	υ.	Univariate	anu	munitivariate	anaryses	U1	prognostic	lactors	101	Dro

Variables	Univariate analysis	P-value	Multivariate analysis	P-value	
( and blob	HR (0E% CI)	1 value	HR (05% CI)	1	
Ago (voors)	HR (95% CI)		HR (95% CI)		
Age (years)	reference		reference		
<u>&gt;60</u>	1 569 (1 167 2 106)	0.002	1 206 (0 886 1 642)	0.225	
>00	1.508 (1.107-2.100)	0.003	1.200 (0.880–1.042)	0.235	
Female					
Female		0.149			
male	0.791 (0.579–1.082)	0.142			
Tuinor size (	(ciii)				
≤4.0 > 4.0	reference	0.005	reference	0.000	
> 4.0	1.512 (1.134–2.015)	0.005	1.182 (0.871–1.603)	0.283	
Grade	<u>,</u>		<u>,</u>		
G1-2	reference	. 0. 0.01	reference	. 0. 001	
G3	2.876 (1.900–4.352)	< 0.001	2.993 (1.967–4.555)	< 0.001	
T stage					
T1-2	reference		reference		
T2-3	5.103 (1.895–13.743)	0.001	5.668 (2.101–15.289)	0.001	
N stage					
N0-1	reference		reference		
N2-3	2.789 (2.054–3.788)	< 0.001	2.500 (1.827-3.420)	< 0.001	
Adjuvant ch	emotherapy				
Yes	reference				
No	1.003 (0.737–1.365)	0.984			
Hemoglobin	(g/L)				
$\leq$ 146.5	reference		reference		
>146.5	0.370 (0.182–0.752)	0.006	0.395 (0.194–0.803)	0.010	
MLR					
$\leq 0.26$	reference				
> 0.26	0.866 (0.650-1.153)	0.324			
NLR					
$\leq$ 3.1	reference		reference		
> 3.1	1.703 (1.224–2.369)	0.002	1.502 (1.075-2.100)	0.017	
WLR					
≤4.4	reference		reference		
>4.4	1.461 (1.063-2.007)	0.019	0.605 (0.263-1.393)	0.238	
PLR					
$\leq 106.3$	reference				
>106.3	1.178 (0.868–1.599)	0.293			
CA12-5 (U/r	nL)				
$\leq 13.3$	reference		reference		
>13.3	1.678 (1.252-2.248)	0.001	1.211 (0.885–1.657)	0.232	
CA19-9 (U/r	nL)				
≤13.9	reference		reference		
>13.9	1.666 (1.251-2.218)	< 0.001	1.399 (1.045–1.872)	0.024	
CEA (ng/mL	)				
≤5.1	reference		reference		
> 5.1	2.026 (1.490-2.754)	< 0.001	1.832 (1.328-2.527)	< 0.001	
HR Hazard	ratio, CI Confidence int	erval.			

The 1-, 2-, and 3-year OS rates in the training cohort were 89.5%,74.6%, and 67.6%, respectively, while the 1-, 2-, and 3-year DFS rates were 86.9%, 72.0%, and 64.2%, respectively. In the validation cohort, the 1-, 2- and 3-year OS rates were 85.7%, 71.8%, and 61.9%, respectively; the 1-, 2-, and 3-year DFS rates were 81.7%, 67.1%, and 59.1%, respectively.

# 3.2. The optimal thresholds for hemoglobin, WLR, MLR, NLR, PLR, CA12-5, CA19-9 and CEA

The most appropriate cut-off values in the ROC curves and the maximum Youden's index were determined in the training cohort. The

optimal cut-off values of variables for predicting the OS and DFS were as follows: 146.5 g/L for hemoglobin, 4.4 for leukocyte-to-lymphocyte ratio (WLR), 0.26 for monocyte-to-lymphocyte ratio (MLR), 3.1 for NLR, 106.3 for platelet-to-lymphocyte ratio (PLR), 13.3 U/mL for cancer antigen 12-5 (CA12-5), 13.9 U/mL for CA19-9, and 5.1 ng/mL for CEA.

# 3.3. Hemoglobin, NLR, CA19-9 and CEA were independent prognostic factors for OS and DFS

Univariate analysis revealed that older age, large tumor size, poor differentiation, advanced T stage, N stage, and overall stage, elevated NLR, lower hemoglobin, and high levels of CA12-5, CA19-9, and CEA were significantly associated with poor survival (Tables 2 and 3). Consistently, the Kaplan–Meier survival analysis revealed that GAC patients with higher NLR, CA19-9, and CEA levels and lower hemoglobin level had poor prognosis (Figure 2).

All the predictors with *P*-value <0.05 in the univariate analysis were included in the multivariate analysis. As shown in Table 2, age, grade, T stage, N stage, hemoglobin, NLR, CA19-9 and CEA were independent indicators of OS. As shown in Table 3, grade, T stage, N stage, hemoglobin, NLR, CA19-9 and CEA were independent indicators of DFS. Although age was associated with DFS in univariate analysis, it lost its significance in the multivariate analysis.

### 3.4. Prognostic nomograms for 1-,2- and 3-year OS and DFS

Based on the results of univariate and multivariate analyses, independent prognostic factors were integrated into the nomograms to predict the 1-, 2-, and 3-year OS and DFS of the training cohort (Figure 3). The C-index of the nomogram for OS was 0.739, which was superior to that of the 8th UICC/AJCC TNM staging system (0.650, P < 0.001). Similarly, the C-index of the nomogram for DFS was 0.735, which was superior to that of the TNM staging system (0.652, P < 0.001). The areas under the time-dependent ROC curves of the nomograms were larger than those of the TNM staging system (Figures 4 and 5). In addition, the 1-, 2-, and 3-year survival probability calibration curves showed that the predicted survival rates of the models were highly consistent with the actual observations (Figure 6A and B). The results indicated an excellent performance of the nomograms in predicting the OS and DFS of the training cohort.

Moreover, the predictive effects of the nomogram models were verified in the internal validation cohort. The C-index of the validation cohort for OS was 0.746, and it was superior to that of the TNM staging system (0.679, P < 0.001). Similarly, the C-index of the nomogram for DFS in the validation cohort was 0.736, which was superior to that of the TNM staging system (0.675, P < 0.001). The calibration curves of the validation cohort showed that the predicted 1-, 2-, and 3-year survival rates of the nomogram models were consistent with the actual observations (Figure 6C and D). Thus, the novel nomogram models constructed in this study were superior to the 8th UICC/AJCC TNM staging system in predicting the 1-, 2-, and 3-year OS and DFS in patients with stage II/III GAC patients undergoing radical surgery.

### 4. Discussion

In this study, we combined the clinicopathologic features, baseline inflammatory parameters, and tumor markers to construct a novel model to predict the prognosis in patients with stage II/III GAC. Our results confirmed the previous findings that age, grade, tumor stage, hemoglobin, NLR, and tumor markers were independent prognostic factors in GC patients. More importantly, we found that the created nomogram prognostic models were superior to the 8th UICC/AJCC TNM staging system in predicting the OS and DFS (OS: C-index = 0.739, 95% CI = 0.706-0.772; DFS: C-index = 0.735, 95% CI = 0.702-0.769) in patients with stage II/III GAC undergoing radical surgery.



Figure 2. Kaplan-Meier survival plots comparing with high and low level of each indicator in the training cohort. (A–D) Survival curves of OS between high and low level of Hemoglobin, NLR, CA19-9 and CEA in stage II/III GAC patients. (E–F) Survival curves of DFS between high and low level of Hemoglobin, NLR, CA19-9 and CEA in stage II/III GAC patients. (E–F) Survival curves of DFS between high and low level of Hemoglobin, NLR, CA19-9 and CEA in stage II/III GAC patients. (Section 2014) (CEA in stage II/III GAC patients. OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; GAC, gastric adenocarcinoma; DFS, disease-free survival.

Previous studies have revealed a strong link between inflammation and cancer, where the systemic inflammatory response plays an important role in carcinogenesis and tumor revascularization [16]. In recent years, it has been recognized that the tumor microenvironment in which inflammatory cells are involved can facilitate tumor initiation, promotion, and progression [17]. Numerous studies have demonstrated that pretreatment counts of peripheral blood neutrophils, lymphocytes, and monocytes were significantly associated with prognosis in different kinds of cancer, including GC [17-19]. The NLR is a highly reproducible, cost-effective, and easily available biomarker, reflecting the systemic chronic inflammatory response. A series of studies have elucidated that high NLR level is associated with poor outcomes in GC and other solid tumors [20]. In the present study, we confirmed the previous findings, showing that the elevated NLR was significantly associated with the shorter OS and DFS in stage II/III GAC patients and that it was also an independent prognostic predictor of GAC.

Anemia is a common symptom in multiple solid tumors [21–23]; bone marrow involvement, tumor-associated blood loss, cytokine-mediated disorder, and iron or folic acid deficiency are the most common causes [24]. Numerous studies have demonstrated that anemia may aggravate tumor hypoxia and reduce tumor oxygenation; thereby, it induces the expression of hypoxia-inducible factor (HIF) family, contributing to

carcinogenesis, tumor progression, and chemo- or radio-resistance via activating target genes, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and erythropoietin [22]. Preoperative anemia has been linked to poor survival in various carcinomas [25-27]. Our results also showed that the lower hemoglobin level was significantly associated with shorter OS and DFS in stage II/III GAC, and it was an independent prognostic factor.

Tumor markers are important tumor-monitoring indicators, and they have widely been used in diagnosis, efficacy evaluation, and tumor monitoring [28-30]. CA12-5, CA19-9, and CEA are frequently used tumor markers, and they are highly expressed in various solid tumors, including GC. A series of studies have explored the prognostic value of the tumor markers and confirmed their important function in prognosis prediction [31-33]. Indeed, high levels of these three tumor markers were significantly associated with peritoneal metastasis and poor survival, and they independently predicted prognosis in GC patients [34-37]. Our results confirmed those from the previous studies and showed that CA12-5, CA19-9, and CEA were independent factors predicting death and progression, and they negatively correlated with survival in stage II/III GC patients.

In the training cohort, age (OS), hemoglobin (OS/DFS), NLR (OS/ DFS), and CA19-9 (OS/DFS) and CEA (OS/DFS) were significant independent prognostic indicators. In addition, older age, poor differentiation and advanced tumor stage were also significantly associated with poor

### А

Points	0	10	20	30	40	50		. 70	. 80		100
Age(years)	< [0]		>60					2			
Grade	<00							5			
T stage	1/2							- /-			3/4
N stage	1/2							2/3			
Hemoglobin(g/l)	0/1	-						_≤ <u>1</u> 4	46.5		
NLR	>146	.5	2	>3.1							
CA199(U/ml)	≤3.1	<u> </u>	13	.9	<b>5</b> 1						
CEA(ng/ml)	$\leq 13.9$	•			≥3.1 _						
<b>Total Points</b>	≤3.1		100	150		· · · ·	50	200	250	400	450
1-year OS rate	0	30	100	150	200		<u> </u>		350	400	450
2-year OS rate					0	0.93		9 0.85		7 0.0 0.	50.4 7
3-year OS rate					0.9	0.	0.8 8 0.7	0.7 0.6	0.50.40	$0.3 \ 0.2 \ 0.1$	0.1

### В



**Figure 3.** Nomogram models constructed based on the training cohort. (A) The momogram for predicting the OS rate at the 1, 2 and 3 year in stage II/III GAC patients. (B) The momogram for predicting the DFS rate at the 1, 2 and 3 year in stage II/III GAC patients. OS, overall survival; DFS, disease-free survival; GAC, gastric adenocarcinoma.

survival and were independent prognostic factors in patients with GC. Thus, we systematically combined these inflammatory indicators, tumor markers, and clinicopathologic features to construct a novel prognostic model. The performance of the nomogram was proven to be excellent, with a good discrimination power and predictive performance (C-index = 0.739). In the internal validation cohort, the nomogram was also well-calibrated for the prediction of OS and DFS, and it was superior to the 8th edition UICC/AJCC TNM staging system (OS: C-index = 0.746 vs. 0.679, DFS: C-index = 0.736 vs. 0.675, P < 0.001).

Some limitations need to be considered when interpreting the results of this study. For example, because this was a retrospective and single-center study, there may be some bias, and there is a lack of external data validation. In addition, all significant variables were included in the multivariate analysis to screen independent factors to build a multi-parameter and multi-dimensional model. Some of these variables have certain commonalities, such as similar clinical values, so there may be collinearity between these variables. And the possible collinearity can affect the *P*-values and the coefficient estimates. Therefore, further multicenter and prospective studies are needed in the future to validate the clinical usage of the nomogram as a prognostic model for GAC patients, and the possible collinearity should be considered and avoided.



**Figure 4.** Time-dependent ROC curves demonstrated the ability of nomogram and TNM stage to predict 1-, 2- and 3-year OS in stage II/III GAC patients. (A–C) Timedependent ROC curves for 1-, 2- and 3-year OS in the training cohort, (D–F) Time-dependent ROC curves for 1-, 2- and 3-year OS in the validation cohort. ROC, receiver operating characteristic curve; AUC, area under the curve; OS, overall survival; GAC, gastric adenocarcinoma.



Figure 5. Time-dependent ROC curves demonstrated the ability of nomogram and TNM stage to predict 1-,2-and 3-year DFS in stage II/III GAC patients. (A–C) Timedependent ROC curves for 1-,2-and 3-year DFS in the training cohort, (D–F) Time-dependent ROC curves for 1-,2-and 3-year DFS in the validation cohort. ROC, receiver operating characteristic curve; AUC, area under the curve; DFS, disease-free survival; GAC, gastric adenocarcinoma.



Figure 6. Calibration plots of nomograms in both training and validation cohorts. (A) and (B) Calibration plots of 1-, 2- and 3-year OS/DFS associated nomogram in training cohort. (C) and (D) Calibration plots of 1-, 2- and 3-year OS/DFS associated nomogram in validation cohort. OS, overall survival; DFS, disease-free survival.

In conclusion, we established and validated a novel model to predict the OS and DFS in stage II/III GAC patients with radical gastrectomy. This model may help physicians to make better treatment decisions in clinical practice.

### Declarations

### Author contribution statement

Jing Li and Hejun Liang: Analyzed and interpreted the data; Wrote the paper. Xiaonan Xue: Performed the experiments; Analyzed and interpreted the data. Can Guo and Pengfei Jiao: Contributed reagents, materials, analysis tools or data. Haifeng Qiu: Conceived and designed the experiments.

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### Data availability statement

Data will be made available on request.

### Declaration of interest's statement

The authors declare no conflict of interest.

#### Additional information

No additional information is available for this paper.

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### J. Li et al.

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