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Retrospective Study

## Prognostic significance of serum inflammation indices for different tumor infiltrative pattern types of gastric cancer

Yu-Fei Wang, Xin Yin, Tian-Yi Fang, Yi-Min Wang, Lei Zhang, Xing-Hai Zhang, Dao-Xu Zhang, Yao Zhang, Xi-Bo Wang, Hao Wang, Ying-Wei Xue

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### Abstract

#### BACKGROUND

Inflammatory indices are considered to be potential prognostic biomarkers for patients with gastric cancer (GC). However, there is no evidence defining the prognostic significance of inflammatory indices for GC with different tumor infiltrative pattern (INF) types.

#### AIM

To evaluate the significance of inflammatory indices and INF types in predicting the prognosis of patients with GC.

#### METHODS

A total of 962 patients who underwent radical gastrectomy were retrospectively selected for this study. Patients were categorized into the expansive growth type (INFa), the intermediate type (INFb), and the infiltrative growth type (INFc) groups. The cutoff values of inflammatory indices were analyzed by receiver operating characteristic curves. The Kaplan-Meier method and log-rank test were used to analyze overall survival (OS). The chi-square test was used to analyze the association between inflammatory indices and clinical characteristics. The independent risk factors for prognosis in each group were analyzed by univariate and multivariate analyses based on logistic regression. Nomogram models were constructed by R studio.

#### RESULTS

The INFc group had the worst OS ( $P < 0.001$ ). The systemic immune-inflammation index ( $P = 0.039$ ) and metastatic lymph node ratio (mLNR) ( $P = 0.003$ ) were

independent risk factors for prognosis in the INFa group. The platelet-lymphocyte ratio (PLR) ( $P = 0.018$ ), age ( $P = 0.026$ ), body mass index ( $P = 0.003$ ), and postsurgical tumor node metastasis (pTNM) stage ( $P < 0.001$ ) were independent risk factors for prognosis in the INFb group. The PLR ( $P = 0.021$ ), pTNM stage ( $P = 0.028$ ), age ( $P = 0.021$ ), and mLNR ( $P = 0.002$ ) were independent risk factors for prognosis in the INFc group. The area under the curve of the nomogram model for predicting 5-year survival in the INFa group, INFb group, and INFc group was 0.787, 0.823, and 0.781, respectively.

### CONCLUSION

The outcome of different INF types GC patients could be assessed by nomograms based on different inflammatory indices and clinicopathologic features.

**Key Words:** Gastric cancer; Tumor infiltrative pattern; Systemic immune-inflammation index; Platelet-lymphocyte ratio; Prognosis; Nomogram

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**Core Tip:** This is a retrospective study to analyze the relationship between peripheral circulating immune cells, inflammatory indices and the tumor infiltrative pattern (INF) types and to verify their ability to evaluate the outcome of gastric cancer (GC) patients. Our results showed that the systemic immune-inflammation index and platelet-lymphocyte ratio were independent prognostic factors for the expansive growth type, the intermediate type, and the infiltrative growth type groups. Based on different inflammatory indicators and clinicopathologic features, the nomogram models can predict the prognosis of different INF types GC patients, which deserve further testing and extension in clinical practice.

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## INTRODUCTION

Gastric cancer (GC) is the sixth most common cancer and the third leading cause of cancer-related death, with more than 865000 deaths every year[1]. To better predict the individual prognosis of GC patients according to tumor biological characteristics, physicians had proposed a variety of classifications[2,3], including the tumor infiltrative pattern (INF) proposed in 1977[4]. The INF types are defined in the Japanese Classification of Gastric Carcinoma[5], which categorizes GC as the expansive growth type (INFa), the intermediate type (INFb), and the infiltrative growth type (INFc). Previous studies have shown that different INF types differ in clinicopathological features and prognosis and can be used as predictors of postoperative recurrence and prognosis in GC patients[6-9]. However, GC is a highly heterogeneous malignant tumor, and the prognosis of patients with the same INF may also show significant differences. Therefore, it is worth further exploring the prognosis of GC patients with different INF types to guide clinical treatment.

With the popularization and development of immunotherapy, the significant role of tumor immunity in malignant tumors has gradually attracted the attention of clinical experts[10]. From 2014 to 2018, the postsurgical tumor node metastasis-immunology (pTNM-I) stage proposed by Galon *et al*[11] and Pagès *et al*[12] was well applied in colon cancer patients. It suggests that the traditional pTNM staging combined with tumor immunity can give more serviceable prognostic and treatment information. Nevertheless, tumor heterogeneity will lead to the restriction of immunohistochemical detection of GC by site selection. As a part of tumor immunity, the peripheral blood immune system also has a significant effect on tumor progression. Our previous studies have confirmed that the inflammatory index plays an important role in the early diagnosis of GC and the evaluation of the outcome of GC patients with different Lauren classification[13,14]. In addition, in liver metastases, different tumor growth pattern subtypes have different levels of lymphocyte infiltration, indicating that they have different immune states in the tumor microenvironment[15]. However, no study has analyzed the relationship between INF and the peripheral blood immune inflammatory response in GC. Therefore, whether the immune difference and prognosis of GC patients with different INF types can be evaluated by peripheral blood inflammatory indices deserves further exploration.

Table 1 Baseline characteristics of the patients

Characteristics	INFa (n = 183)	INFb (n = 331)	INFc (n = 448)
Sex			
Male	133 (72.7)	248 (74.9)	308 (68.8)
Female	50 (27.3)	83 (25.1)	140 (31.2)
Age (yr)	58.81 ± 9.59	59.30 ± 9.73	57.06 ± 10.55
Borrmann type			
0-1	31 (16.9)	51 (15.4)	21 (4.7)
2	62 (33.9)	105 (31.7)	104 (23.2)
3	74 (40.4)	138 (41.7)	242 (54.0)
4-5	16 (8.8)	37 (11.2)	81 (18.1)
Tumor location			
Lower third	156 (85.2)	227 (68.6)	329 (73.4)
Middle third	21 (11.5)	64 (19.3)	75 (16.8)
Upper third	4 (2.2)	33 (10.0)	31 (6.9)
Entire stomach	2 (1.1)	7 (2.1)	13 (2.9)
Tumor size (mm)	44.40 ± 24.85	53.06 ± 25.78	56.31 ± 27.38
pTNM stage			
I	72 (39.3)	70 (21.1)	36 (8.0)
II	60 (32.8)	127 (38.4)	137 (30.6)
III	51 (27.9)	134 (40.5)	275 (61.4)
Histological type			
Well and medium differentiation	112 (61.2)	149 (45.0)	126 (28.1)
Poor differentiation	46 (25.1)	88 (26.6)	207 (46.2)
Others	25 (13.7)	94 (28.4)	115 (25.7)
mLNR	0.09 ± 0.16	0.12 ± 0.17	0.19 ± 0.22
Vascular infiltration			
No	137 (74.9)	231 (69.8)	317 (70.8)
Yes	46 (25.1)	100 (30.2)	131 (29.2)
Nerve infiltration			
No	123 (67.2)	198 (59.8)	251 (56.0)
Yes	60 (32.8)	133 (40.2)	197 (44.0)
Postoperative chemotherapy			
Yes	58 (31.7)	90 (27.2)	167 (37.3)
No	125 (68.3)	241 (72.8)	281 (62.7)

Tumor infiltrative pattern, tumor location, postsurgical tumor node metastasis stage, histological type, mLNR, vascular infiltration and nerve infiltration were according to the postoperative pathology report. INF: Tumor infiltrative pattern; INFa: Expansive growth type; INFb: Intermediate type; INFc: Infiltrative growth type; mLNR: Metastatic lymph node ratio; pTNM: Postsurgical tumor node metastasis.

From September 2012 and July 2015, 962 patients at Harbin Medical University Cancer Hospital were included in the study. The clinical applicability of different inflammatory indices, including the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), was evaluated. At the same time, the difference of peripheral blood immune cells in different INF types was further analyzed. Finally, we constructed predictive models by combining inflammatory indices with the clinicopathological features of patients based on INF types.

Table 2 Chi-square test analysis of the associations between the inflammation index and clinicopathological features

Characteristics	INFa		P value	INFb		P value	INFc		P value
	SII ≤ 523.01 (119)	SII > 523.01 (64)		PLR ≤ 134.02 (195)	PLR > 134.02 (136)		PLR ≤ 134.02 (273)	PLR > 134.02 (175)	
Sex			0.443			0.979			0.489
Male	84 (70.6)	49 (76.6)		146 (74.9)	102 (75.0)		191 (70.0)	117 (66.9)	
Female	35 (29.4)	15 (23.4)		49 (25.1)	34 (25.0)		82 (30.0)	58 (33.1)	
Age (yr)			0.126			0.878			< 0.001
≤ 60	68 (57.1)	29 (45.3)		103 (52.8)	73 (53.7)		191 (70.0)	86 (49.1)	
> 60	51 (42.9)	35 (54.7)		92 (47.2)	63 (46.3)		82 (30.0)	89 (50.9)	
BMI			0.105			0.038			0.592
≤ 22.49	52 (43.7)	36 (56.3)		85 (43.6)	75 (55.1)		138 (50.5)	93 (53.1)	
> 22.49	67 (56.3)	28 (43.7)		110 (56.4)	61 (44.9)		135 (49.5)	82 (46.9)	
CEA			0.064			0.608			0.782
≤ 5 ng/mL	108 (90.8)	52 (81.2)		162 (83.1)	110 (80.9)		235 (86.1)	149 (85.1)	
> 5 ng/mL	11 (9.2)	12 (18.8)		33 (16.9)	26 (19.1)		38 (13.9)	26 (14.9)	
CA19-9			0.014			0.198			0.156
≤ 37 U/mL	112 (94.1)	53 (82.8)		168 (86.2)	110 (83.7)		246 (90.1)	150 (85.7)	
> 37 U/mL	7 (5.9)	11 (17.2)		27 (13.8)	26 (16.3)		27 (9.9)	25 (14.3)	
Borrmann type			0.005			0.051			0.454
0-2	71 (59.7)	22 (34.4)		84 (43.1)	72 (53.0)		80 (29.3)	45 (25.7)	
3	40 (33.6)	34 (53.1)		92 (47.2)	46 (33.8)		141 (51.6)	101 (57.7)	
4	8 (6.7)	8 (12.5)		19 (9.7)	18 (13.2)		52 (19.1)	29 (16.6)	
Tumor diameter (mm)			< 0.001			< 0.001			< 0.001
≤ 50	95 (79.8)	31 (48.4)		131 (67.2)	63 (46.3)		172 (63.0)	75 (42.9)	
> 50	24 (20.2)	33 (51.6)		64 (32.8)	73 (53.7)		101 (37.0)	100 (57.1)	
Tumor location			0.992			0.051			0.423
Middle and upper third	16 (13.4)	9 (14.0)		57 (29.2)	40 (29.4)		62 (22.7)	44 (25.1)	
Lower third	102 (85.7)	54 (84.4)		137 (70.3)	90 (66.2)		205 (75.1)	124 (70.9)	
Entire stomach	1 (0.9)	1 (1.6)		1 (0.5)	6 (4.4)		6 (2.2)	7 (4.0)	
Histological type			< 0.001			0.041			< 0.001
Well and medium differentiation	74 (62.2)	38 (59.4)		99 (50.8)	50 (36.8)		78 (28.6)	48 (27.4)	
Poor differentiation	2 (1.7)	19 (30.0)		47 (24.1)	41 (30.1)		120 (43.9)	87 (49.7)	
Others	18 (15.1)	7 (10.9)		49 (25.1)	45 (33.1)		75 (27.5)	40 (22.9)	
pTNM stage			< 0.001			0.022			< 0.001
I	61 (51.3)	11 (17.2)		51 (26.2)	19 (14.0)		29 (10.6)	7 (4.0)	
II	36 (30.2)	24 (37.5)		73 (37.4)	54 (39.7)		96 (35.2)	41 (23.4)	
III	22 (18.5)	29 (45.3)		71 (36.4)	63 (46.3)		148 (54.2)	127 (72.6)	
mLNR			0.019			0.290			0.001
≤ 0.07	84 (70.6)	34 (53.1)		109 (55.9)	68 (50.0)		131 (48.0)	56 (32.0)	
> 0.07	35 (29.4)	30 (46.9)		86 (44.1)	68 (50.0)		142 (52.0)	119 (68.0)	

Vascular infiltration			0.494			<b>0.030</b>		0.146
No	91 (76.5)	46 (71.9)		145 (74.4)	86 (63.2)		200 (73.3)	117 (66.9)
Yes	28 (23.5)	18 (28.1)		50 (25.6)	50 (36.8)		73 (26.7)	58 (33.1)
Nerve infiltration			0.098			0.592		0.238
No	85 (71.4)	38 (59.4)		119 (61.0)	79 (58.1)		159 (58.2)	92 (52.6)
Yes	34 (28.6)	26 (40.6)		76 (39.0)	57 (41.9)		114 (41.8)	83 (47.4)

Carcino-embryonic antigen and carbohydrate antigen 19-9 were according to the tumor marker examination. Tumor infiltrative pattern, tumor location, postsurgical tumor node metastasis stage, histological type, mLNR, vascular infiltration and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ( $P < 0.05$ ). INF: Tumor infiltrative pattern; INFa: Expansive growth type; INFb: Intermediate type; INFc: Infiltrative growth type; BMI: body mass index; CEA: Carcino-embryonic antigen; CA19-9: Carbohydrate antigen 19-9; mLNR: Metastatic lymph node ratio; pTNM: Postsurgical tumor node metastasis.

## MATERIALS AND METHODS

### Patients

All GC patients underwent radical gastrectomy according to their respective conditions[16]. GC was diagnosed by tissue specimens obtained during gastroscopy and confirmed by pathologists examining tissue samples after surgery. The patients underwent routine pre-operative auxiliary examinations, including abdominal ultrasound, gastric computed tomography (CT)/magnetic resonance imaging, chest X-ray, tumor markers examination, hematology examination, and electrocardiogram during hospitalization. If necessary, patients underwent positron emission tomography (PET)/CT. Patients were followed up until the date of death or for 5 years, whichever came first.

The exclusion criteria were as follows: (1) preoperative neoadjuvant therapy; (2) platelet therapy was performed within 3 mo before surgery; (3) severe heart disease; (4) active hemorrhage; (5) intravascular coagulation; (6) severe infection; (7) hematological malignancies; and (8) steroid drug treatment.

Formulation of postoperative chemotherapy regimens were according to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[17]. For GC patients with stage II or III, oxaliplatin + capecitabine and oxaliplatin + S-1 were the main treatment options. A total of 315 patients who underwent complete postoperative chemotherapy were included in our study.

### Clinicopathological data

Clinicopathological data of patients were saved in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, <http://www.sjihmu.com>), including age, gender, body mass index (BMI), Borrmann type, tumor location, tumor diameter, histological type, metastatic lymph node ratio (mLNR), nerve infiltration, vascular infiltration, resection, pTNM stage, postoperative chemotherapy and laboratory examination. pTNM stage is consistent with the eighth edition of the American Joint Commission on Cancer. Other auxiliary examinations (CT, ultrasound, and gastroscopy) or tumor markers were performed on all patients every 3-6 mo postoperatively. In addition, PET/CT examinations are performed as needed.

### Definition of INF types

The pathological INF types were diagnosed by two institutional pathologists, which using paraffin sections stained with hematoxylin and eosin. GC tissue specimens were classified as INFa (tumor grows expansively and has an obvious boundary with the surrounding tissue), INFb (tumor shows an intermediate type between the expansive growth type and the infiltrative growth type), and INFc (tumor grows infiltratively and has no obvious boundary with the surrounding tissue), according to the Japanese Classification of Gastric Carcinoma[5] (Figure 1).

### Blood sample

Blood samples were taken on an empty stomach the day after admission. Venous blood was collected from the cubital vein. Then, it was sent to the blood laboratory to separate the serum and calculate the corresponding inflammatory index. NLR = neutrophil count (N)/lymphocyte count (L), PLR = platelet count (P)/L, SII =  $N \times P/L$ .

### Statistical analysis

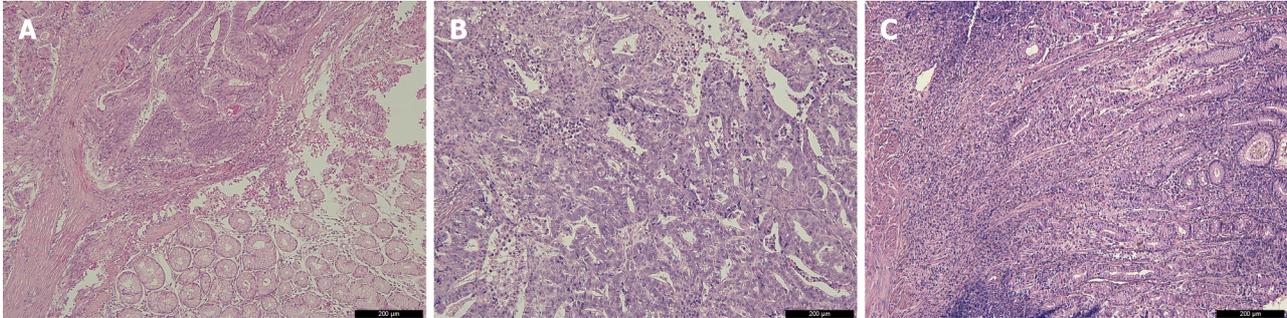
Overall survival (OS) was defined as the time from surgery to death or the last surviving follow-up visit. OS is shown as the mean and 95%CI. Receiver operating characteristic curve (ROC) analysis and the area under the curve (AUC) were used to compare the diagnostic significance of each inflammatory index. The Youden index was used to analyzed the optimal cutoff value of each inflammatory index, which was calculated by the equation: sensitivity-(1-specificity). The optimal cutoff value of each

**Table 3 Prognostic factors of patients with gastric cancer by univariate and multivariate analyses based on logistic regression analysis in the expansive growth type group**

Characteristics	INFa			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Sex		0.584		
Male	1			
Female	1.261 (0.550-2.894)			
Age (yr)	1.019 (0.979-1.061)	0.349		
BMI	0.880 (0.772-1.003)	0.055		
SII	1.002 (1.001-1.003)	<b>0.001</b>	1.001 (1.000-1.003)	<b>0.039</b>
ALT	0.988 (0.954-1.023)	0.491		
Total protein	0.968 (0.916-1.023)	0.251		
CEA	1.030 (0.996-1.065)	0.087		
CA19-9	1.002 (0.998-1.006)	0.278		
Borrmann type		<b>0.007</b>		0.272
0-1	1		1	
2	3.818 (0.448-32.517)	0.220	5.312 (0.450-62.711)	0.185
3	8.947 (1.135-70.530)	<b>0.038</b>	5.450 (0.496-59.870)	0.166
4-5	23.333 (2.525-215.647)	<b>0.005</b>	14.134 (0.944-211.701)	0.055
Tumor location		0.691		
Lower third	1			
Middle third	1.176 (0.366-3.782)	0.785		
Upper third	1.667 (0.167-16.657)	0.664		
Entire stomach	5.000 (0.303-82.520)	0.261		
Tumor size (mm)	1.032 (1.016-1.049)	<b>&lt; 0.001</b>	1.012 (0.989-1.034)	0.310
pTNM stage		<b>&lt; 0.001</b>		0.796
I	1		1	
II	2.615 (0.747-9.159)	0.133	0.660 (0.154-2.830)	0.576
III	10.968 (3.457-34.794)	<b>&lt; 0.001</b>	0.532 (0.080-3.525)	0.513
Histological type		0.160		
Well and medium differentiation	1			
Poor differentiation	2.282 (0.972-5.360)	0.058		
Others	1.617 (0.527-4.959)	0.401		
mLNR	438.799 (38.101-5053.535)	<b>&lt; 0.001</b>	471.355 (8.218-27035.275)	<b>0.003</b>
Vascular infiltration		0.080		
No	1			
Yes	2.065 (0.917-4.647)			
Nerve infiltration		<b>0.025</b>		0.621
No	1		1	
Yes	2.432 (1.118-5.288)		1.286 (0.474-3.490)	
Postoperative chemotherapy		0.720		
Yes	1			

No	1.159 (0.517-2.597)
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Carcinoembryonic antigen and carbohydrate antigen 19-9 were according to the tumor marker examination. Tumor infiltrative pattern, tumor location, postsurgical tumor node metastasis stage, histological type, metastatic lymph node ratio, vascular infiltration and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ( $P < 0.05$ ). INF: Tumor infiltrative pattern; INFa: Expansive growth type; INFb: Intermediate type; INFc: Infiltrative growth type; HR: Hazard ratio; BMI: Body mass index; SII: Systemic immune-inflammation index; ALT: Alanine transaminase; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; mLNR: Metastatic lymph node ratio; pTNM: Postsurgical tumor node metastasis.



**Figure 1 Representative hematoxylin and eosin staining patterns of samples of each tumor infiltrative pattern type.** A: The expansive growth type; B: The intermediate type; C: The infiltrative growth type. INFa: The expansive growth type; INFb: The intermediate type; INFc: The infiltrative growth type.

inflammatory index was determined by the maximum value of the Youden index. The chi-square test was used to analyze the association between the inflammatory indices and clinicopathological factors. Survival curves for different INF types were analyzed by the log-rank test and Kaplan–Meier method. Based on logistic regression, univariate and multivariate analyses were used to analyze the independent prognostic factors for different INF types. Hazard ratios (HRs) and 95% CIs of each factor were shown. Boxplots and scatterplots were drawn by GraphPad Prism 8. The nomogram models were drawn through R studio by the “SvyNom” and “rms” packages. SPSS version 25.0 (SPSS Inc., Chicago, IL, United States) was used for analysis, and  $P < 0.05$  was considered statistically significant.

## RESULTS

### **Clinicopathological characteristics and survival based on INF**

In the INFa group, the age range was 33–87 years (median 55 years), and the ratio of male to female was 133:50. In the INFb group, the age range was 30–79 years (median 60 years), and the ratio of male to female was 248:83. In the INFc group, the age range was 24–85 years (median 57 years), and the ratio of male to female was 308:140. **Table 1** shows the clinicopathological features of the three groups.

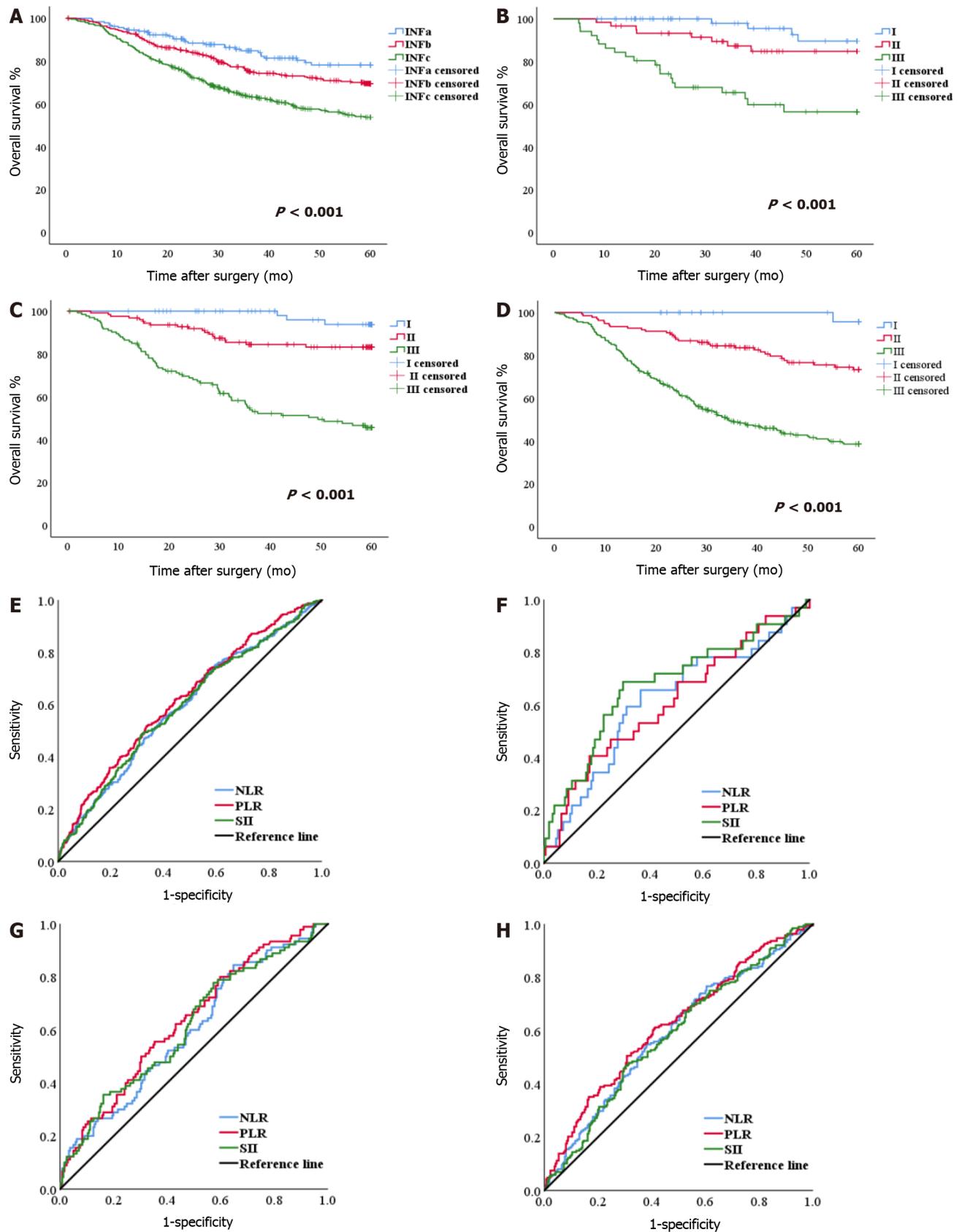
There were statistically significant differences in OS among the INFa, INFb and INFc groups ( $P < 0.001$ ). The OS of patients with INFc was worse than the OS of patients with INFa and INFb (**Figure 2A**). In the three groups, the OS of patients with stage I, II, and III GC was significantly different (all  $P < 0.001$ ) (**Figure 2B–D**). These results are shown in the supplementary materials (**Supplementary Table 1**).

### **NLR, PLR and SII scores**

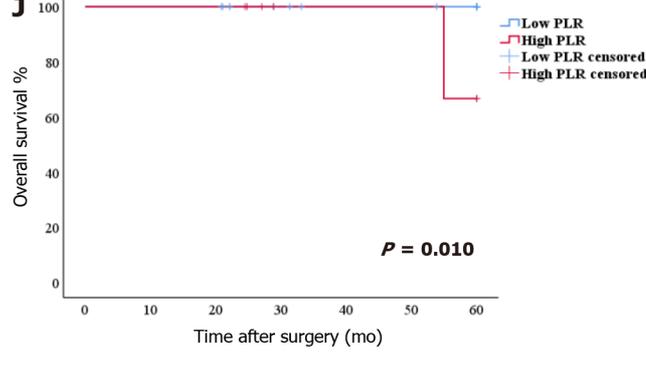
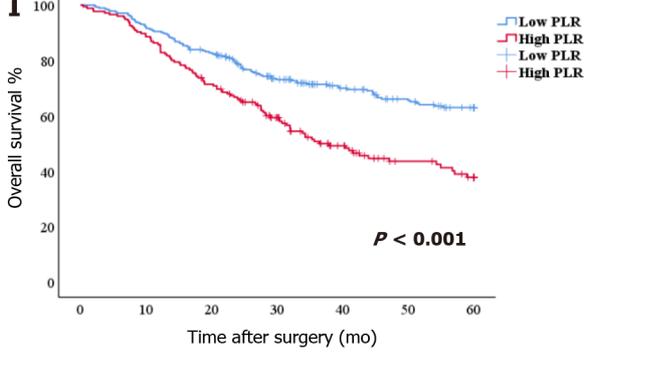
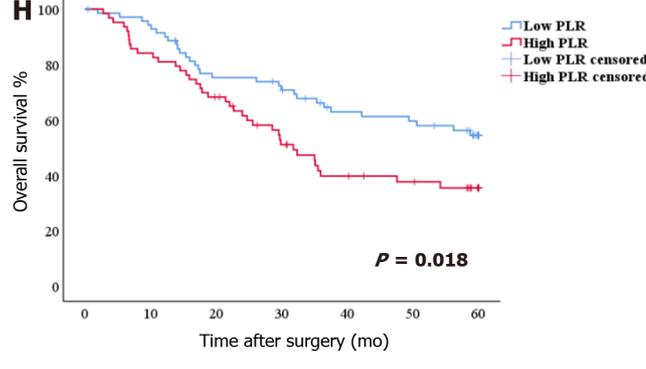
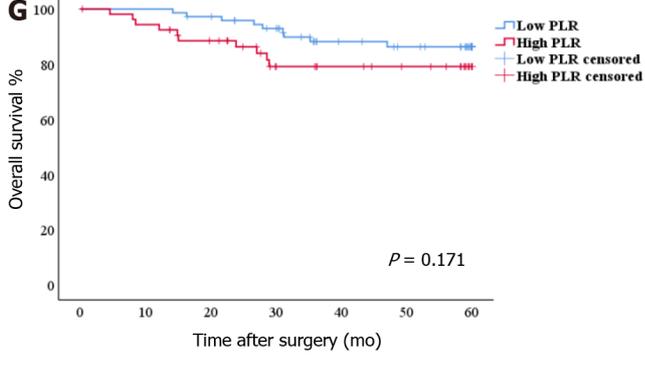
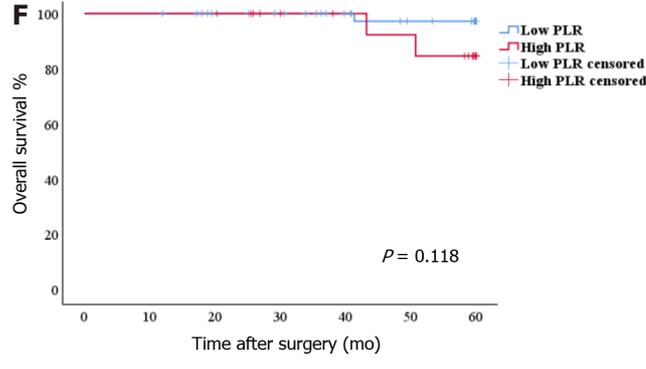
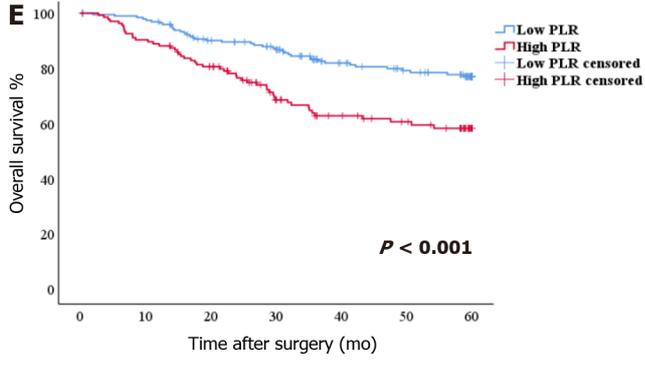
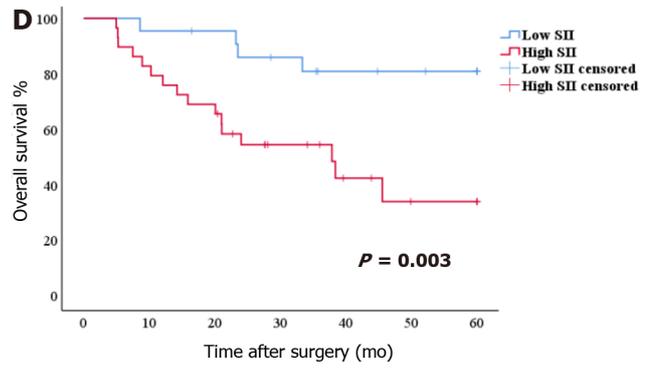
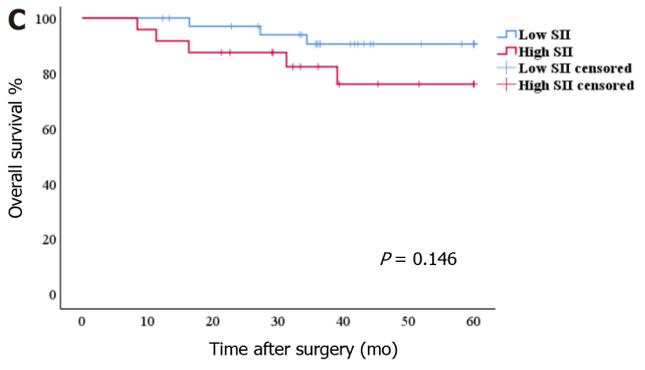
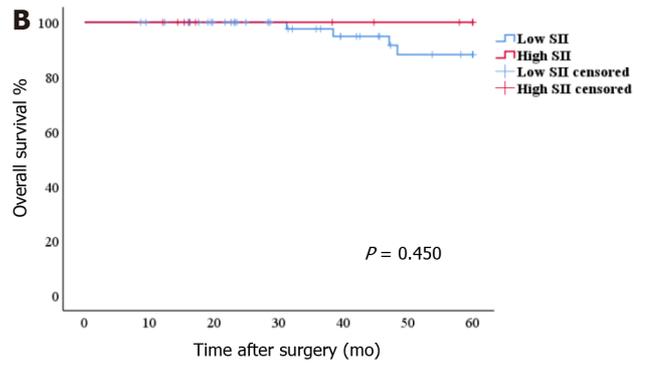
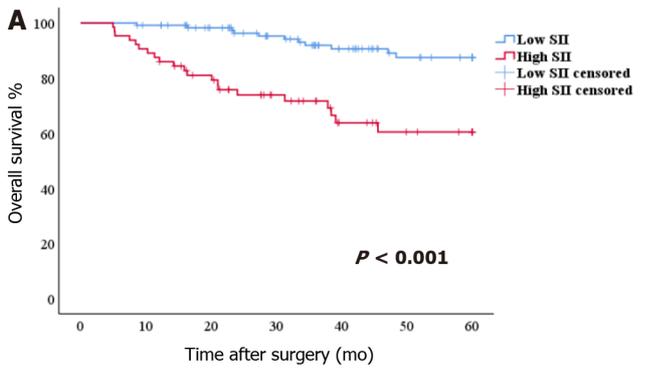
The NLR, PLR, and SII scores of 1.99, 126.90, and 529.24, respectively, were calculated as the most appropriate cutoff thresholds by the Youden index of the ROC for all patients based on preoperative hematology. The AUCs were 0.591 (95% CI: 0.553–0.630), 0.620 (95% CI: 0.583–0.658), and 0.594 (95% CI: 0.555–0.632), respectively (**Figure 2E**). The AUCs of NLR, PLR, and SII for the INFa, INFb and INFc groups are shown in the **Supplementary Table 2** (**Figure 2F–H**).

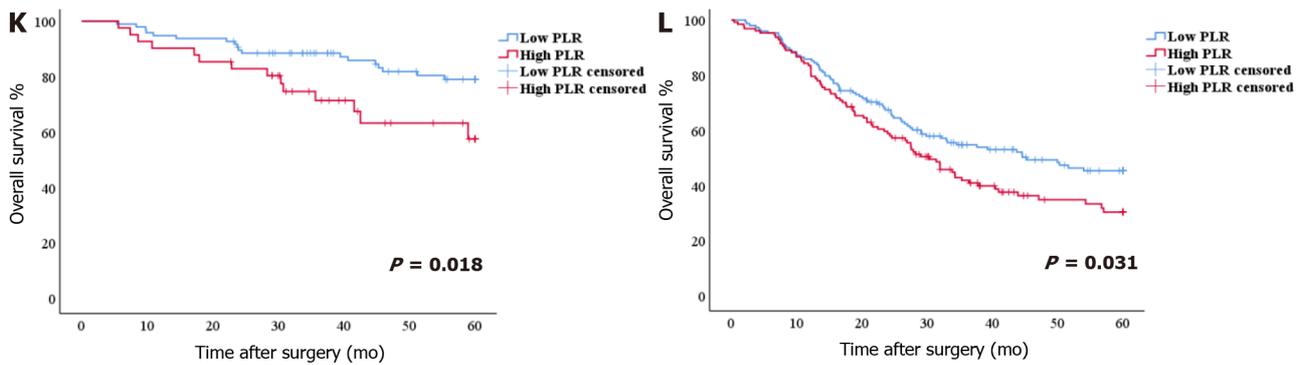
### **Inflammatory indices and patient survival**

In patients with INFa, a significant difference in OS was found between patients with  $SII > 523.01$  and those with  $SII \leq 523.01$  (OS: 56.55 mo vs 44.98 mo,  $P < 0.001$ ; HR: 4.502, 95% CI: 2.166–9.355). According to the pTNM stage, for stages I and II, the difference in OS between patients with  $SII > 523.01$  and those with  $SII \leq 523.01$  was not significant ( $P = 0.450$  and  $P = 0.146$ ). For stage III, patients with  $SII \leq 523.01$  had better survival ( $P = 0.003$ ) (**Figure 3A–D**). The SII score was significantly associated with carbohydrate antigen 19-9 (CA19-9), Borrmann type, tumor diameter, histological type, pTNM stage, and mLNR, as determined by the chi-square test of clinicopathologic features (all  $P < 0.05$ ) (**Table 2**).



**Figure 2** Survival curve analyses for patients and receiver operating characteristic curves of inflammatory indices. A: Survival curves of all patients; B-D: Survival curves of patients with the expansive growth type (INFa), the intermediate type (INFb), and the infiltrative growth type (INFc); E-H: Receiver operating characteristic curve of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and systemic immune-inflammation index in all patients, INFa group, INFb group, and INFc group. INFa: The expansive growth type; INFb: The intermediate type; INFc: The infiltrative growth type; ROC: Receiver operating characteristic; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.





**Figure 3** Survival curve analyses based on the systemic immune-inflammation index and platelet-lymphocyte ratio. A-D: Survival curves of patients with the expansive growth type based on the systemic immune-inflammation index in all stages, stage I, stage II, and stage III; E-H: Survival curves of patients with the intermediate type based on the platelet-lymphocyte ratio (PLR) in all stages, stage I, stage II, and stage III; I-L: Survival curves of patients with the infiltrative growth type based on the PLR in all stages, stage I, stage II, and stage III. INFa: The expansive growth type; INFb: The intermediate type; INFc: The infiltrative growth type; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

In patients with INFb, a significant difference in OS was found between patients with  $PLR > 134.02$  and those with  $PLR \leq 134.02$  (OS: 52.47 mo *vs* 44.37 mo,  $P < 0.001$ ; HR: 2.191, 95%CI: 1.444-3.323). According to the pTNM stage, for stages I and II, the difference in OS between patients with  $PLR > 134.02$  and those with  $PLR \leq 134.02$  was not significant ( $P = 0.118$  and  $P = 0.171$ ). For stage III, the OS of patients with  $PLR \leq 134.02$  was better ( $P = 0.018$ ) (Figure 3E-H). The PLR score was significantly associated with BMI, tumor diameter, histological type, pTNM stage, and mLNR, as determined by the chi-square test of clinicopathologic features (all  $P < 0.05$ ) (Table 2).

In patients with INFc, a significant difference in OS was found between patients with  $PLR > 134.02$  and those with  $PLR \leq 134.02$  (OS: 46.53 mo *vs* 37.97 mo,  $P < 0.001$ ; HR: 1.956, 95%CI: 1.467-2.307). According to the pTNM stage, for stages I, II, and III, patients with  $PLR \leq 134.02$  had better survival ( $P = 0.010$ ,  $P = 0.018$  and  $P = 0.031$ ) (Figure 3I-L). The PLR score was significantly associated with age, tumor diameter, histological type, pTNM stage, and mLNR, as determined by the chi-square test of clinicopathologic features (all  $P < 0.05$ ) (Table 2).

### Inflammatory indices and postoperative chemotherapy

For INFa and INFb GC, there were no statistically significant differences in OS between patients with and without postoperative chemotherapy (all  $P > 0.05$ ) (Figure 4A-F). For INFc GC, in the  $PLR \leq 134.02$  group, the OS of patients with postoperative chemotherapy was significantly better than that of patients without postoperative chemotherapy (OS: 50.22 mo *vs* 43.90 mo,  $P = 0.030$ ) (Figure 4H). However, in the overall group and the  $PLR > 134.02$  group, there were no statistically significant differences in OS between patients with and without postoperative chemotherapy ( $P = 0.057$  and  $P = 0.770$ ) (Figure 4G and I).

### Immune cells and INF

According to pTNM stage, peripheral circulating immune cell parameters, including neutrophil percentage, lymphocyte percentage and platelet count were analyzed. For I-III stage GC patients, the percentages of neutrophils and lymphocytes were not significantly different among the three groups ( $P > 0.05$ ) (Figure 5A-F). For patients with stage I GC, the platelet count of INFc group was significantly higher than that of INFa group ( $P < 0.05$ ) (Figure 5G). For patients with stage II GC, the platelet count of INFc group was significantly lower than that of INFb group ( $P < 0.05$ ) (Figure 5H). For patients with stage III GC, the platelet count of INFc group was significantly lower than that of INFa and INFb group ( $P < 0.05$ ) (Figure 5I).

### Univariate and multivariate regression analyses in the three groups

To identify the independent risk factors for prognosis in the three groups, univariate and multivariate analyses based on the logistic risk regression model were implemented. In the INFa group, univariate analysis and multivariate analysis showed that SII ( $P = 0.039$ ) and mLNR ( $P = 0.003$ ) were independent prognostic factors for INFa GC (Table 3). In the INFb group, univariate analysis and multivariate analysis showed that age ( $P = 0.026$ ), BMI ( $P = 0.003$ ), PLR ( $P = 0.018$ ) and pTNM stage ( $P < 0.001$ ) were independent risk factors for the prognosis of INFb GC (Table 4). In the INFc group, univariate analysis and multivariate analysis showed that age ( $P = 0.021$ ), PLR ( $P = 0.021$ ), pTNM stage ( $P = 0.028$ ) and mLNR ( $P = 0.002$ ) were independent prognostic factors for INFc GC (Table 5).

**Table 4 Prognostic factors of patients with gastric cancer by univariate and multivariate analyses based on logistic regression analysis in the intermediate type group**

Characteristics	INFb			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Sex		0.115		
Male	1			
Female	0.617 (0.339-1.124)			
Age (yr)	1.033 (1.007-1.061)	<b>0.014</b>	1.036 (1.004-1.069)	<b>0.026</b>
BMI	0.814 (0.746-0.888)	<b>&lt; 0.001</b>	0.861 (0.781-0.950)	<b>0.003</b>
PLR	1.008 (1.003-1.012)	<b>&lt; 0.001</b>	1.006 (1.001-1.012)	<b>0.018</b>
ALT	0.976 (0.949-1.004)	0.094		
Total protein	0.975 (0.946-1.004)	0.092		
CEA	1.004 (0.995-1.014)	0.338		
CA19-9	1.003 (1.001-1.006)	<b>0.012</b>	1.000 (0.998-1.003)	0.650
Borrmann type		<b>0.005</b>		0.226
0-1	1		1	
2	1.031 (0.430-2.473)	0.945	0.715 (0.246-2.079)	0.538
3	2.410 (1.081-5.372)	<b>0.031</b>	1.530 (0.554-4.223)	0.412
4-5	3.182 (1.201-8.429)	<b>0.020</b>	1.339 (0.374-4.797)	0.654
Tumor location		0.088	-	-
Lower third	1			
Middle third	1.195 (0.641-2.228)	0.575		
Upper third	1.527 (0.697-3.345)	0.290		
Entire stomach	7.634 (1.441-40.446)	<b>0.017</b>		
Tumor size (mm)	1.021 (1.012-1.032)	<b>&lt; 0.001</b>	1.007 (0.994-1.021)	0.302
pTNM stage		<b>&lt; 0.001</b>		<b>&lt; 0.001</b>
I	1		1	
II	3.929 (1.120-13.785)	<b>0.033</b>	2.036 (0.528-7.856)	0.302
III	23.010 (6.895-76.795)	<b>&lt; 0.001</b>	8.306 (2.053-33.597)	<b>0.003</b>
Histological types		0.739		
Well and medium differentiation	1			
Poor differentiation	1.105 (0.617-1.977)	0.738		
Others	0.853 (0.472-1.542)	0.599		
mLNR	87.343 (18.612-409.881)	<b>&lt; 0.001</b>	2.267 (0.291-17.641)	0.434
Vascular infiltration		<b>&lt; 0.001</b>		0.149
No	1		1	
Yes	3.160 (1.897-5.263)		1.585 (0.848-2.963)	
Nerve infiltration		<b>0.003</b>		0.859
No	1		1	
Yes	2.097 (1.283-3.428)		1.057 (0.573-1.951)	
Postoperative chemotherapy		0.493		
Yes	1			

No	0.823 (0.472-1.436)
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Carcinoembryonic antigen and carbohydrate antigen 19-9 were according to the tumor marker examination. Tumor infiltrative pattern, tumor location, postsurgical tumor node metastasis stage, histological type, metastatic lymph node ratio, vascular infiltration and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold (*P* < 0.05). INF: Tumor infiltrative pattern; INFa: Expansive growth type; INFb: Intermediate type; INFc: Infiltrative growth type; HR: Hazard ratio; BMI: Body mass index; PLR: Platelet-lymphocyte ratio; ALT: Alanine transaminase; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; mLNR: Metastatic lymph node ratio; pTNM: Postsurgical tumor node metastasis.

### Nomogram

We combined independent prognostic risk factors to construct nomogram models to evaluate the prognosis of patients in different INF groups (Figure 6A, D and G). For predicting the survival of patients with INFa, INFb and INFc GC within 3 and 5 years after radical resection, ROC analysis showed that the AUCs of the nomogram models were both greater than those of pTNM stage alone (Figure 6B, C, E, F, H and I). The results of the nomogram models are shown in the Supplementary Table 3.

## DISCUSSION

In East Asia, INF has gradually become a clinicopathological feature for routine evaluation in surgical specimens[7]. Hematoxylin eosin staining is easy to determine it, which is convenient for clinical application. Recent retrospective studies have further demonstrated that INF can be an ideal predictor of recurrence and metastasis patterns after radical gastrectomy. INFc is an independent risk factor for peritoneal metastasis and is more prone to lymph node metastasis, while the liver metastasis rate of INFa/b is significantly higher than that of INFc[6,8,9]. Our study also confirmed that the prognosis of patients with INFa and INFb GC was better than that of patients with INFc GC. This evidence shows that INF can effectively help clinical experts predict the recurrence pattern and prognosis of GC patients. In addition, with the great achievements of tumor immunotherapy, it has been found that the tumor microenvironment and immune inflammatory response in peripheral blood can effectively reduce the impact of GC heterogeneity, providing more comprehensive information for the personalized treatment of patients[14,18]. This study was aimed at investigating the peripheral blood immune response is great value to different INF types GC patients in evaluating prognosis and individualized chemotherapy.

As the significant role of the systemic immune inflammatory response in gastrointestinal tumors has gradually become widely recognized by clinical experts, inflammatory indices, such as NLR, PLR and LMR, have been indicated to be prognostic markers of GC, esophageal cancer or colorectal cancer[19, 20]. These indices can also evaluate the possible benefits and prospects of immunotherapy according to their baseline levels to support personalized immunotherapy[21]. As a part of systemic immunity, peripheral blood immunity also plays a significant role in the process of tumor metastasis. The proliferation of tumor cells causes them to break through mechanical pressure, escape immune monitoring, enter peripheral veins and form circulating tumor cells (CTCs)[22]. In this process, the close relationship between neutrophils and CTCs promotes the cell cycle process of CTCs and expands the metastatic potential of CTCs[23]. In addition, cytokines, such as tumor necrosis factor  $\alpha$  released by CTC-associated neutrophils, play a key role in promoting tumor cell proliferation[23]. Lymphocytes can restrain the migration and proliferation of CTCs by secreting cytokines such as perforin/granzyme[24]. In addition, platelets can form aggregates with CTCs to escape host immune monitoring and release transforming growth factor  $\beta$  (TGF- $\beta$ ), inducing epithelial-mesenchymal transformation to promote distant metastasis [25]. The current research results showed that the higher the levels of the inflammatory indices SII and PLR are, the greater the possibility of early distant metastasis and the worse the prognosis. The AUC of the SII was higher in patients with INFa GC in ROC analysis, and the SII was an independent prognostic factor. This finding also showed that the pivotal role of neutrophils, lymphocytes and platelets for patients with INFa GC in the external circulation immunity. Besides, PLR also was a key predictor of the prognosis of patients with INFb and INFc GC. This finding further suggests that in peripheral circulating immunity of different INF types, the subsets of immune cells that play a major part are different.

In this study, we found that there was no significant difference in the percentages of neutrophils and lymphocytes among the three groups. In patients with stage II and III GC, the platelet count of INFc group was significantly lower than that of INFa and INFb group, which seems to contradict the conclusion that the prognosis of patients with INFc GC was poor. The reason for this may be that different INF groups differ greatly in their sensitivity to peripheral immune cells. Due to the influence of GC heterogeneity, the immune microenvironment of different subtypes of GC patients is greatly different[26]. Because of the unique biological characteristics of infiltrative growth with no distinct border with the surrounding tissue, tumor cells in patients with INFc GC may be more likely to enter

**Table 5 Prognostic factors of patients with gastric cancer by univariate and multivariate analyses based on logistic regression analysis in the infiltrative growth type group**

Characteristics	INFc			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Sex		0.570		
Male	1			
Female	0.889 (0.592-1.335)			
Age (yr)	1.028 (1.009-1.047)	<b>0.003</b>	1.026 (1.004-1.049)	<b>0.021</b>
BMI	0.965 (0.915-1.017)	0.184		
PLR	1.007 (1.004-1.010)	<b>&lt; 0.001</b>	1.004 (1.001-1.008)	<b>0.021</b>
ALT	0.984 (0.966-1.003)	0.096		
Total protein	0.995 (0.973-1.018)	0.683		
CEA	1.006 (0.998-1.014)	0.161		
CA19-9	1.000 (1.000-1.006)	<b>0.020</b>	1.001 (0.999-1.004)	0.387
Borrmann type		<b>&lt; 0.001</b>		0.055
0-1	1		1	
2	2.104 (0.574-7.708)	0.262	1.193 (0.290-4.903)	0.807
3	4.298 (1.233-14.981)	<b>0.022</b>	1.781 (0.460-6.891)	0.403
4-5	14.250 (3.837-52.919)	<b>&lt; 0.001</b>	3.735 (0.835-16.696)	0.085
Tumor location		<b>&lt; 0.001</b>		0.059
Lower third	1		1	
Middle third	2.791 (1.669-4.670)	<b>&lt; 0.001</b>	1.952 (1.052-3.622)	<b>0.034</b>
Upper third	1.985 (0.947-4.160)	0.069	1.955 (0.820-4.658)	0.130
Entire stomach	22.330 (2.867-173.902)	<b>0.003</b>	4.687 (0.523-41.965)	0.167
Tumor size (mm)	1.028 (1.020-1.037)	<b>&lt; 0.001</b>	1.004 (0.993-1.016)	0.433
pTNM stage		<b>&lt; 0.001</b>		<b>0.028</b>
I	1		1	
II	10.667 (1.405-80.956)	<b>0.022</b>	8.549 (1.073-68.125)	<b>0.043</b>
III	45.208 (6.106-334.716)	<b>&lt; 0.001</b>	13.795 (1.693-112.382)	<b>0.014</b>
Histological types		0.643		
Well and medium differentiation	1			
Poor differentiation	1.026 (0.656-1.604)	0.912		
Others	0.826 (0.493-1.384)	0.468		
mLNR	93.645 (30.921-283.603)	<b>&lt; 0.001</b>	11.042 (2.407-50.664)	<b>0.002</b>
Vascular infiltration		<b>&lt; 0.001</b>		0.783
No	1		1	
Yes	2.899 (1.905-4.411)		1.080 (0.623-1.874)	
Nerve infiltration		<b>0.029</b>		0.471
No	1		1	
Yes	1.524 (1.044-2.226)		1.187 (0.745-1.892)	
Postoperative chemotherapy		0.315		
Yes	1			

No	0.891 (0.554-1.209)
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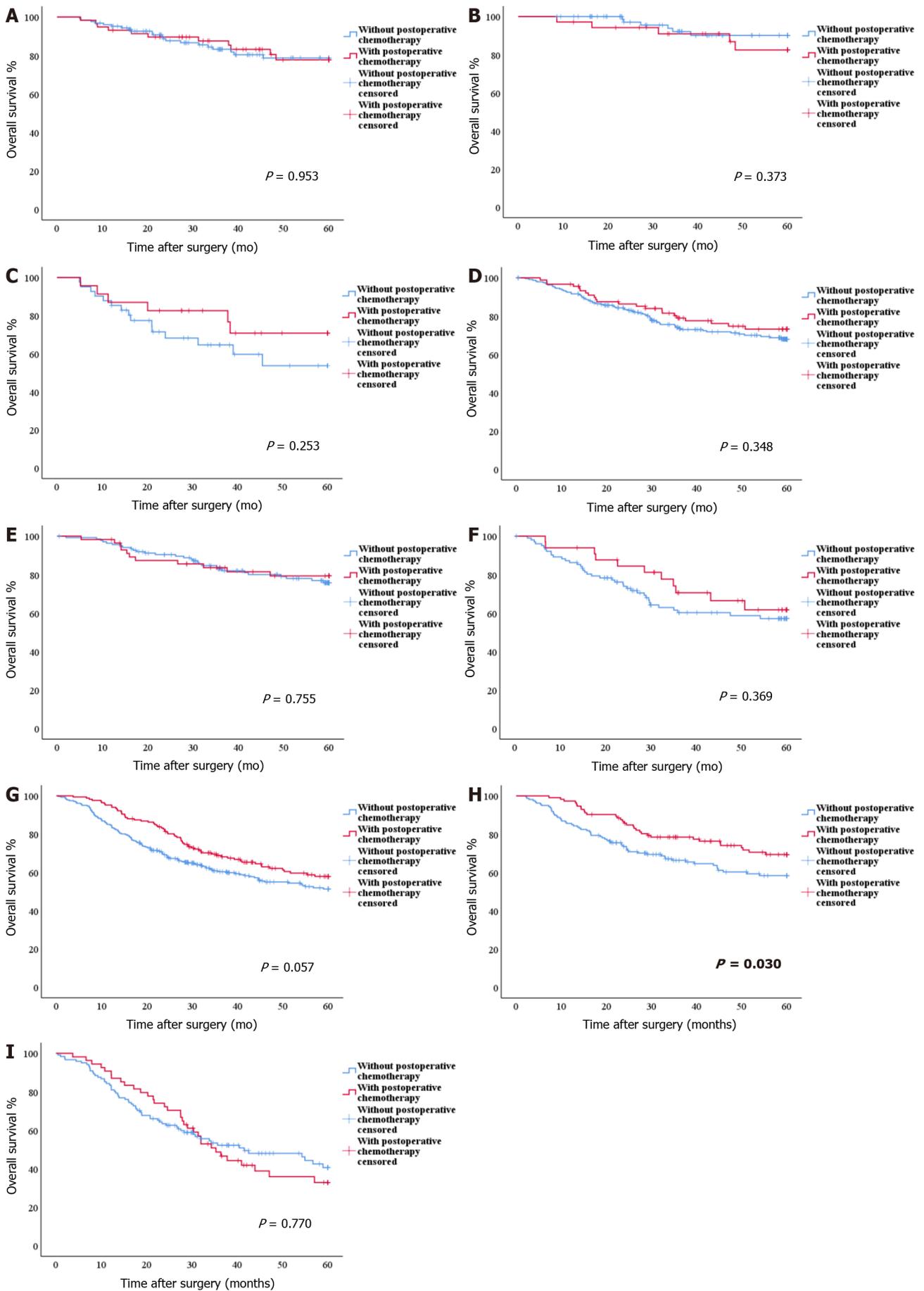
Carcinoembryonic antigen and carbohydrate antigen 19-9 were according to the tumor marker examination. Tumor infiltrative pattern, tumor location, postsurgical tumor node metastasis stage, histological type, metastatic lymph node ratio, vascular infiltration and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ( $P < 0.05$ ). INF: Tumor infiltrative pattern; INFa: Expansive growth type; INFb: Intermediate type; INFc: Infiltrative growth type; HR: Hazard ratio; BMI: Body mass index; PLR: Platelet-lymphocyte ratio; ALT: Alanine transaminase; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; mLNR: Metastatic lymph node ratio; pTNM: Postsurgical tumor node metastasis.

the peripheral circulation to form CTCs. This results in that even if the platelets of patients with INFc GC being lower than those of patients with INFa and INFb GC in the same period, their peripheral circulating platelets are more likely to form aggregates with CTCs in patients with INFc GC, thus avoiding host immune monitoring and causing distant metastasis. In addition, we found that the platelet count of patients with INFc GC did not increase with increasing pTNM stage. The platelet count of patients with stage I disease was higher than that of patients with stage II and III disease. This may be related to the small number of INFc patients with stage I disease included in our study. Therefore, our next research direction is to explore the distribution and function of immune cell subsets according to INF.

We found that for the INFc group, patients with a low PLR were more sensitive to postoperative chemotherapy. The therapeutic effect of chemotherapy on different individuals depends not only on the sensitivity of cancer cells to chemotherapeutic drugs, but also on the immune status of tumor microenvironment. Ohe *et al*[27] also found that GC patients with a low PLR were more sensitive to chemotherapy. Platelets in peripheral blood are released from damaged endothelial cells by cisplatin-based chemotherapy, adhere to and accumulate on the vascular wall through von Willebrand factor [28]. Coalesced and activated platelets secrete multifarious cytokines, such as TGF- $\beta$  and vascular endothelial growth factor A (VEGF-A). They induce the up regulation of cancer cell metastasis and drug resistance by acting on epithelial-mesenchymal transformation[29,30]. In addition, peripheral blood lymphocytes continually enter and exit lymph nodes, which leads to the initiation and activation of antigen-presenting dendritic cells (DCs). DCs can recognize the neoantigens of tumor cells induced by chemotherapy immunogenicity and make tumor cells sensitive to T cell-mediated killing[31]. This evidence suggests that patients with a low PLR GC are more sensitive to chemotherapy than other patients due to fewer platelets and more lymphocytes in their peripheral circulation. Our study also found that chemotherapy had better efficacy in the INFc group than in the other two groups. Wang *et al* [32] found that the survival rate of patients with early neutropenia after postoperative chemotherapy was higher. In addition, neutrophils and platelets in peripheral blood can inhibit natural killer cells by releasing chemical mediators, such as interleukin-1 and VEGF-A, and advance the immune resistance and escape of CTCs to chemotherapy drugs[33-36]. Our results showed that the percentages of neutrophils and platelets in INFc were lower than those in INFa and INFb in stage II and III GC patients, which may be why INFc is more sensitive to chemotherapy. Therefore, it is necessary to further investigate whether targeted therapy can improve postoperative survival in patients with INFa and INFb GC.

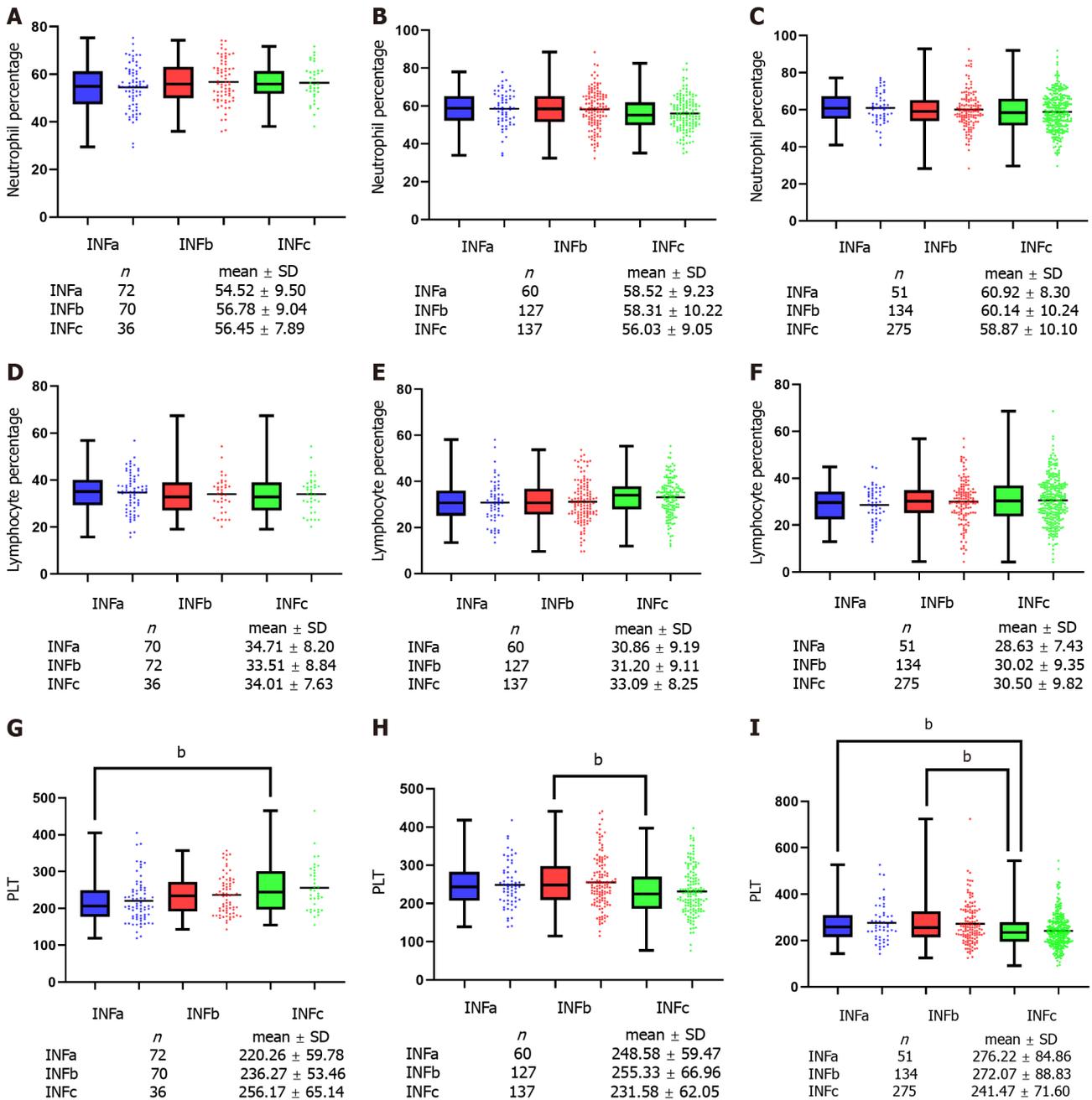
Clinically, some clinicians have realized that pTNM stage depends on postoperative pathology can provide efficacious but imperfect information for individual treatment. The same stage patients show significant individual differences in prognosis. Many studies have suggested that tumor immunity can bring into play an efficacious supplementary role[37,38]. Analyzing the proportion of immune cells in body fluids can effectively evaluate the prognosis of metastatic GC patients and provide them with more personalized treatment[39]. Li *et al*[20] constructed a nomogram based on inflammation and nutritional markers to predict the prognosis of GC patients receiving neoadjuvant chemotherapy and D2 Lymph node dissection. As a result, this type of prediction model constructed by combining inflammatory markers with clinicopathological features has the advantages of more accurate and individualized evaluation of patient prognosis and reducing the differences caused by heterogeneity. Based on the logistic risk regression model, our study found that the SII and mLNR were independent risk factors related to the prognosis of INFa GC patients. PLR, age, BMI and pTNM stage are independent risk factors related to the prognosis of INFb GC patients. PLR, age, pTNM stage and mLNR are independent risk factors related to the prognosis of INFc GC patients. Then, the nomogram models were constructed to predict the prognosis of patients with different INF types. We found that the nomogram models were better than the conventional pTNM stage alone in predicting the prognosis of patients with different INF types of GC within 3 years and 5 years after radical resection. The prediction models for evaluating the prognosis of different INF types patients combining inflammatory biomarkers and clinicopathological features were effective, which deserve further testing and extension in clinical practice.

There were some limitations in this study. First, the existence of internal bias and heterogeneity were inevitable as it was a retrospective study. Second, this was a single-center study, focusing only on Asian populations. Whether these results are widely applicable to other populations needs to be further studied by enlarging the sample size and source.



**Figure 4** Survival curve analyses based on postoperative chemotherapy. A-C: Survival curves with and without postoperative chemotherapy in all the

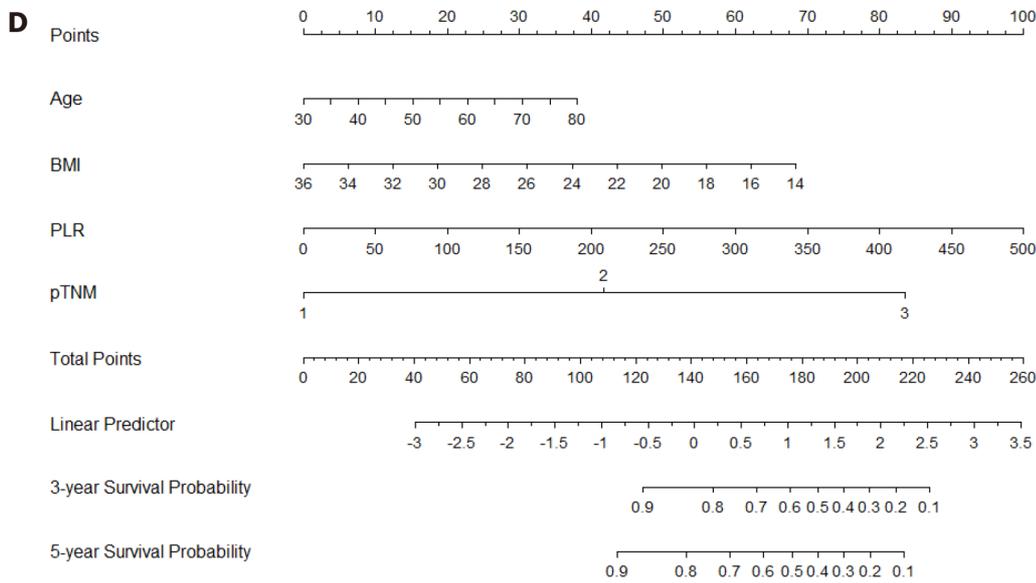
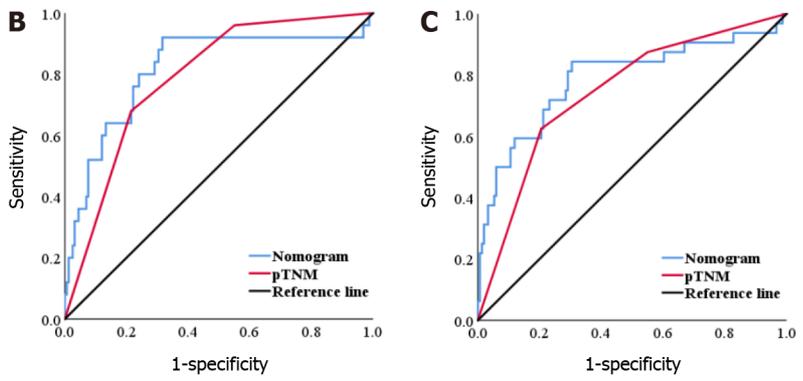
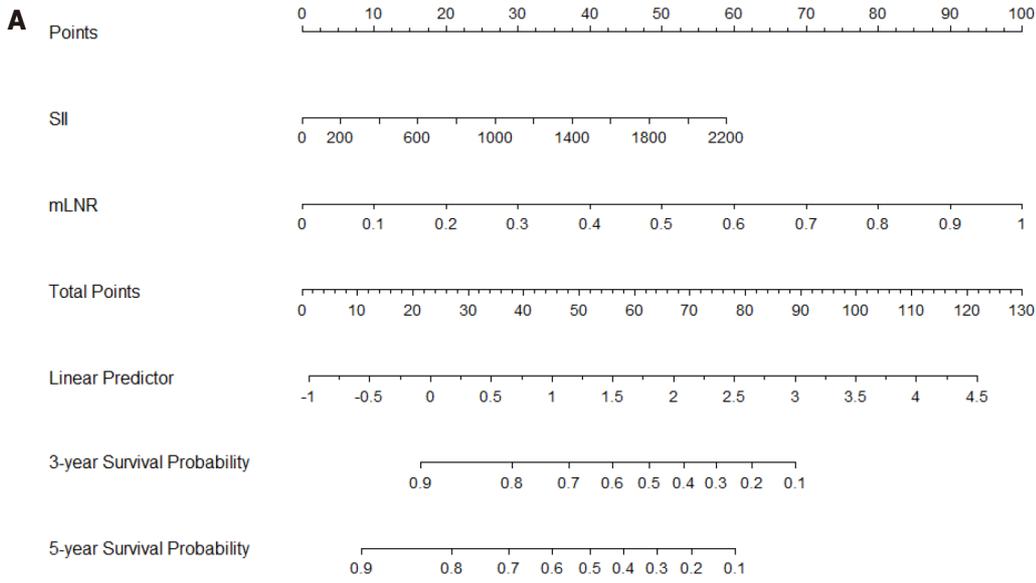
expansive growth type (INFa) gastric cancer (GC) patients, INFa GC patients with systemic immune-inflammation index (SII)  $\leq 523.01$ , and INFa GC patients with SII  $> 523.01$ ; D-F: Survival curves with and without postoperative chemotherapy in all the intermediate type (INFb), GC patients, INFb GC patients with platelet-lymphocyte ratio (PLR)  $\leq 134.02$ , and INFb GC patients with PLR  $> 134.02$ ; G-I: Survival curves with and without postoperative chemotherapy in all the infiltrative growth type (INFc) GC patients, INFc GC patients with PLR  $\leq 134.02$ , and INFc GC patients with PLR  $> 134.02$ . INFa: The expansive growth type; INFb: The intermediate type; INFc: The infiltrative growth type; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

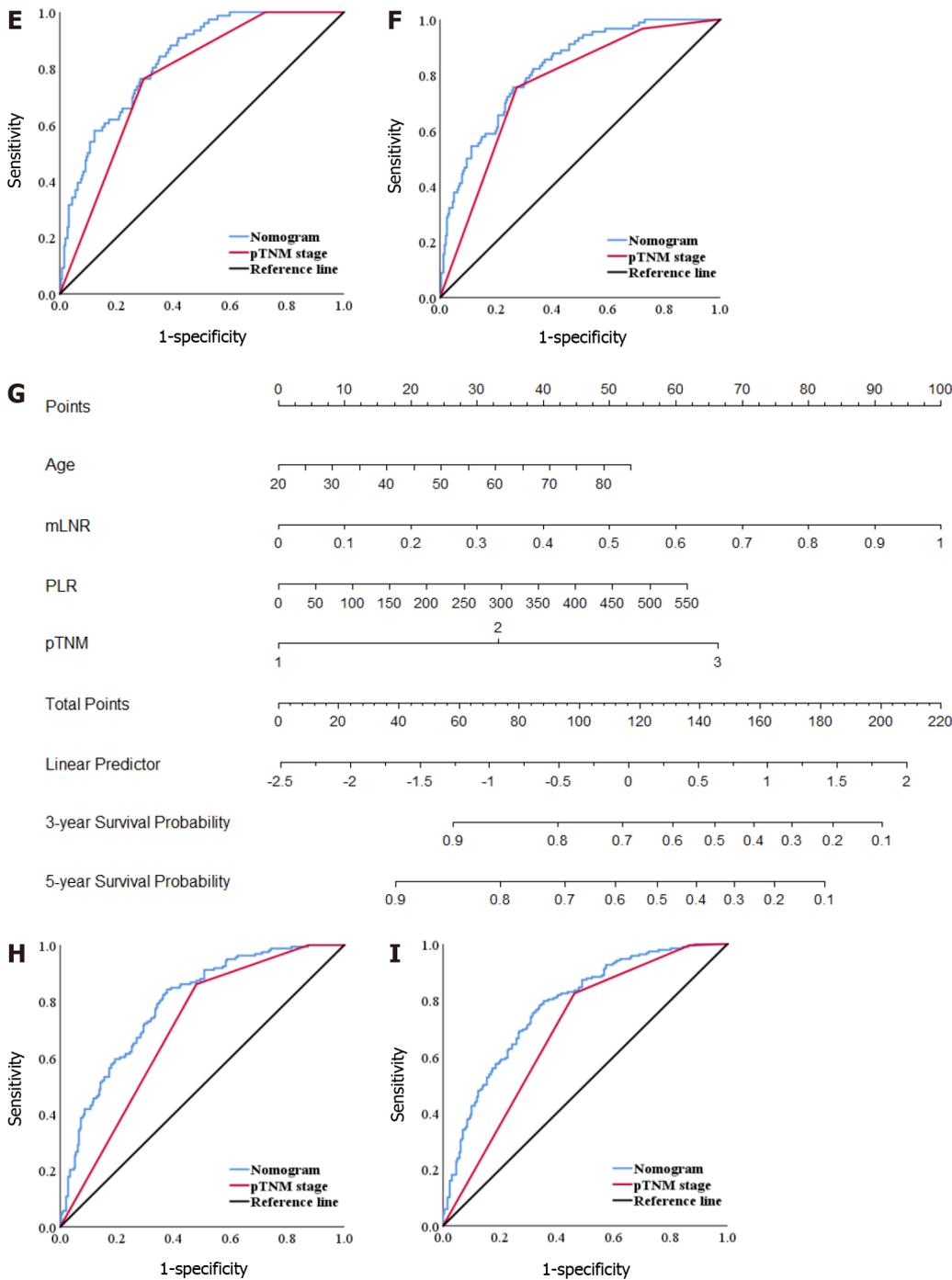


**Figure 5** The relationship between peripheral circulating immune cells and different tumor infiltrative pattern types. A-C: Boxplot combined with scatterplot of neutrophil percentage based on tumor infiltrative pattern (INF) types in stage I, stage II, and stage III; D-F: Boxplot combined with scatterplot of lymphocyte percentage based on INF types in stage I, stage II, and stage III; G-I: Boxplot combined with scatterplot of platelet count based on INF types in stage I, stage II, and stage III. INFa: The expansive growth type; INFb: The intermediate type; INFc: The infiltrative growth type; PLT: Platelet.

## CONCLUSION

The SII and PLR were independent risk factors for the prognosis of patients with GC in the INFa, INFb and INFc groups. The nomogram based on these two inflammatory biomarkers combined with clinicopathologic features can evaluate the prognosis of GC patients with different INF types, and its predictive ability is better than that of the traditional pTNM stage alone.





**Figure 6** Nomogram models predicting the survival of patients with different tumor infiltrative pattern types. A, D and G: Nomogram models predicting the 3-year and 5-year survival of patients with the expansive growth type (INFa), the intermediate type (INFb), and the infiltrative growth type (INFc) gastric cancer (GC); B and C: Receiver operating characteristic (ROC) of the nomogram model and postsurgical tumor node metastasis (pTNM) stage predicting the 3-year and 5-year survival of patients with INFa GC; E and F: ROC of the nomogram model and pTNM stage predicting the 3-year and 5-year survival of patients with INFb GC; H and I: ROC curve of the nomogram model and pTNM stage predicting the 3-year and 5-year survival of patients with INFc GC. INFa: The expansive growth type; INFb: The intermediate type; INFc: The infiltrative growth type; ROC: Receiver operating characteristic curve; mLNR: Metastatic lymph node ratio; BMI: Body mass index; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

## ARTICLE HIGHLIGHTS

### Research background

Gastric cancer (GC) is an important public health burden worldwide. In East Asia, the tumor infiltrative pattern (INF) has gradually become a clinicopathologic feature routinely evaluated in surgically resected specimens. The INF type categorizes GC as the expansive growth type (INFa), the intermediate type (INFb), and the infiltrative growth type (INFc). Different INF types differ in clinicopathological features and prognosis and can be used as predictors of postoperative recurrence and prognosis in GC

patients. Many studies have shown that inflammatory indices are potential prognostic indices for GC patients. However, there is no evidence defining the prognostic significance of immune inflammatory indices for GC with different INF types.

### Research motivation

Evaluating whether inflammatory indices have prognostic significance for GC with different INF types will provide a basis for clinicians to treat and predict the prognosis of these patients in the future.

### Research objectives

To analyze the relationships among peripheral circulating immune cells, inflammatory indices and INF types and to evaluate their ability to evaluate the outcome of patients with GC.

### Research methods

This retrospective study analyzed the clinicopathological characteristics and long-term survival data of 962 patients who underwent radical gastrectomy. Patients were categorized into the INFa, INFb, and INFc groups. The differences of clinicopathological features between the three groups were analyzed by chi-square test. The cutoff values of inflammatory indices were analyzed by receiver operating characteristic curves. The Kaplan–Meier and log-rank tests were used to analyze overall survival (OS). The independent risk factors for patients prognosis were analyzed by univariate and multivariate analyses based on the logistic regression. The nomogram models were constructed by R studio.

### Research results

Based on the postoperative pathology report, there were 183, 331 and 448 patients in the INFa, INFb, and INFc groups, respectively. The OS of the INFc group was significantly lower than that of the other two groups ( $P < 0.001$ ). The systemic immune-inflammation index ( $P = 0.039$ ) and metastatic lymph node ratio (mLNR) ( $P = 0.003$ ) were independent risk factors for prognosis in the INFa group. The platelet-lymphocyte ratio (PLR) ( $P = 0.018$ ), age ( $P = 0.026$ ), body mass index ( $P = 0.003$ ), and postsurgical tumor node metastasis (pTNM) stage ( $P < 0.001$ ) were independent risk factors for prognosis in the INFb group. The PLR ( $P = 0.021$ ), age ( $P = 0.021$ ), pTNM stage ( $P = 0.028$ ), and mLNR ( $P = 0.002$ ) were independent risk factors for prognosis in the INFc group. The area under the curve of the nomogram model for predicting 5-year survival in the INFa group, INFb group, and INFc group was 0.787, 0.823, and 0.781, respectively.

### Research conclusions

The nomogram model based on different inflammatory indices and clinicopathological features can be used to evaluate the prognosis of different INF types GC patients.

### Research perspectives

Further multicentric studies are needed to expansion of the sample size and external validation of nomogram model was performed to determine its predictive ability.

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## FOOTNOTES

**Author contributions:** Wang YF and Yin X designed and conceived this project, and they contributed equally to this work; Wang YF, Yin X, Fang TY and Wang YM, Zhang L, Zhang XH interpreted and analyzed the data; Xue YW revised the manuscript for important intellectual content; Wang YF, Yin X, Fang TY, Wang YM, Zhang L, Zhang XH, Zhang DX, Zhang Y, Wang XB, Wang H participated in the patient information collection; all authors read and approved the final manuscript.

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**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

**Conflict-of-interest statement:** All the authors have no conflict of interest related to the manuscript.

**Data sharing statement:** Patients' data were saved in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, <http://www.sghmu.com>).

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