

Nomogram Based on Preoperative Fibrinogen and Systemic Immune-Inflammation Index Predicting Recurrence and Prognosis of Patients with Borrmann Type III Advanced Gastric Cancer

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Background and Objectives: The prognosis is known to differ significantly among advanced gastric cancer (AGC) with Borrmann type III. This study aimed to evaluate the prognosis of these patients more individually.

Methods: We selected 542 AGC patients with Borrmann type III. We used the receiver operating characteristic curve to analyze the cutoff values of inflammation indexes, and used Kaplan–Meier and Log rank tests to analyze recurrence-free survival (RFS) and overall survival (OS). The independent risk factors for recurrence and prognosis were analyzed by Cox proportional hazards regression model. The nomogram models were constructed by R studio.

Results: Patients with high preoperative fibrinogen (F) and systemic immune-inflammation index (SII) levels had worse RFS and OS and higher risk of postoperative locoregional recurrence, hematogenous metastasis and lymph node metastasis. F and SII can combine with different clinicopathological features (all $P < 0.05$) to construct nomograms to predict 5-year recurrence and prognosis, which both were superior to pTNM stage alone.

Conclusion: The nomogram models based on F and SII can evaluate AGC with Borrmann type III postoperative recurrence and prognosis.

Keywords: gastric cancer, Borrmann classification, fibrinogen, systemic immune-inflammation index, recurrence, nomogram

Introduction

Gastric cancer (GC) is the third malignant tumor that causes cancer death, with about 865,000 deaths annually.¹ There were of 60% early GC patients in Korea and Japan, while more than 80% advanced GC (AGC) in China.^{2,3} In order to evaluate the AGC patients prognosis, experts have proposed a variety of classification methods according to tumor biological characteristics.^{4,5} Since 1926, the Borrmann classification according to tumor macroscopic characteristics,⁶ and the most common macro type of AGC is Borrmann III,^{7,8} which has significant prognostic differences according to different clinicopathological features. Hosoda et al⁹ considered that tumor size was related to the prognosis of AGC with Borrmann III. The five -year survival rate of patients with preoperative tumor diameter ≥ 10 cm was lower than those with tumor size < 10 cm (27.9% vs 49.9%). Zhai et al¹⁰ found that the presence or absence of vascular infiltration had a significant impact on the survival of AGC with Borrmann type III (16.4% vs 29.1%). Therefore, combining the clinicopathological features to build prognostic models to evaluate prognosis of AGC patients with Borrmann III will contribute to individualized treatment.

Tumor immunity plays a crucial role in immunotherapy, because clinical experts can select the specific immune trigger point.¹¹ Galon proposed the pTNM-I (Immunology) stage, which suggests that the tumor immunity can provide comprehensive prognosis information.^{12,13} However, the selection of tissue section sites limits immunohistochemical staining. Then, peripheral blood immune also plays an important role in the occurrence of tumors and progress. Fibrinogen (F) plays an important role in the coagulation process and inflammatory response, and elevated levels suggest a poor prognosis in patients with GC.¹⁴ Our research team found that for early diagnosis of GC, the predicted performance of neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) were significantly better than traditional tumor markers.¹⁵ Furthermore, there are significant differences in the peripheral immune status of patients with different Lauren type patients.¹⁶ Borrmann type III AGC as an infiltrative ulcerative carcinoma usually has a large ulcer surface, and may be associated with a stronger inflammatory response.^{17,18} However, there is no research to analyze its relationship with the peripheral immune inflammatory response. Thus, whether peripheral inflammation indexes and clinicopathological features can assess Borrmann III AGC patients' prognosis needs in-depth research.

Hence, we compared the values of different inflammation indexes in predicting the postoperative recurrence and prognosis of Borrmann III AGC. After that, build a prediction model based on inflammation indexes to predict patients' prognosis.

Methods

Patients

This study retrospectively analyzed 542 patients diagnosed with Borrmann type III AGC between January 4, 2013 and December 30, 2014. All GC patients underwent radical gastrectomy according to their respective conditions.¹⁹ The diagnosis of GC was based on tissue samples obtained during gastroscopy and confirmation by pathologists through examination of postoperative tissue specimens.

Exclusion criteria were: (1) preoperative chemotherapy; (2) severe heart disease; (3) platelet therapy within 3 months before surgery; (4) active bleeding; (5) intravascular coagulation; (6) severe infection; (7) hematological malignancies; (8) steroid drug treatment.

Postoperative chemotherapy regimens were based on the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.²⁰ To ensure that the research is accurate, we included 220 patients who received complete postoperative chemotherapy in our institution. We did not include patients who have not received chemotherapy in our institution, or patients have returned to the local hospital chemotherapy without complete chemotherapy records.

Datasets

The datasets were saved in the Harbin Medical University Cancer Hospital, including gender, age, body mass index (BMI), tumor size, tumor location, metastatic lymph node ratio (mLNR), pTNM stage, vascular infiltration, nerve infiltration, postoperative chemotherapy and laboratory examination. The pTNM staging conforms to the eighth edition of American Joint Commission on Cancer (AJCC). The tumor invasion exceeds the muscular propria (T2), and without considering lymph nodes status, which was defined as AGC.²¹ All patients were discharged by phone, email or at the outpatient department of Harbin Medical University Cancer Hospital for regular follow-up examination, including hematological analysis, tumor markers, gastroscopy, abdominal ultrasound, abdominal CT, and PET-CT according to the condition of some patients. Stage I patients are followed every 12 months, stage II patients are followed up every 6 months, and stage III patients are followed every 3–6 months. According to the medical history, imaging examination, cytological examination, and the organization biopsy determine recurrence and metastasis. Chest or abdominal CT is performed for suspected tumor recurrence or tumor marker levels higher than pathological levels, and bone scan for suspected bone metastases. The types of recurrence and metastasis can be divided into locoregional recurrence (anastomotic or gastric remnant),

hematogenous recurrence (liver, bone or other sites of metastatic disease), peritoneal recurrence and lymph node recurrence.^{22,23}

Inflammation Indexes

Calculate the inflammatory indexes based on the results of the peripheral blood test. The calculation formula is as follows, neutrophil–lymphocyte ratio (NLR) = N/L, platelet–lymphocyte ratio (PLR) = P/L, systemic immune-inflammation index (SII) = $N \times P / L$ (N = Neutrophil count, L = Lymphocyte count, and P = Platelet count).

Statistical methods

Recurrence-free survival (RFS) was defined as the time from surgery to recurrence or the last recurrence-free follow-up. OS was defined as the time from surgery to death or the last surviving follow-up. The Receiver operating characteristic curve (ROC) was used to compare the predictive performance of the inflammatory indexes and compare the area under the curve (AUC). Judging the cutoff values of inflammatory indexes according to the Youden index. The relationship between clinical pathological characteristics and inflammation indexes was judged by chi-square test. The Log rank test and Kaplan–Meier method were used to analyze survival curves. Cox regression model analysis recurrence and independent risk factors related to prognosis. Hazard ratios (HRs) and 95% CIs were estimated for each factor. The nomogram models were drawn through the R studio by “SvyNom” and “rms” packages. SPSS version 25.0 was used for analysis and $P < 0.05$ was considered statistically significant.

Results

Clinical Characteristics

In this study, the median white blood cell count was $6.10 \pm 1.95 \times 10^9/L$, the median age was 58 (range 23–87). There were 408 men (75.3%) and 134 women (24.7%). Patients with pTNM stage I, II and III were 52 (9.6%), 184 (34.3%) and 306 (56.1%), respectively (Table 1). Two hundred and six patients (38.0%) had tumor recurrence or metastasis, and 197 (36.3%) died within 5 years after radical gastrectomy. The number of patients with recurrence patterns of locoregional recurrence, peritoneal metastasis, hematogenous metastasis and lymph node metastasis were 32 (5.9%), 64 (11.8%), 68 (12.5%) and 41 (7.6%), respectively. At least two types of recurrence occurred in 16 patients, and no specific recurrence patterns were observed in 19 patients.

NLR, PLR, Fibrinogen and SII

For preoperative NLR, PLR, Fibrinogen (F) and SII of patients, 1.94, 133.56, 3.24 and 489.90, respectively, were found to be the optimal cutoff values for assessing the risk of recurrence. For these values, AUC was 0.633 (95% CI: 0.584–0.681), 0.648 (95% CI: 0.601–0.696), 0.652 (95% CI: 0.604–0.699) and 0.666 (95% CI: 0.619–0.714), respectively (Figure 1A). The optimal cutoff values for assessing patient’s prognosis were 1.94, 133.56, 3.27 and 489.90. The AUC was 0.638 (95% CI: 0.589–0.687), 0.651 (95% CI: 0.603–0.700), 0.656 (95% CI: 0.608–0.704) and 0.672 (95% CI: 0.624–0.720), respectively (Figure 1B). Therefore, F and SII (F-SII) scoring system was constructed according to the optimal cutoff values. Patients who were both lower than the optimal values were 0 points, patients who were both higher than the optimal values were 2 points, and only one index higher than the optimal values was 1 point.

F-SII and RFS

Chi-square found that F-SII was significantly correlated with clinicopathological characteristics, including tumor diameter and pTNM stage (Table 2). RFS of patients with F-SII=0, 1 and 2 was 50.88 (95% CI: 48.739–53.017), 42.37 (95% CI: 39.252–45.479) and 31.34 (95% CI: 26.602–36.082) months. The 5-year RFS rate was 74.1%, 56.8% and 24.7%, respectively ($P < 0.001$) (Figure 2A).

For patients with stage I/II and III, there were significant differences in RFS based on F-SII score. For patients with stage I/II, RFS of patients with F-SII=0, 1 and 2 was 56.08 (95% CI: 54.148–58.003), 52.68 (95% CI:

Table 1 Baseline Characteristics of the Patients

Characteristics	Cases	Percentage (%)
Sex		
Male	408	75.3
Female	134	24.7
Age (years)		
≤60	328	60.5
>60	214	39.5
BMI (kg/m ²)		
≤24	395	72.9
>24	147	27.1
Tumor diameter (mm)		
≤50	310	57.2
>50	232	42.8
Tumor location		
Upper	66	12.2
Middle	88	16.2
Lower	384	70.9
Total	4	0.7
Resection		
Proximal gastrectomy	31	5.7
Distal gastrectomy	357	65.9
Total gastrectomy	154	28.4
Histological type		
Moderate+Well	222	41.0
Poor	217	40.0
Others	103	19.0
pT stage		
T2	94	17.3
T3	246	45.4
T4	202	37.3
pN stage		
N0	145	26.8
N1	126	23.2
N2	113	20.8
N3	158	29.2
pTNM stage		
I	52	9.6
II	186	34.3
III	304	56.1
Vascular infiltration		
Yes	148	27.3
No	394	72.7
Nerve infiltration		
Yes	216	39.9
No	326	60.1
Postoperative chemotherapy		
Yes	220	40.6
No	322	59.4
Patterns of recurrence		
Locoregional recurrence	32	5.9
Peritoneal metastasis	64	11.8
Hematogenous metastasis	68	12.5
Lymph node metastasis	41	7.6
Undefined patterns	19	3.5
Recurrence	206	38.0
Death	197	36.3

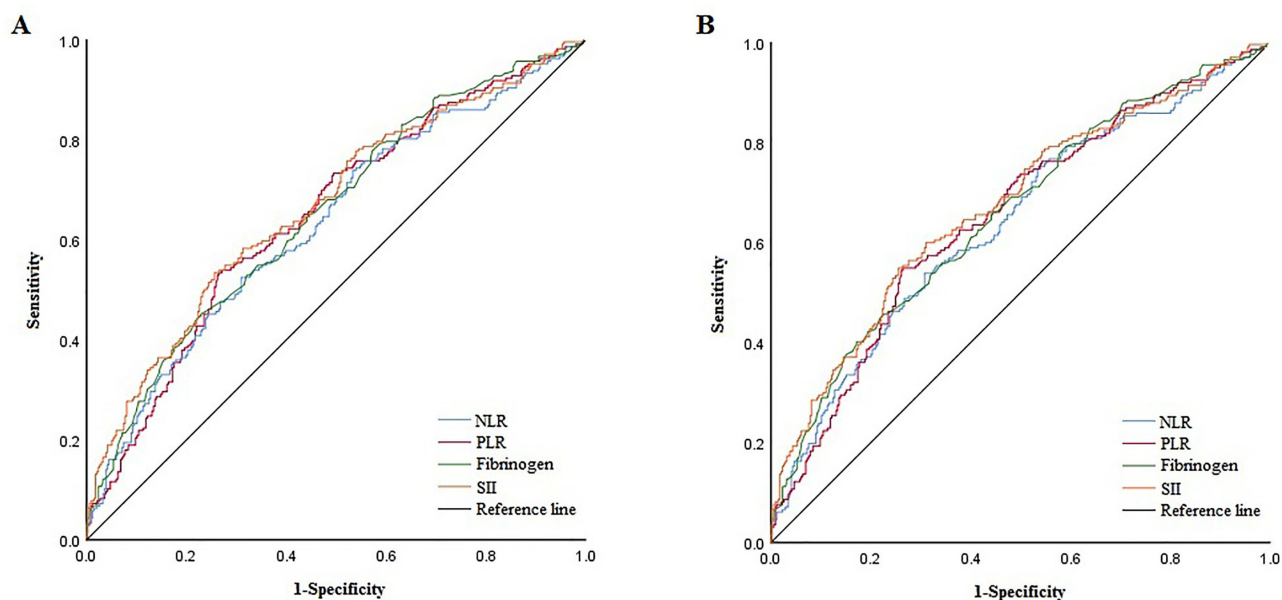


Figure 1 ROC of different inflammation indexes of patients. **(A)** Assessing the risk of recurrence. **(B)** Assessing prognosis.

48.967–56.399) and 43.85 (95% CI: 34.854–52.841) months, respectively. The 5-year RFS rate was 86.5%, 81.8% and 53.8%, respectively ($P<0.001$) (Figure 2B). For patients with stage III, RFS of patients with F-SII=0, 1 and 2 was 45.11 (95% CI: 41.405–48.816), 35.45 (95% CI: 31.336–39.570) and 26.63 (95% CI: 21.557–31.697) months, respectively. The 5-year RFS rate was 60.0%, 39.9% and 13.1%, respectively ($P<0.001$) (Figure 2C). RFS of patients based on F-SII differed significantly with tumor diameter ($P<0.001$) (Figure 2D and E).

There were 146 (146/459, 31.8%) patients in the F-SII=0-1 group and 60 (60/83, 72.3%) in the F-SII=2 group with tumor recurrence ($P<0.001$). We also found that the incidence of locoregional recurrence, hematogenous metastasis and lymph node metastasis in the F-SII=2 group was significantly higher than that in the F-SII=0-1 group (14.5% vs 4.4%, 21.7% vs 10.9%, 15.7 vs 6.1%, respectively) ($P<0.05$), while peritoneal metastasis had no significant difference (15.7% vs 11.1%) ($P=0.915$) (Figure 3).

Univariate analysis showed that age, tumor diameter, metastatic lymph node ratio (mLNR), pTNM stage, body mass index (BMI), F, SII, alanine aminotransferase (ALT), carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19–9, vascular infiltration and nerve infiltration were statistically significant. Multivariate analysis showed that age, mLNR, pTNM stage, BMI, F and SII were independent risk factors associated with recurrence (Table 3).

We combined the independent risk factors associated with recurrence to construct a nomogram that was used to evaluate recurrence (Figure 4a). For predicting recurrence within 3 and 5 years after radical resection, the AUC of the nomogram models both were greater than that of pTNM stage alone, 0.793 (95% CI: 0.753–0.832) and 0.805 (95% CI: 0.767–0.842) vs 0.706 (95% CI: 0.662–0.750) and 0.703 (95% CI: 0.660–0.747). The sensitivity were 74.4% and 71.7%, respectively, and the specificity were 73.7% and 77.4% (Figure 4b and c).

F-SII and OS

Chi-square analysis showed that F-SII was significantly correlated with clinicopathological characteristics, including tumor diameter and pTNM stage (both $P<0.001$) (Table 2). OS of patients with F-SII=0, 1 and 2 was 52.51 (95% CI: 50.640–54.376), 45.02 (95% CI: 42.220–47.826) and 35.35 (95% CI: 30.901–39.804) months, respectively. The 5-year OS rate was 75.9%, 56.9% and 25.3%, respectively ($P<0.001$) (Figure 5A).

For patients with stage I/II and III, there were significant differences in OS based on F-SII score. For patients with stage I/II, the OS of patients with F-SII=0, 1 and 2 was 56.60 (95% CI: 54.816–58.374), 54.75 (95% CI: 51.628–57.872)

Table 2 Chi-Square Test Analysis of the Connection Between F-SII and Clinicopathological Features for RFS and OS

Characteristics	RFS				OS			
	0 (259)	1 (200)	2 (83)	p value	0 (264)	1 (197)	2 (81)	p value
Sex				0.788				0.844
Male	196 (75.7)	152 (76.0)	60 (72.3)		199 (75.4)	150 (76.1)	59 (72.8)	
Female	63 (24.3)	48 (24.0)	23 (27.7)		65 (24.6)	47 (23.9)	22 (27.2)	
Age (years)				0.074				0.063
≤60	167 (64.5)	119 (59.5)	42 (50.6)		171 (64.8)	116 (58.9)	41 (50.6)	
>60	92 (35.5)	81 (40.5)	41 (49.4)		93 (35.2)	81 (41.1)	40 (49.4)	
BMI (kg/m ²)				0.991				0.945
≤24	189 (73.0)	146 (73.0)	60 (72.3)		194 (73.5)	142 (72.1)	59 (72.8)	
>24	70 (27.0)	54 (27.0)	23 (27.7)		70 (26.5)	55 (27.9)	22 (27.2)	
Tumor diameter (mm)				<0.001				<0.001
≤50	173 (66.8)	104 (52.0)	33 (39.8)		175 (66.3)	104 (52.8)	31 (38.3)	
>50	86 (33.2)	96 (48.0)	50 (60.2)		89 (33.7)	93 (47.2)	50 (61.7)	
Tumor location				0.382				0.351
Upper	27 (10.4)	28 (14.0)	11 (13.2)		28 (10.6)	27 (13.7)	11 (13.6)	
Middle	43 (16.6)	29 (14.5)	16 (19.3)		44 (16.7)	28 (14.2)	16 (19.7)	
Lower	188 (72.6)	142 (71.0)	54 (65.1)		191 (72.3)	141 (71.6)	52 (64.2)	
Entire stomach	1 (0.4)	1 (0.5)	2 (2.4)		1 (0.4)	1 (0.5)	2 (2.5)	
Resection				0.374				0.320
Proximal gastrectomy	14 (5.4)	13 (6.5)	4 (4.8)		15 (5.7)	12 (6.1)	4 (5.0)	
Distal gastrectomy	177 (68.3)	132 (66.0)	48 (57.8)		180 (68.2)	131 (66.5)	46 (56.8)	
Total gastrectomy	68 (26.3)	55 (27.5)	31 (37.4)		69 (26.1)	54 (27.4)	31 (38.2)	
Histological type				0.473				0.542
Moderate+Well	101 (39.0)	86 (43.0)	35 (42.2)		104 (39.4)	85 (43.2)	33 (40.7)	
Poor	114 (44.0)	72 (36.0)	31 (37.3)		115 (43.6)	71 (36.0)	31 (38.3)	
Others	44 (17.0)	42 (21.0)	17 (20.5)		45 (17.0)	41 (20.8)	17 (30.0)	
pTNM stage				<0.001				<0.001
I	34 (13.1)	15 (7.5)	3 (3.6)		34 (12.9)	15 (7.6)	3 (3.7)	
II	101 (39.0)	66 (33.0)	19 (22.9)		104 (39.4)	65 (33.0)	17 (21.0)	
III	124 (47.9)	119 (59.5)	61 (73.5)		126 (47.7)	117 (59.4)	61 (75.3)	
Vascular infiltration				0.856				0.853
Yes	72 (27.8)	52 (26.0)	24 (28.9)		74 (28.0)	51 (25.9)	23 (28.4)	
No	187 (72.2)	148 (74.0)	59 (71.1)		190 (72.0)	146 (74.1)	58 (71.6)	
Nerve infiltration				0.530				0.354
Yes	106 (40.9)	84 (42.0)	29 (34.9)		105 (39.8)	84 (42.6)	27 (33.3)	
No	153 (59.1)	116 (58.0)	54 (65.1)		159 (60.2)	113 (57.4)	54 (66.7)	

Notes: Tumor location, histological type, pTNM stage, vascular infiltration and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold (*P*<0.05).

Abbreviations: F-SII, fibrinogen and systemic immune-inflammation index, RFS, recurrence-free survival, OS, overall survival, BMI, body mass index.

and 45.87 (95% CI: 37.981–53.762) months, respectively. The 5-year OS rate was 86.6%, 83.6% and 50.0%, respectively (*P*<0.001) (Figure 5B). For patients with stage III, the OS of patients with F-SII=0, 1 and 2 was 47.94 (95% CI: 44.717–51.171), 38.49 (95% CI: 34.742–42.232) and 31.75 (95% CI: 26.757–36.747) months. The 5-year OS rate was 63.8%, 38.8% and 16.0% (*P*<0.001) (Figure 5C). OS of patients based on F-SII differed significantly with tumor diameter (*P*<0.001) (Figure 5D and E).

Univariate analysis showed that age, tumor diameter, mLNR (*P*<0.001), pTNM stage, BMI, F, SII, ALT, CEA, CA19-9, vascular infiltration and nerve infiltration were significant. In multivariate analysis, age, mLNR, pTNM stage, BMI, F, SII and nerve infiltration were independent risk factors associated with prognosis (Table 4).

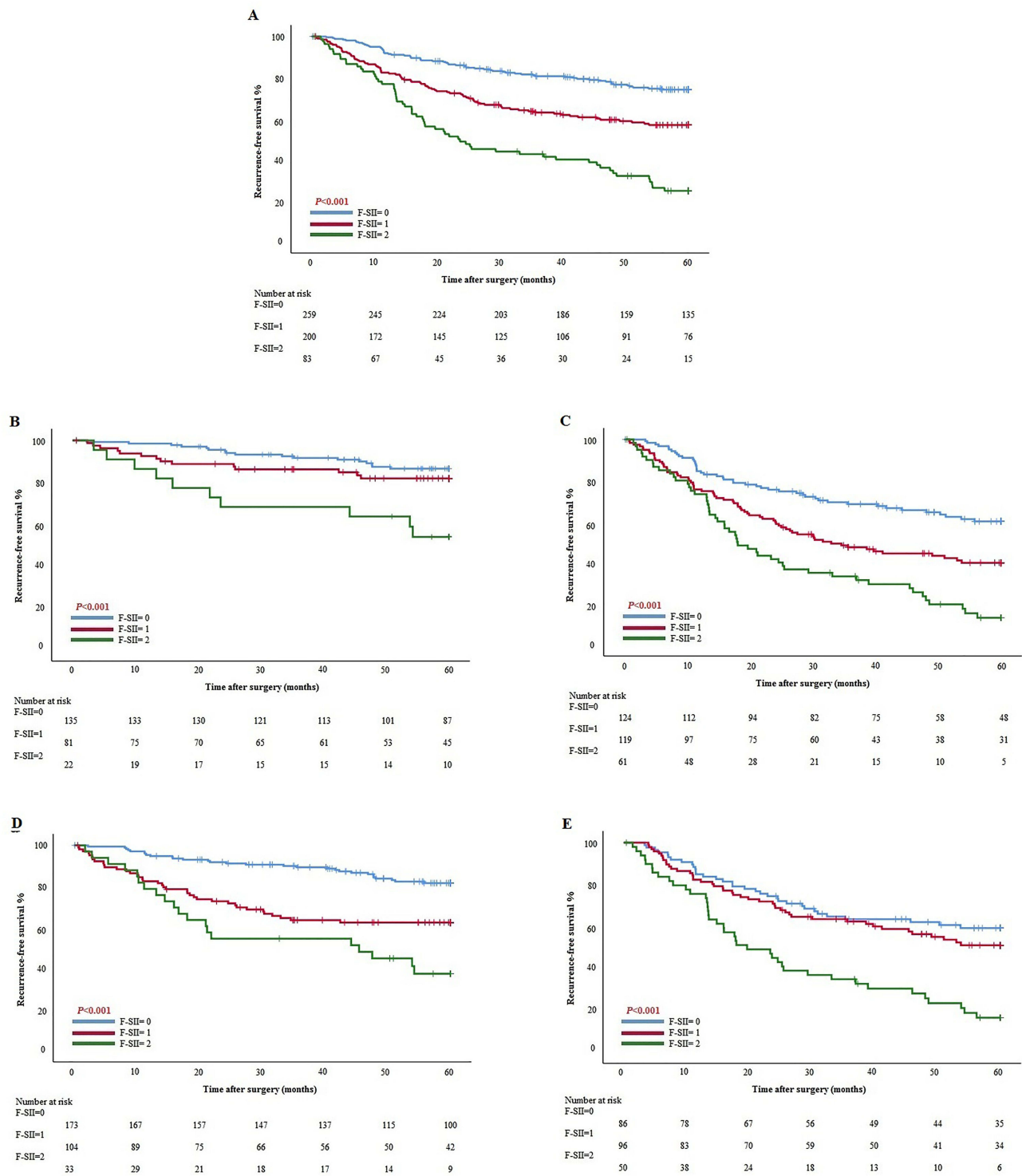


Figure 2 Kaplan–Meier curves analyses for RFS based on F-SII score. **(A)** All patients. **(B)** Stage I/II. **(C)** Stage III. **(D)** Tumor diameter ≤50 mm. **(E)** Tumor diameter >50 mm.

We combined the independent risk factors associated with prognosis to construct a nomogram that was used to evaluate prognosis (Figure 6a). The results showed that the AUC of the nomogram models both were greater than that of the pTNM stage alone, 0.797 (95% CI: 0.757–0.837) and 0.806 (95% CI: 0.769–0.844) vs 0.701 (95% CI: 0.656–0.746)

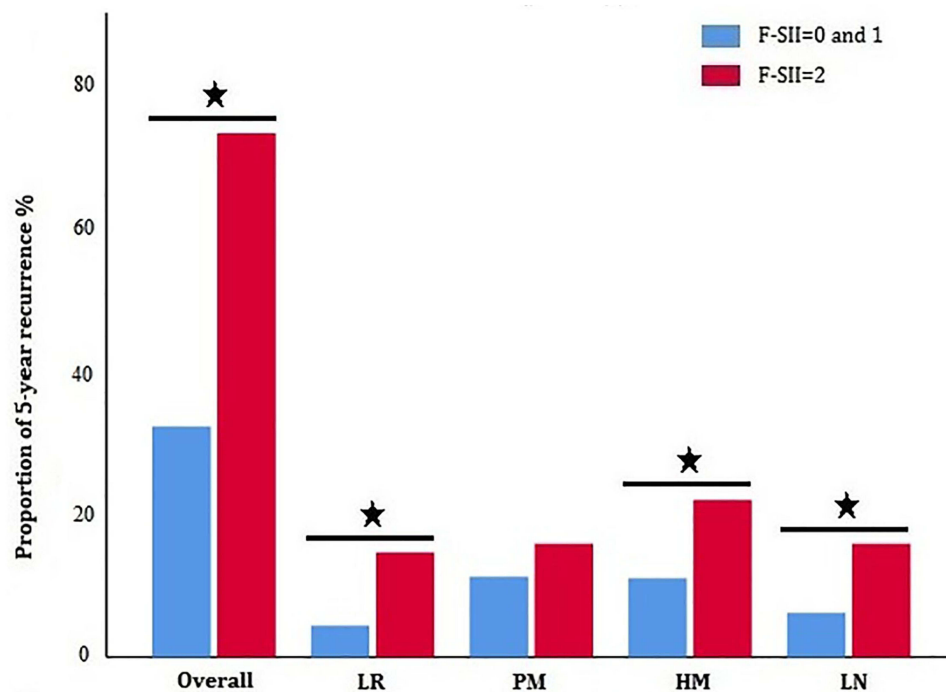


Figure 3 Recurrence patterns based on F-SII score. LR: locoregional recurrence, PM: peritoneal metastasis, HM: hematogenous metastasis, LN: lymph node metastasis. (★: $P<0.05$).

and 0.701 (95% CI: 0.657–0.745). The sensitivity were 75.0% and 71.6%, respectively, and the specificity were 72.6% and 76.8% (Figure 6b and c).

Discussion

Borrmann classification was proposed based on the macro characteristics of GC, and has played an important role clinically since 1926.^{6,24} Borrmann type IV GC has unique clinicopathological characteristics²⁵ and has attracted a lot of clinical research. The clinical characteristics of Borrmann III are indirectly reflected by the research of other types. The proportion of Borrmann III accounts for 40.6%–58.9% of AGC and the five-year survival rate was 46.0%–51.6%.^{7,8} When the diameter of the tumor is greater than 8cm or the combined vascular infiltration, the prognosis of Borrmann III is similar to Borrmann IV.^{10,26,27} Thus, we still need to develop a new biomarker evaluation Borrmann III AGC patients' prognosis.

Some inflammation indexes, such as NLR, PLR can evaluate the prognosis of patients and be used for individualized adjuvant treatment.^{28–30} The proliferation of tumor cells will make it break through mechanical pressure and escape immune monitoring, and enter the peripheral vein to become circulating tumor cells (CTCs).³¹ In this process, interleukin (IL)-1 β and IL-6 released by neutrophils play a crucial part in promoting the proliferation of tumor cells. Neutrophils can also promote distant metastasis of CTCs in peripheral blood, and elevated level of CTCs and neutrophil clusters is associated with worse RFS.³² However, lymphocytes can secrete interferon- γ to inhibit CTCs migrating.³³ Besides, platelets can induce epithelial–mesenchymal transformation by transforming growth factor β to promote distant metastasis and form aggregates with CTCs to promote migration.³⁴ Wang et al³⁵ found that preoperative SII level was an independent prognostic factor for OS in GC patients. Our study found that preoperative SII level was an independent prognostic factor for RFS and OS in Borrmann type III AGC patients. Similarly, as an important component of peripheral blood immunity, F acts as a scaffold to support the adhesion of CTCs, promote the proliferation and migration of CTCs, and ultimately affect the whole process of tumor growth and metastasis.³⁶ Yamamoto et al³⁷ believed that F level was an independent prognostic factor of RFS and could be used to predict postoperative GC recurrence. Our study not only

Table 3 Univariate and Multivariate Analyses of Factors Associated with RFS

Characteristics	RFS			
	Univariate Analyses		Multivariate Analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex		0.897	–	–
Male	1.000			
Female	0.979 (0.714–1.344)			
Age (years)	1.018 (1.004–1.032)	0.014	1.018 (1.004–1.033)	0.012
Tumor diameter (mm)	1.018 (1.012–1.023)	<0.001	1.005 (0.998–1.012)	0.146
Resection		0.053	–	–
Distal gastrectomy	1.000			
Proximal gastrectomy	1.193 (0.674–2.114)	0.544		
Total gastrectomy	1.436 (1.071–1.926)	0.016		
Histological type		0.160	–	–
Moderate+Well	1.000			
Poor	1.279 (0.938–1.744)	0.120		
Others	1.657 (0.953–2.004)	0.088		
mLNR	19.621 (11.541–33.358)	<0.001	6.776 (3.243–14.157)	<0.001
pTNM stage		<0.001		<0.001
I	1.000		1.000	
II	3.924 (1.211–12.713)	0.023	2.498 (0.761–8.199)	0.131
III	13.955 (4.452–43.740)	<0.001	5.670 (1.749–18.380)	0.004
BMI (kg/m ²)	0.915 (0.875–0.957)	<0.001	0.919 (0.879–0.962)	<0.001
Fibrinogen (g/L)	1.146 (1.084–1.211)	<0.001	1.140 (1.059–1.228)	0.001
SII	1.286 (1.160–1.425)	<0.001	1.232 (1.081–1.404)	0.002
ALT (U/L)	0.980 (0.965–0.996)	0.012	1.000 (0.985–1.015)	0.970
Total protein (g/L)	0.995 (0.982–1.008)	0.453	–	–
PNI	0.995 (0.983–1.007)	0.388	–	–
CEA (ng/mL)	1.003 (1.002–1.005)	<0.001	1.002 (1.000–1.004)	0.086
CA19-9 (U/mL)	1.001 (1.001–1.002)	<0.001	1.001 (1.000–1.001)	0.204
Vascular infiltration		<0.001		0.832
No	1.000		1.000	
Yes	1.911 (1.439–2.536)		1.037 (0.740–1.454)	
Nerve infiltration		0.002		0.052
No	1.000		1.000	
Yes	1.550 (1.179–2.038)		1.349 (0.998–1.825)	
Postoperative chemotherapy		0.356	–	–
Yes	1.000			
No	0.879 (0.667–1.157)			

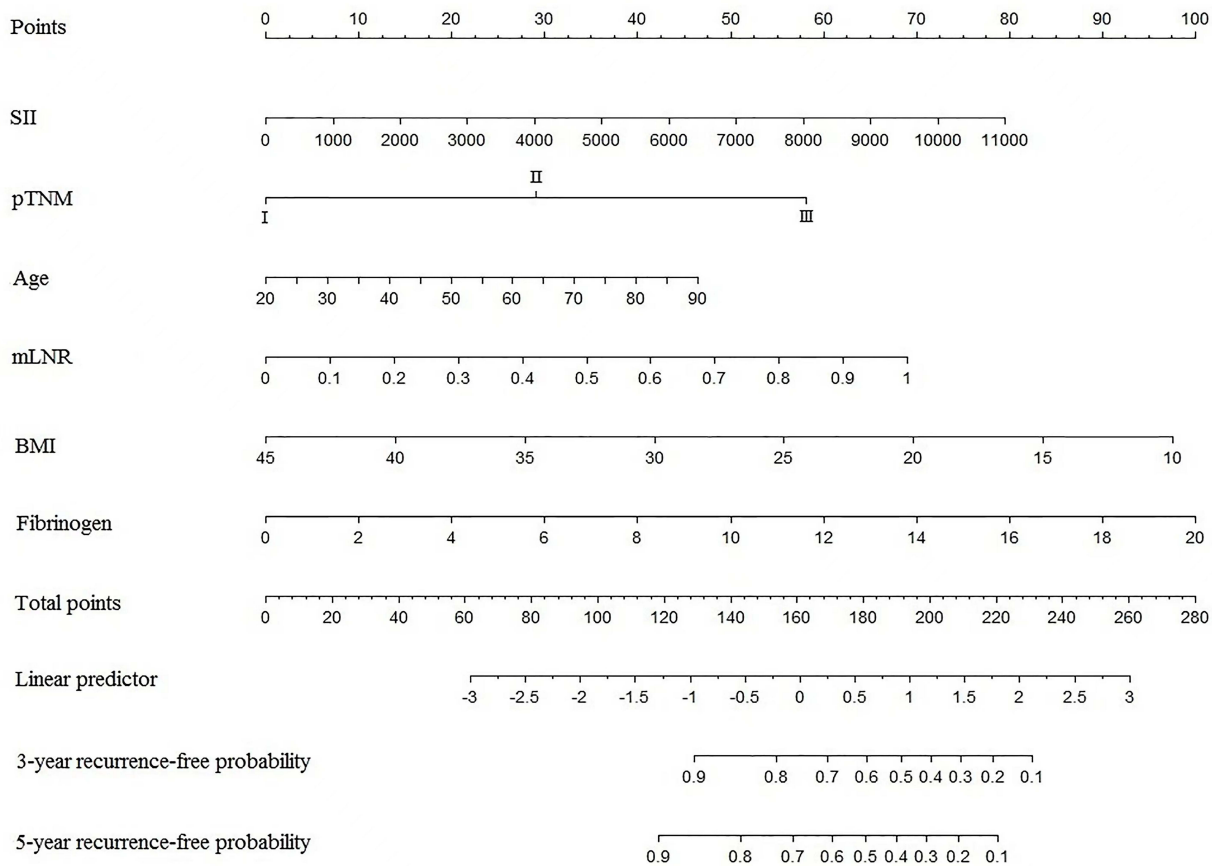
Notes: CEA and CA19-9 were according to the tumor marker examination. Tumor location, histological type, mLNR, pTNM stage, vascular infiltration and nerve infiltration were according to the postoperative pathology report. Statistically significant P values are in bold ($P < 0.05$).

Abbreviations: RFS, recurrence-free survival, HR, hazard ratio, CI, confidence interval, mLNR, metastatic lymph node ratio, BMI, body mass index, SII, systemic immune-inflammation index, ALT, alanine transaminase, PNI, prognostic nutritional index, CEA, carcinoembryonic antigen, CA19-9, carbohydrate antigen 19–9.

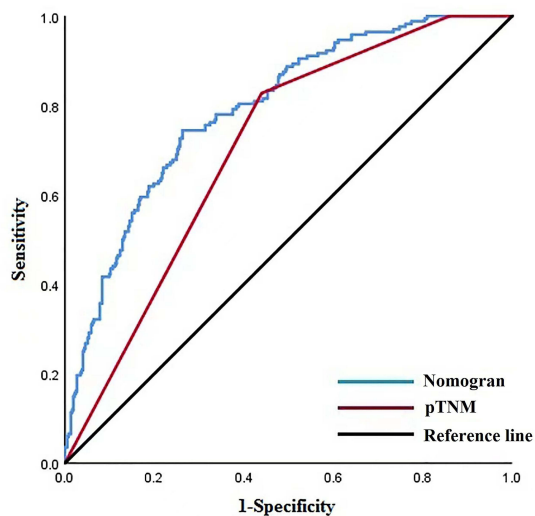
found that F level was an independent risk factor for postoperative recurrence in patients with Borrmann III AGC, but also further investigated the patterns of recurrence.

Inflammation indexes also predict different recurrence patterns of GC. Yamashita et al³⁸ retrospectively analyzed the preoperative plasma F level of 405 patients with AGC undergoing radical surgery, and found that high plasma F level (310 mg/dl) was independently associated with lymph node and liver metastases. Our study found that F-SII score predicted the recurrence risk of AGC with Borrmann type III, and had clinical significance for predicting different postoperative recurrence patterns. Patients with F-SII=2 were more likely to have locoregional recurrence, hematogenous

a



b



c

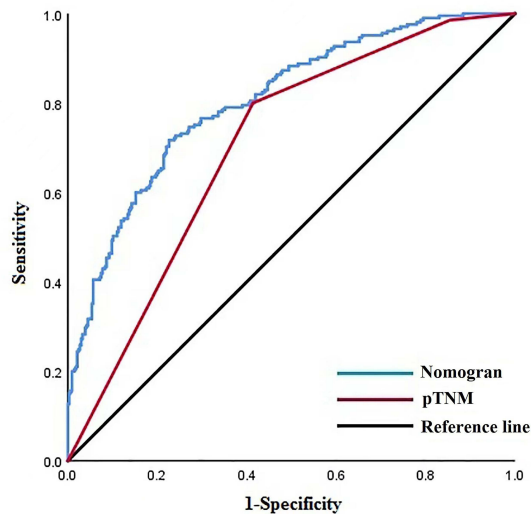


Figure 4 Nomogram models predicting recurrence of patients. (a) Nomogram models predicting 3- and 5-year recurrence. (b) ROC of nomogram model and pTNM stage predicting 3-year recurrence. (c) ROC of nomogram model and pTNM stage predicting 5-year recurrence.

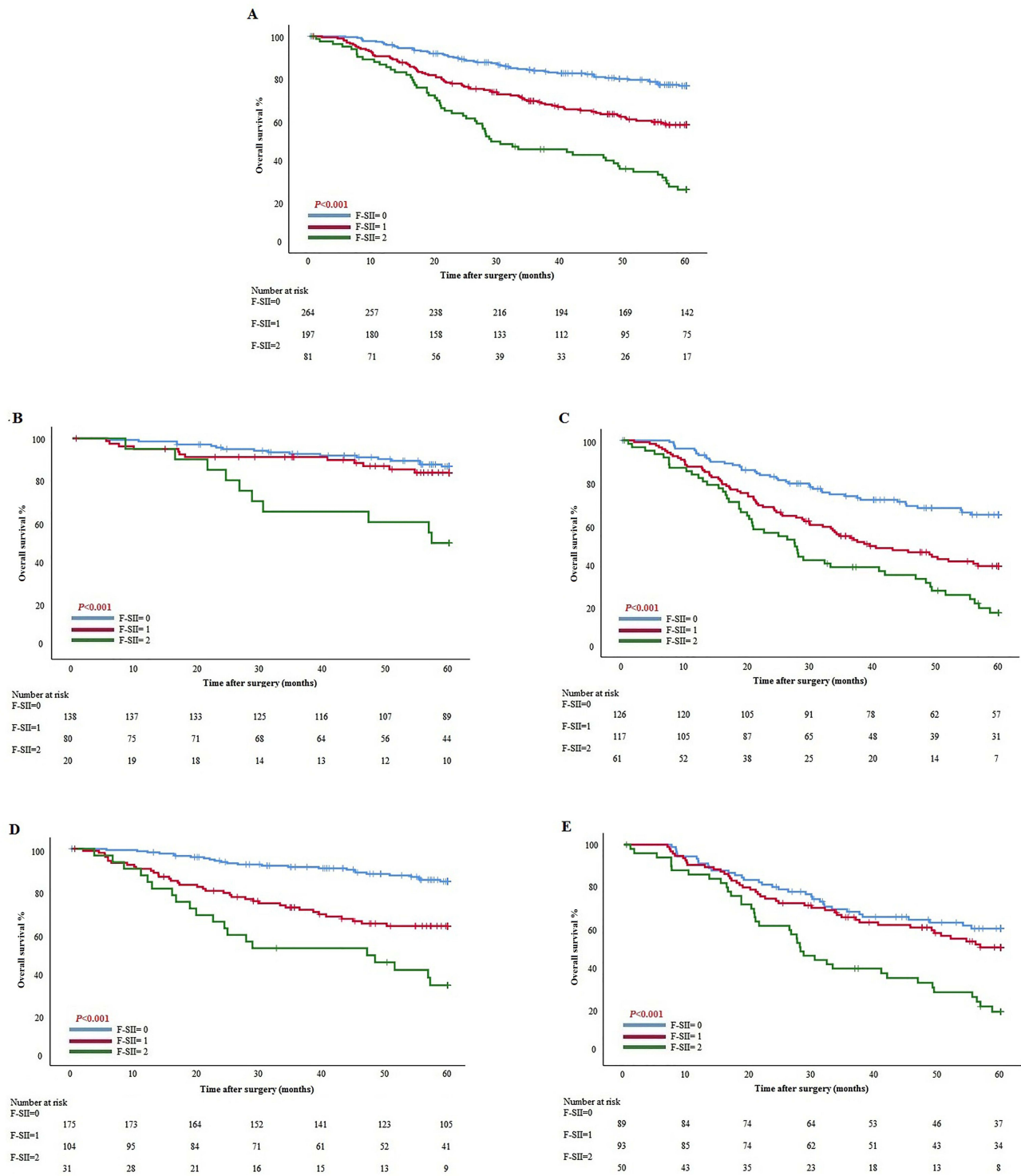


Figure 5 Kaplan–Meier curves analyses for OS based on F-SII score. **(A)** All patients. **(B)** Stage I/II. **(C)** Stage III. **(D)** Tumor diameter ≤50 mm. **(E)** Tumor diameter >50 mm.

metastasis and lymph node metastasis. Peripheral blood inflammatory cytokines play an important role in tumor metastasis by interacting with CTCs. Borrmann type III AGC with a higher level of preoperative F and SII may activate adhesion, proliferation and migration of CTCs, so as to promote hematogenous and distant lymph node metastases. In addition, inflammation in the surrounding tissues of GC is considered an important factor in the locoregional recurrence of cancer.³⁹ Although Chen et al⁴⁰ showed that the inflammatory index PLR is an independent predictor of GC peritoneal

Table 4 Univariate and Multivariate Analyses of Factors Associated with OS

Characteristics	OS			
	Univariate Analyses		Multivariate Analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex		0.890	–	–
Male	1.000			
Female	0.977 (0.708–1.350)			
Age (years)	1.020 (1.005–1.035)	0.007	1.022 (1.007–1.037)	0.004
Tumor diameter (mm)	1.017 (1.012–1.023)	<0.001	1.004 (0.997–1.011)	0.215
Resection		0.071	–	–
Distal gastrectomy	1.000			
Proximal gastrectomy	1.140 (0.629–2.064)	0.666		
Total gastrectomy	1.422 (1.054–1.920)	0.021		
Histological type		0.237	–	–
Moderate+Well	1.000			
Poor	1.261 (0.919–1.729)	0.151		
Others	1.326 (0.906–1.943)	0.147		
mLNR	18.402 (10.758–31.477)	<0.001	6.044 (2.846–12.836)	<0.001
pTNM stage		<0.001		<0.001
I	1.000		1.000	
II	5.713 (1.377–23.705)	0.016	3.534 (0.842–14.836)	0.085
III	19.878 (4.926–80.219)	<0.001	8.289 (2.000–34.364)	0.004
BMI (kg/m ²)	0.908 (0.867–0.951)	<0.001	0.914 (0.873–0.957)	<0.001
Fibrinogen (g/L)	1.148 (1.086–1.214)	<0.001	1.140 (1.058–1.228)	0.001
SII	1.299 (1.172–1.440)	<0.001	1.256 (1.103–1.430)	0.001
ALT (U/L)	0.979 (0.963–0.995)	0.009	0.999 (0.983–1.015)	0.908
Total protein (g/L)	0.993 (0.980–1.007)	0.329	–	–
PNI	0.994 (0.982–1.007)	0.374	–	–
CEA (ng/mL)	1.003 (1.001–1.004)	0.001	1.001 (0.999–1.003)	0.237
CA19-9 (U/mL)	1.001 (1.001–1.002)	<0.001	1.001 (1.000–1.001)	0.141
Vascular infiltration		<0.001		0.712
No	1.000		1.000	
Yes	1.904 (1.425–2.544)		0.937 (0.661–1.327)	
Nerve infiltration		0.001		0.026
No	1.000		1.000	
Yes	1.607 (1.215–2.126)		1.421 (1.043–1.935)	
Postoperative chemotherapy		0.703	–	–
Yes	1.000			
No	0.947 (0.714–1.254)			

Notes: CEA and CA19-9 were according to the tumor marker examination. Tumor location, histological type, mLNR, pTNM stage, vascular infiltration and nerve infiltration were according to the postoperative pathology report. Statistically significant P values are in bold ($P < 0.05$).

Abbreviations: OS, overall survival, HR, hazard ratio, CI, confidence interval, mLNR, metastatic lymph node ratio, BMI, body mass index, SII, systemic immune-inflammation index, ALT, alanine transaminase, PNI, prognostic nutritional index, CEA, carcinoembryonic antigen, CA19-9, carbohydrate antigen 19-9.

metastasis, cancer cells penetrating the serosa are considered the main source of peritoneal seeding or metastasis, and further studies have proved that serosal infiltration is the strongest indicator of GC peritoneal metastasis.^{41,42} Therefore, whether peripheral blood inflammatory markers could be used as an independent indicator to predict GC peritoneal metastasis needs verification.

In various studies, predictive models have been shown to provide quick and accurate preoperative prognostic information. However, GC is a highly heterogeneous gastrointestinal malignancy, and different tumor characteristics

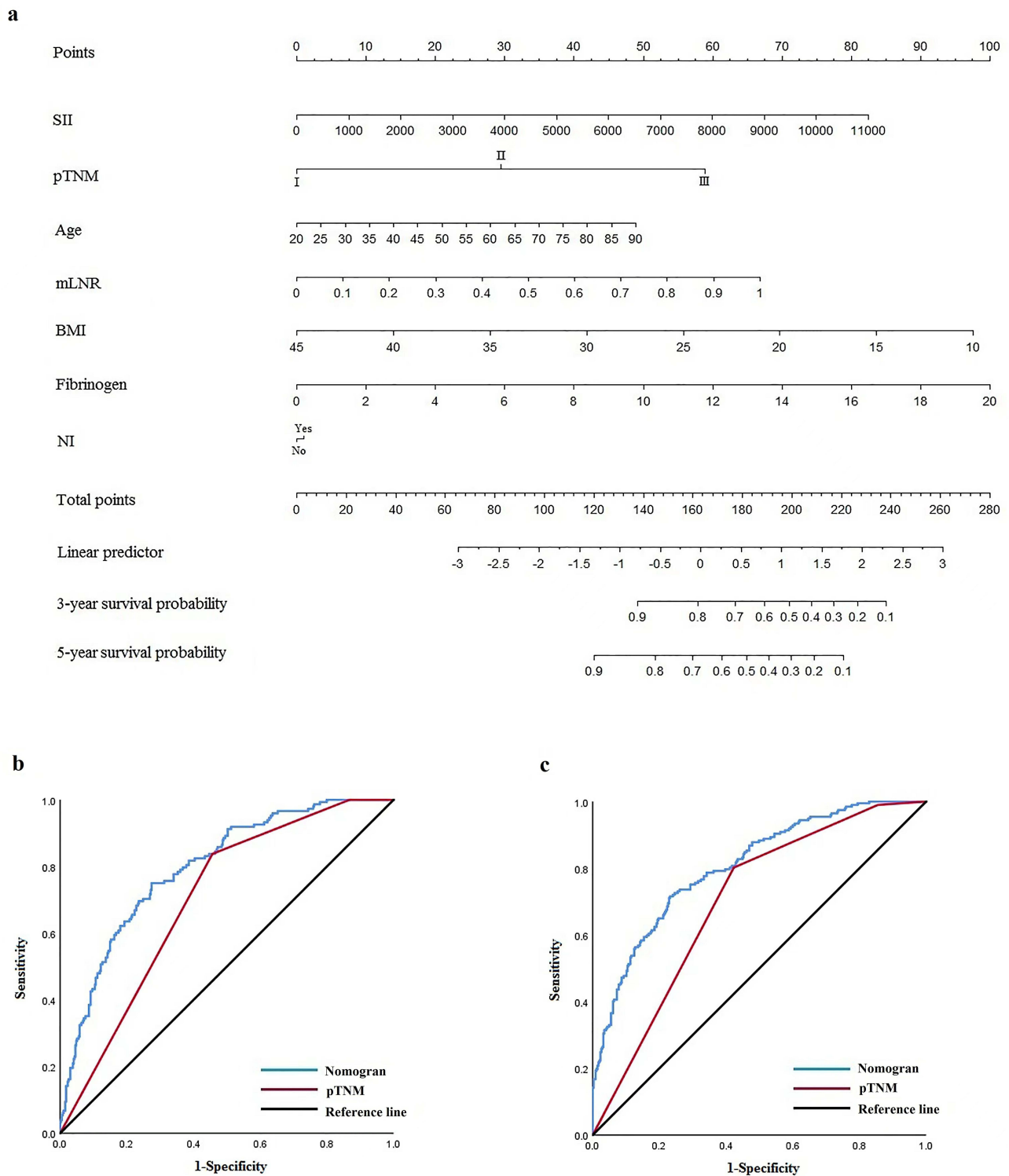


Figure 6 Nomogram models predicting survival of patients. (a) Nomogram model predicting 3- and 5-year survival. (b) ROC of nomogram model and pTNM stage predicting 3-year survival. (c) ROC of nomogram model and pTNM stage predicting 5-year survival.

can greatly influence the immune status of the patient, which in turn affects the predictive performance of various predictors. Therefore, considering their clinical utility, the selection of appropriate predictors can help in a comprehensive assessment of tumor biology and facilitate personalized predictions. Some retrospective studies have provided evidence that different inflammation indices have varying predictive abilities for different biological behaviors of GC. For

instance, Ye et al reported that NLR had better predictive performance than PLR in predicting peritoneal metastases,⁴³ while Fang et al found that NLR had higher sensitivity than PLR in early diagnosis of GC.¹⁵ Yin et al found that PLR had better predictive performance than NLR and SII for diffuse/mixed GC.¹⁶ Moreover, Wang et al observed a significant correlation between SII and tumor size and Borrmann type.³⁵ We also found that F-SII was significantly associated with tumor diameter. Therefore, we speculate that SII may be more appropriate for assessing the prognosis of patients with Borrmann type III and larger tumor size. These findings provide a theoretical basis for individualizing the assessment of tumor biology using different inflammation indices in clinical practice.

Immunotherapy has demonstrated remarkable success in clinical practice. However, despite a higher response rate compared to chemotherapy alone, there is still a need to identify biomarkers that can predict immune response. Previous studies have revealed a correlation between immune infiltration in the TME and GC immunotherapy response.^{44,45} However, the clinical utility of immunohistochemistry-based detection methods is limited due to the heterogeneity of GC. Yuang et al discovered a significant correlation between immune infiltration in the TME and peripheral blood levels of NLR, PLR, and SII. These inflammatory indices accurately predicted the prognosis of GC patients receiving anti-PD-1/PD-L1 immunotherapy.⁴⁵ These findings suggest that inflammatory indices offer insights into the effectiveness of immunotherapy and the heterogeneity of the immune environment.

We found that F and SII both had higher AUCs, and were independent risk factors associated with recurrence and prognosis, which suggested that peripheral blood neutrophils, lymphocytes, platelets and fibrinogen were the main components of peripheral immunity of AGC patients with Borrmann III, and F-II was significantly correlated with tumor diameter and pTNM stage. Tumor cells can secrete various cytokines, and chemokines cause an increased inflammatory response,⁴⁶ and often lead to an elevated inflammatory response when tumor aggressiveness increases.⁴⁷ We found that Borrmann type III GC, especially in patients with a higher pTNM stage and a larger tumor diameter, tends to lead to a significantly elevated inflammatory response, which in turn leads to a poor prognosis. It confirmed our previous suspicion that a larger ulcer surface indicates a stronger inflammatory response in AGC with Borrmann III. In this study, we also found that the risk of recurrence and metastasis in the F-SII score 2 group was significantly higher than in the 0–1 group, and F-SII score predicted different recurrence patterns. As a result, the F-SII score could not only evaluate Borrmann type III AGC patients prognosis, but also assess the risk of recurrence and metastasis. For patients with high F-SII, we suggest that the corresponding treatment should be improved, and regular review and close follow-up should be carried out.

Tumor immunity complements the pTNM stage with comprehensive prognostic information.^{48,49} For example, analysis of the ratio of cytokines to immune cells in body fluids can predict the prognosis of patients with metastatic GC.⁵⁰ Liu et al⁵¹ constructed a nomogram based on inflammation indexes, which can better predict the prognosis of GC patients. We found that age, mLNR, pTNM stage, BMI, F and SII were independent risk factors associated with recurrence, and age, mLNR, pTNM stage, BMI, F, SII and nerve infiltration were independent risk factors associated with prognosis. After that, the above factors are integrated and constructed a nomogram. ROC showed that the AUC of predicting 3 and 5 years recurrence were 0.793 and 0.805. The AUC of predicting 3 and 5 years prognosis were 0.797 and 0.806. This indicates that the prediction performance of the nomogram is better than the pTNM stage, which is worthy of clinical application.

This study has some limitations. Firstly, this was a single center study, focusing only on Asian populations. The results need to be further verified. Secondly, we only include blood samples before surgery, and the dynamic changes in inflammation before and after surgery are also worth studying.

Conclusions

Preoperative F and SII were independent risk factors for recurrence and prognosis of Borrmann type III AGC. The nomogram models based on these two inflammatory biomarkers and clinicopathological features were used to evaluate the recurrence and prognosis of Borrmann type III AGC, and its predictive ability is superior to traditional pTNM stage alone.

Data Sharing Statement

The datasets generated and/or analysed during the current study are available in the [Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital] repository, [Copyright No. 2013SR087424, <http://www.sghmu.com>].

Ethics Approval and Consent to Participate

All programs followed were according to the ethical standards of the Human Subjects Responsibility Committee (institutions and countries), as well as the 1964 Helsinki Declaration and subsequent editions. This research was approved by the Ethics Committee of the Harbin Medical University Cancer Hospital (Approval Number: 2019-57-IIT). All patients provided written informed consent to the use and publication of their information.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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