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ORIGINAL RESEARCH

The Clinical Value of the Combined Detection of Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Prognostic Nutritional Index (PNI) in Early Diagnosis of Gastric Cancer

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Objective: Gastric cancer (GC) is a common malignant tumor of the digestive tract. Accumulating studies suggest that inflammation is linked with the pathogenesis of GC. The study delves into novel hematological inflammatory markers, such as systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and prognostic nutritional index (PNI), to explore their potential applications in early diagnosis of GC.

Methods: From October 2020 and August 2024, 1339 GC patients admitted to our hospital were enrolled in this study. The pre-treatment SII, SIRI, and PNI was calculated from peripheral blood samples. Univariate and multivariate logistic regression analyses were utilized to verify independent risk factors for patients, and constructed the nomograms. The correlation between hematological indicators and tumor-node-metastasis (TNM) stage was assessed through Spearman's analysis.

Results: Eligible patients and healthy controls were grouped by gender. The diagnostic ability of PNI was significantly superior to other indicators to diagnose male GC (area under the curve [AUC]=0.908, 95% CI: 0.892–0.925) and female GC (AUC=0.890, 95% CI: 0.865–0.914). Besides, the combination of hematological indicators is more effective in diagnosing GC patients, especially for male patients (AUC=0.916, 95% CI: 0.901–0.932, sensitivity: 84.98%, specificity: 84.29%). The C-statistic of Nomogram model was 0.917 for males and 0.875 for females. In both male and female cohorts, CEA, SII, and SIRI were positively correlated with TNM stage, while PNI was negatively correlated. The AUC of CEA, SII, SIRI, and PNI combined for the diagnosis in the early stage of male GC patients was 0.897 (95% CI: 0.875–0.918, sensitivity: 86.57%, specificity: 80.30%) is higher than that of in the advanced stage (AUC: 0.745, 95% CI: 0.710–0.780, sensitivity: 56.53%, specificity: 82.86%).

Conclusion: The combined CEA, SII, PNI, and SIRI could be used as screening biomarkers in diagnosing GC, especially in the early stage of male GC patients.

Keywords: gastric cancer, early diagnosis, systemic immune-inflammation index, SII, systemic inflammation response index, SIRI, prognostic nutritional index, PNI

Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third-leading cause of cancer deaths worldwide, with high morbidity and mortality.[1,2] Despite the advancement of medical technology and innovative approaches for

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treating cancer, it remains an important public health problem.[3] Most GC cases are detected at advanced stages due to the cancer lacking early detectable symptoms, with 5-year overall survival of no more than 30%.[4,5] Therefore, diagnosing GC as early as possible is key to effective treatment and prognosis. Currently, gastroscopy is still the most effective guideline recommended method for GC. However, due to the uncomfortable experience and high economic burden, its widespread application in early cancer screening is still difficult. Thus, the development of inexpensive, reliable, and quantitative biomarkers such as hematological tests is essential for the early diagnosis of GC.[6]

The tumor microenvironment is altered by inflammation, which creates a suitable environment for cancer cells to proliferate.[7] Related study has demonstrated that the important determinants of tumor progression include cancer-associated inflammation, which is associated with changes in peripheral blood leukocytes.[8] Growing evidence indicated that the pathophysiological process of GC is closely related to the tumor inflammatory microenvironment.[9,10] The systemic immune-inflammation index (SII) is a novel inflammatory biomarker of various diseases, calculated based on peripheral blood neutrophil, platelet, and lymphocyte, which can represent different immune and immunologic pathways with greater stability in vivo.[11,12] An increasing number of studies have indicated that SII can predict the prognosis of malignant tumors such as colorectal cancer,[13] urothelial carcinoma,[14] and breast cancer.[15] On the other hand, SII can also serve as a diagnostic indicator for some diseases, in lung cancer-related venous thromboembolism, SII > 851.51 (odds ratio [OR] = 3.355, 95% confidence interval [CI]: 1.849–6.088) was a significant independent risk factor, with an area under the curve (AUC) value of 0.708 in nomogram model.[16] Moreover, SII may be used to promote the diagnosis of acute appendicitis, with an AUC value of 0.764 (95% CI: 0.709–0.819), sensitivity of 82.0%, and specificity of 66.7%.[17] The systemic inflammation response index (SIRI) indicates the balance between the inflammatory response and immune status.[18] It is based on peripheral neutrophil, monocyte, and lymphocyte counts, and served as a biomarker to predict the survival of patients with multiple malignant tumors.[19–21] And then, the prognostic nutritional index (PNI), as a simple and noninvasive peripheral blood-based biomarker reflecting host immune and nutritional status,[22] and is widely used to predict the prognosis of various malignancies.[23–25] Research has revealed that PNI was associated with overall survival (hazard ratio [HR]=1.89, 95% CI: 1.03–3.48, P=0.04) in older adults with cancer and PNI markers (albumin, total lymphocyte count) could be seen as markers of inflammation rather than nutrition.[26] Despite this, there are few studies using blood-based inflammation markers SII, SIRI, and PNI to evaluate the diagnostic value and significance of GC, especially by gender grouping.

In this study, we performed a retrospective analysis to evaluate the diagnostic value of hematological indicators (SII, SIRI, and PNI) and traditional tumor markers (CEA, CA19-9, and CA125) in male and female GC patients, respectively. Firstly, we analyzed the differences in laboratory indicators between GC and healthy control groups to identify significant risk factors for GC. Secondly, the optimal cut-off value for GC was determined using ROC-AUC analysis. Then, univariate and multivariate logistic regression analyses were utilized to verify independent risk factors for GC. Subsequently, the relationship between the TNM stage and hematological indicators (CEA, SII, SIRI, and PNI) was evaluated through Spearman's analysis. Finally, we assessed the clinical value of the combination of CEA, SII, SIRI, and PNI in the early diagnosis of GC.

Materials and Methods

Study Patients

The present study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Clinical Research Ethics Committee of Jiangsu cancer hospital. A total of 1,339 patients with GC in the Department of General Surgery, Jiangsu Cancer Hospital, from October 2020 through August 2024 were enrolled. The diagnosis was based on the tissue sample obtained during gastroscopy and confirmed by postoperative pathology. Patients were included if they met the following criteria: (1) Age at 18–75 years; (2) Primary gastric cancer; (3) Not receiving any therapeutic procedures before the surgery. (4) Complete collection of clinical or pathological data. Patients were excluded if they presented with the following: (1) History of other malignant tumors or hematological disorders; (2) Distant metastasis; (3) Recurrent tumors or residual gastric cancer. (4) Gastrointestinal stromal tumor. (5) History of malignant hematologic disease, severe hepatic or renal disease; (6) History of serious immune disorders. All patients were staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 8th edition staging system. What is more, we retrospectively analyzed the physical examination data of our hospital staff in

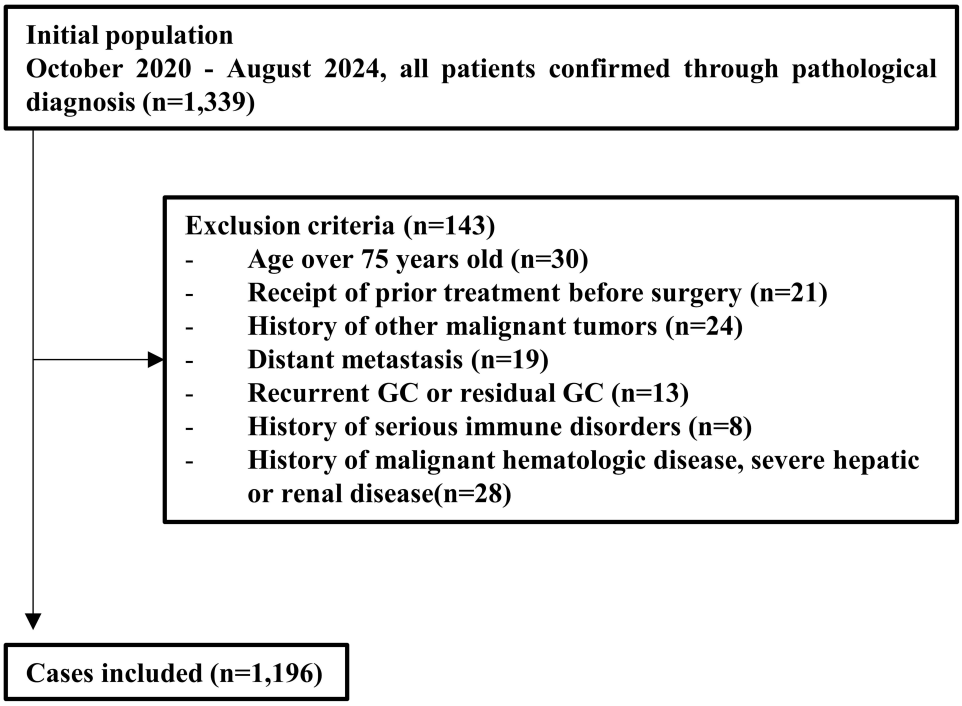

Figure 1 Flow diagram of subjects enrolled in this study.

2021–2023 as a healthy control group. None of the selected population had any history of inflammatory disease, antiplatelet therapy, or cancer and hematological diseases. The need for informed consent was waived due to the retrospective nature of this study. A flow diagram of subjects enrolled in this study is provided in Figure 1.

Hematology Analysis

Peripheral venous blood samples were collected form all subjects in a fasting state within 1 week before the cases received surgery treatment. Sysmex XE-2100 and XN-9100 hematology analyzer (Sysmex, Kobe, Hyogo, Japan) were used to detect blood cell count. The cobas® 8000 modular analyzer (Roche Diagnostics, Indianapolis, IN, USA) was used to detect the concentration of albumin. The calculation formula of SII, SIRI, and PNI according to the following equations: SII = (neutrophil count × platelet count)/lymphocyte count, and SIRI = (neutrophil count × monocyte count)/lymphocyte count, PNI = albumin (g/L) + 5 × lymphocyte count. Besides, the tumor markers (CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19–9, and CA125: carbohydrate antigen 125) were measured with electrochemiluminescence assays in a Roche E601 Immunoassay Analyzer according to manufacturer's protocols.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 20.0, GraphPad Prism v9.4.1 and R version 4.2.1. Continuous variables were expressed as medians with 25th and 75th percentiles or means ± standard deviations, and the results were compared using Mann–Whitney *U*-test or Student's *t*-test, when appropriate. Categorical variables were presented as frequencies and percentages and compared with Chi-square tests. The diagnostic accuracy of all biomarkers for GC was calculated using the receiver operating characteristic (ROC) curve, and the AUC was also calculated. The sensitivity–specificality relationship was determined using the highest Youden's index. Univariate and multivariate logistic regression analyses of relative risks for patients with GC, and OR and 95% CI were calculated. Nomograms were developed to predict the occurrence of GC based on the results of the multivariate logistic regression. The correlations between variables and the TNM stage were determined using Spearman's analysis. Two-sided *P*-value of less than 0.05 was considered statistically significant.

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Results

Clinicopathological Features of Patients with GC

Patients clinical and pathological features are summarized in Table 1. Of the 1,196 eligible patients, 865 (72.32%) were male and 331 (27.68%) were female. Compared with the healthy control group, age, CEA, SII, and SIRI were significantly increased, and PNI was significantly decreased in gender-specific analysis (all $P<0.001$). Additionally, CA19-9 was higher in male GC ($P<0.001$), while there was no significant difference in CA19-9 and CA125 for female GC ($P>0.05$). Subgroup analysis of male patients showed that Lauren classification predominated with intestinal (32.95%), and the majority of tissues moderately or poorly differentiated (50.17%). Furthermore, patients without lymph node metastasis accounted for 40.58% of the total. In female patients, Lauren classification was dominated by the diffuse (47.73%), with most of tissues at a poor differentiation (46.23%). And patients without lymph node metastasis accounted for 39.58% of the total.

Diagnostic Efficiency of Hematological Indicators for Patients with GC

ROC analysis was conducted to determine the ability of the hematological indicators to diagnose GC (Figure 2). In the group of male patients, the cut-off value of the CEA for GC diagnosis was 1.87 ng/mL (AUC=0.677, 95% CI:

Table 1 Baseline Characteristics of Gastric Cancer Patients and Healthy Controls

Characteristics	Male		*P* value	Female		
	HC (n=350)	GC (n=865)		HC (n=337)	GC (n=331)	*P* value
Age	44(34–58)	64(55–69)	<0.001	54(34–65)	63(55–69)	<0.001
CEA (ng/mL)	1.52(0.93–2.45)	2.35(1.45–3.88)	<0.001	1.17(0.70–1.90)	1.83(1.08–3.13)	<0.001
CA19-9 (U/mL)	7.89(4.96–12.43)	9.13(5.72–17.30)	<0.001	9.95(6.59–15.30)	9.40(6.13–16.50)	0.994
CA125 (U/mL)	–	–	–	10.90(8.10–14.10)	9.97(7.44–14.40)	0.155
PNI	59.78(57.25–62.86)	50.55(46.50–54.38)	<0.001	58.75(55.75–61.25)	51.25(47.00–54.10)	<0.001
SII	324.49(244.77–445.04)	431.64(299.33–647.46)	<0.001	360.08(270.68–441.45)	420.38(271.39–614.34)	<0.001
SIRI	0.59(0.46–0.78)	0.89(0.63–1.35)	<0.001	0.53(0.39–0.69)	0.69(0.47–1.08)	<0.001
Lauren classification						
Intestinal		285(32.95)			64(19.34)	
Diffuse		244(28.21)			158(47.73)	
Mixed		271(31.33)			84(25.38)	
Unknown		65(7.51)			25(7.55)	
Differentiation						
Well		4(0.46)			1(0.30)	
Well or moderately		21(2.43)			11(3.32)	
Moderately		138(15.95)			27(8.16)	
Moderately or poor		434(50.17)			139(41.99)	
Poor		268(30.99)			153(46.23)	
TNM stage						
Ia		190(21.97)			72(21.75)	
Ib		60(6.94)			23(6.95)	
IIa		113(13.06)			45(13.60)	
IIb		104(12.02)			46(13.90)	
IIIa		186(21.50)			70(21.15)	
IIIb		144(16.65)			45(13.60)	
IIIc		68(7.86)			30(9.05)	
LNM						
N0		351(40.58)			131(39.58)	
N1		143(16.53)			65(19.64)	
N2		159(18.38)			62(18.73)	
N3		212(24.51)			73(22.05)	

Notes: The measurement data were expressed as the median and quartile (25–75%), and the enumeration data were expressed as frequency and rate (%).
Abbreviations: GC, gastric cancer; HC, Healthy controls; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; CA125, carbohydrate antigen 125; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, the systemic inflammation response index; LNM, lymph nodes metastasis.

0.645–0.709, sensitivity: 63.70%, specificality: 61.14%), the cut-off value of the CA19-9 was 16.55 U/mL (AUC=0.580, 95% CI: 0.547–0.614, sensitivity: 26.36%, specificality: 90.57%), the cut-off value of the PNI was 55.33 (AUC=0.908, 95% CI: 0.892–0.925, sensitivity: 80.12%, specificality: 87.43%), the cut-off value of the SII was 462.69 (AUC=0.655, 95% CI: 0.624–0.687, sensitivity: 46.59%, specificality: 79.14%), and the cut-off value of the SIRI was 0.77 (AUC=0.720, 95% CI: 0.689–0.750, sensitivity: 62.20%, specificality: 72.86%). The AUC for combined detection with the above indicators was 0.916 (95% CI: 0.901–0.932, sensitivity: 84.98%, specificity: 84.29%). In the group of female patients, the best cut-off values of CEA, PNI, SII, and SIRI for the presence of GC using the Youden's index were 2.04 ng/mL, 54.18, 504.32, and 0.79, respectively. And then, the AUC of CEA was 0.681 (95% CI: 0.641–0.721, sensitivity: 45.92%, specificity: 78.92%), the AUC of PNI was 0.890 (95% CI: 0.865–0.914, sensitivity: 76.13%, specificality: 87.83%), the AUC of SII was 0.593 (95% CI: 0.550–0.637, sensitivity: 37.76%, specificality: 85.46%), the AUC of SIRI was 0.654 (95% CI: 0.613–0.696, sensitivity: 41.39%, specificality: 84.27%). The AUC for combined detection with CEA, PNI, SII, and SIRI was 0.893 (95% CI: 0.869–0.918, sensitivity: 78.55%, specificality: 86.94%). The results of both male and female groups displayed that PNI was superior to other hematological indicators. In addition, the combination of the tumor markers and inflammatory markers is more effective in diagnosing patients with GC, especially for male patients. Details of the accuracy, positive predictive value (PPV), and negative predictive value (NPV), optimal cut-off and Youden's index are shown in Table 2.

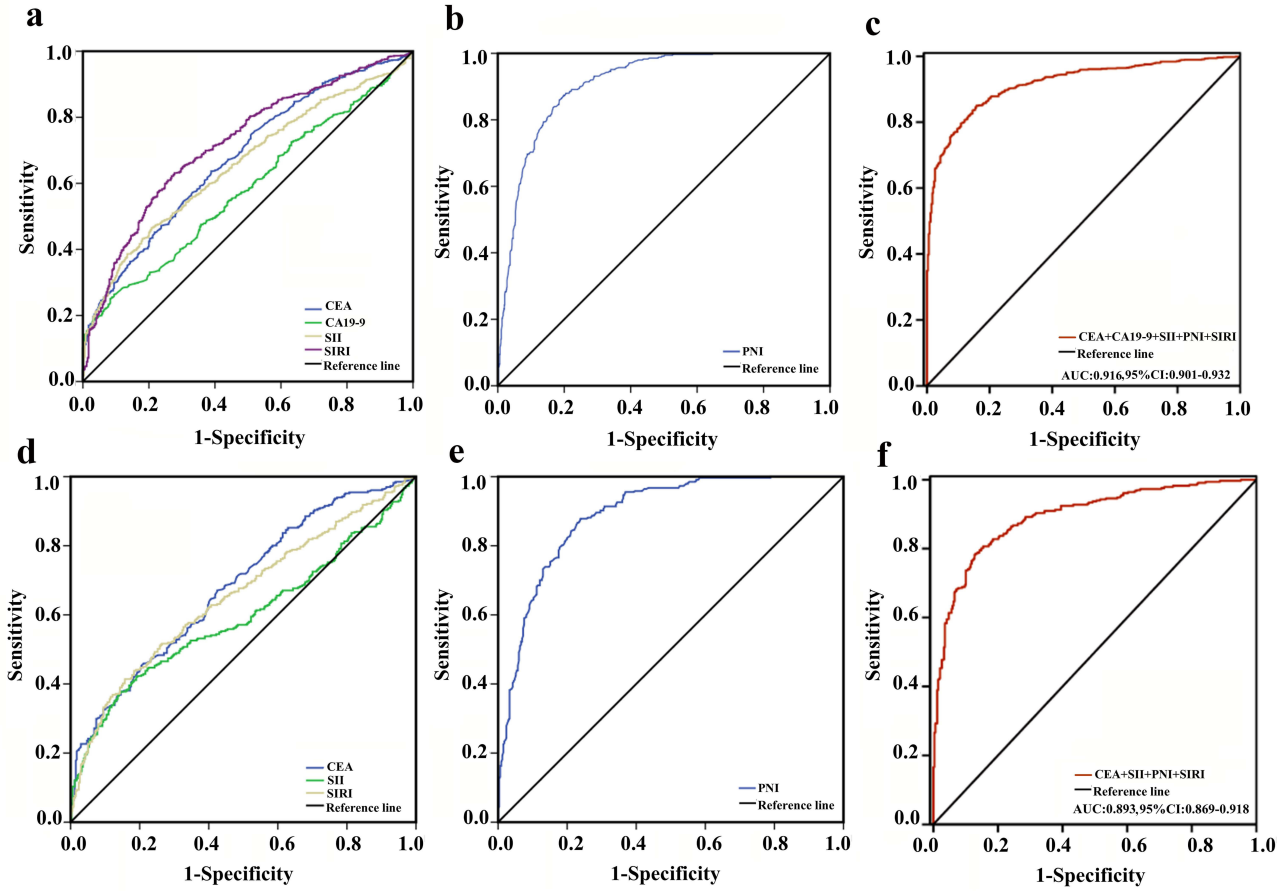

Figure 2 ROC curves of hematological indicators for diagnosing GC (**a** and **b**) CEA, CA19-9, SII, SIRI and PNI in diagnosis of male GC patients. (**c**) Combined diagnostic value of CEA, CA19-9, SII, SIRI and PNI in male GC patients. (**d** and **e**) CEA, SII, SIRI and PNI in diagnosis of female GC patients. (**f**) Combined diagnostic value of CEA, SII, SIRI and PNI in female GC patients.

Abbreviations: ROC, receiver-operator characteristic curve; AUC, area under curve; CI, confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, the systemic inflammation response index.

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Table 2 Diagnostic Efficiency of Hematological Indicators for Patients with GC

Factors	AUC (95%)	Se (%)	Sp (%)	Ac (%)	PPV (%)	NPV (%)	Cutoff Value	Youden's Index
Male								
CEA (ng/mL)	0.677(0.645–0.709)	63.70	61.14	62.96	80.20	40.53	1.87	0.248
CA19-9 (U/mL)	0.580(0.547–0.614)	26.36	90.57	44.86	87.36	33.23	16.55	0.169
PNI	0.908(0.892–0.925)	80.12	87.43	82.22	94.03	64.02	55.33	0.675
SII	0.655(0.624–0.687)	46.59	79.14	55.97	84.66	37.48	462.69	0.257
SIRI	0.720(0.689–0.750)	62.20	72.86	65.27	84.99	43.81	0.77	0.351
Combination	0.916(0.901–0.932)	84.98	84.29	84.77	93.04	69.41	–	–
Female								
CEA (ng/mL)	0.681(0.641–0.721)	45.92	78.92	62.58	68.16	59.78	2.04	0.249
PNI	0.890(0.865–0.914)	76.13	87.83	82.04	86.01	78.93	54.18	0.640
SII	0.593(0.550–0.637)	37.76	85.46	61.83	71.84	58.30	504.32	0.232
SIRI	0.654(0.613–0.696)	41.39	84.27	63.02	72.11	59.41	0.79	0.257
Combination	0.893(0.869–0.918)	78.55	86.94	82.78	85.53	80.50	–	–

Abbreviations: GC, gastric cancer; HC, Healthy controls; AUC, area under curve; CI, confidence interval; Se, sensitivity; Sp, specificity; Ac, accuracy; PPV, positive predictive value; NPV, negative predictive value; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, the systemic inflammation response index.

Univariate and Multivariate Logistic Regression Analysis

Perform univariate logistic regression analysis with the occurrence of GC as the dependent variable (negative = 0, positive = 1), age (≤55 = 0, >55 = 1), CEA (≤1.87 ng/mL = 0, >1.87 ng/mL = 1), CA19-9 (≤16.55 U/mL = 0, >16.55 U/mL = 1, SII (≤462.69 = 0, >462.69 = 1), PNI (≤55.33 = 0, >55.33 = 1), and SIRI (≤0.77 = 0, >0.77 = 1) as independent variables. The results showed that the above indicators were significantly associated with GC in males (all $P<0.001$). The multivariable analysis demonstrated that the age (OR=4.105, $P<0.001$), CEA (OR=1.923, $P<0.001$), CA19-9 (OR=1.742, $P=0.025$), PNI (OR=0.055, $P<0.001$), and SIRI (OR=2.211, $P<0.001$) were independent risk factors for male GC patients. Similar results were also found in female GC patients. Age, CEA, PNI, SII, and SIRI were significantly associated with GC (all $P<0.001$). And then, the multivariable analysis revealed that age (OR=1.855, $P=0.005$), CEA (OR=2.576, $P<0.001$), SII (OR=1.867, $P=0.038$), PNI (OR=0.058, $P<0.001$), and SIRI (OR=1.934, $P=0.023$) were independent risk factors for female GC patients (Table 3).

Table 3 Univariate and Multivariate Logistic Analysis in Patients with GC

Male	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (years)			<0.001			<0.001
≤55	1			1		
>55	12.051	9.143–15.884		4.105	2.891–5.827	
CEA (ng/mL)			<0.001			<0.001
≤1.87	1			1		
>1.87	2.720	2.107–3.512		1.923	1.353–2.735	
CA19-9 (U/mL)			<0.001			0.025
≤16.55	1			1		
>16.55	3.418	2.316–5.044		1.742	1.072–2.830	
SII			<0.001			0.546
≤462.69	1			1		
>462.69	3.310	2.476–4.425		1.144	0.739–1.771	

(*Continued*)

Table 3 (Continued).

Male	Univariate			Multivariate		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
PNI			<0.001			<0.001
≤55.33	1			1		
>55.33	0.036	0.025–0.051		0.055	0.038–0.080	
SIRI			<0.001			<0.001
≤0.77	1			1		
>0.77	4.372	3.323–5.753		2.211	1.481–3.302	
Female	**Univariate**			**Multivariate**		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age (years)			<0.001			0.005
≤55	1			1		
>55	2.927	2.119–4.043		1.855	1.203–2.858	
CEA (ng/mL)			<0.001			<0.001
≤2.04	1			1		
>2.04	3.219	2.287–4.531		2.576	1.634–4.062	
SII			<0.001			0.038
≤504.32	1			1		
>504.32	3.566	2.450–5.193		1.867	1.035–3.368	
PNI			<0.001			<0.001
≤54.18	1			1		
>54.18	0.046	0.031–0.069		0.058	0.038–0.089	
SIRI			<0.001			0.023
≤0.79	1			1		
>0.79	3.737	2.592–5.389		1.934	1.095–3.416	

Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, the systemic inflammation response index; OR, odds ratio; CI, confidence interval.

Nomogram Model for Risk Assessment of GC

Based on the multivariable logistic regression model, we establish a nomogram model for GC patients using the R language rms package. The C statistic of its evaluation was 0.917 for males, with a sensitivity of 83.29% and a specificity of 90.57%, and 0.875 for females, with a sensitivity of 80.06% and a specificity of 85.16%, demonstrating that the model had high accuracy. Then, the plotting function was constructed, and the nomogram was plotted (Figure 3). Furthermore, as shown in Table 4, the risk of GC can be predicted based on the total points.

Correlation Analysis of Hematological Indicators Within Subgroups

Since age is one of the independent risk factors for GC, we conducted a subgroup analysis stratified by age (Figure 4). Participants were categorized into 3 age groups: 18–44 years, 45–60 years, and 61–75 years. In male GC patients, there was a negative correlation between PNI and SII (r= −0.401, −0.255 and −0.303, all P<0.05, Figure 4a) in the three groups, and a positive correlation between SIRI and SII (r= 0.524, 0.781, and 0.731, all P<0.001, Figure 4b). And then, the latter 2 groups displayed negative correlations between PNI and SIRI (r = −0.244, and −0.268, all P<0.001, Figure 4c). In the group of female patients, the 61–75 years age group exhibited negative correlations between PNI and SII (r = −0.262, P<0.001, Figure 4d), SIRI (r = −0.247, P<0.001, Figure 4e). Similarly, the three groups exhibited positive correlations between SII and SIRI, with the 61–75 years age group showing a more prominent trend than the other groups (r= 0.825, P<0.001, Figure 4f).

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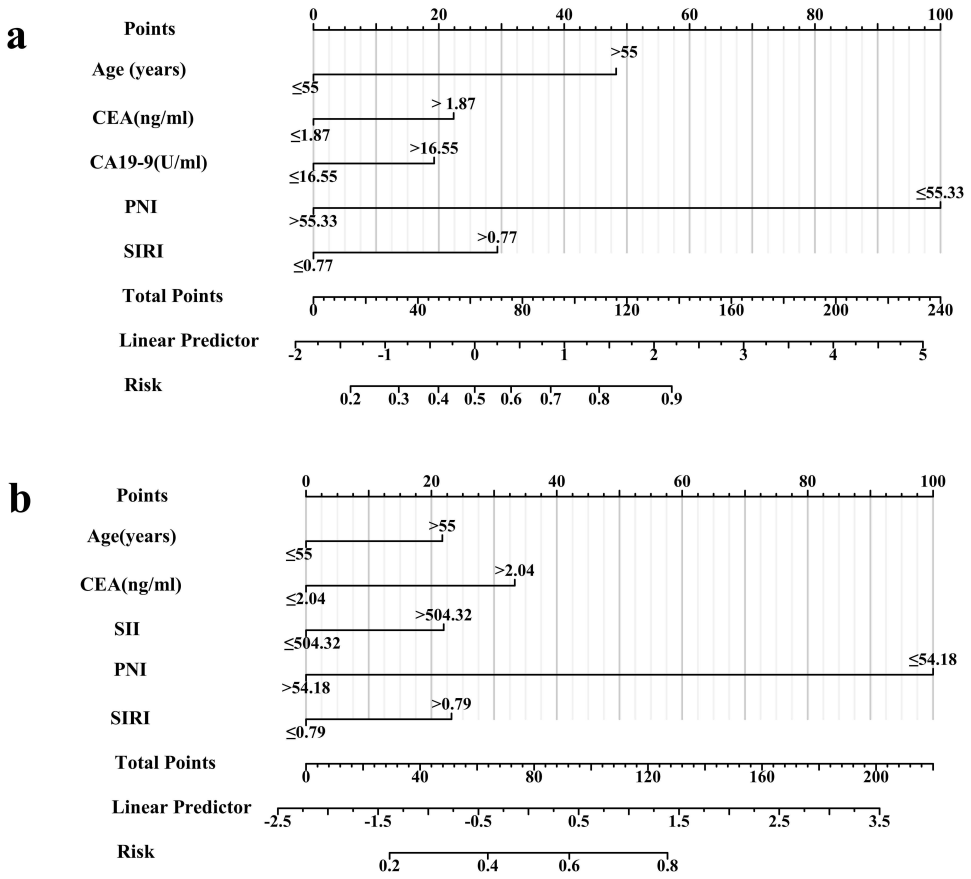

Figure 3 Nomogram to estimate the risk of patients with GC. (**a**) Nomogram model to predict male GC occurrence. (**b**) Nomogram model to predict female GC occurrence.

Abbreviations: GC, gastric cancer; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; SIRI, the systemic inflammation response index.

Association Between TNM Stage and Hematological Indicators

The relationship between the TNM stage and hematological indicators was evaluated through Spearman's analysis. According to the TNM staging, we divided it into 7 group cohorts: Ia, Ib, IIa, IIb, IIIa, IIIb, and IIIc. In both male and female, CEA, SII, and SIRI were positively correlated with TNM stage, while PNI was negatively correlated with TNM stage (all $P<0.05$, Figure 5).

Table 4 Relationship Between Total Points and Risk of GC

Male		Female	
Total Points	**Risk of GC (%)**	**Total Points**	**Risk of GC (%)**
<16	<20	<32	<20
16–32	20–30	32–64	20–40
33–48	31–40	65–92	41–60
49–64	41–50	93–128	61–80
65–76	51–60	>128	>80
77–92	61–70	–	–
93–108	71–80	–	–
109–136	81–90	–	–
>136	>90	–	–

Abbreviation: GC, gastric cancer.

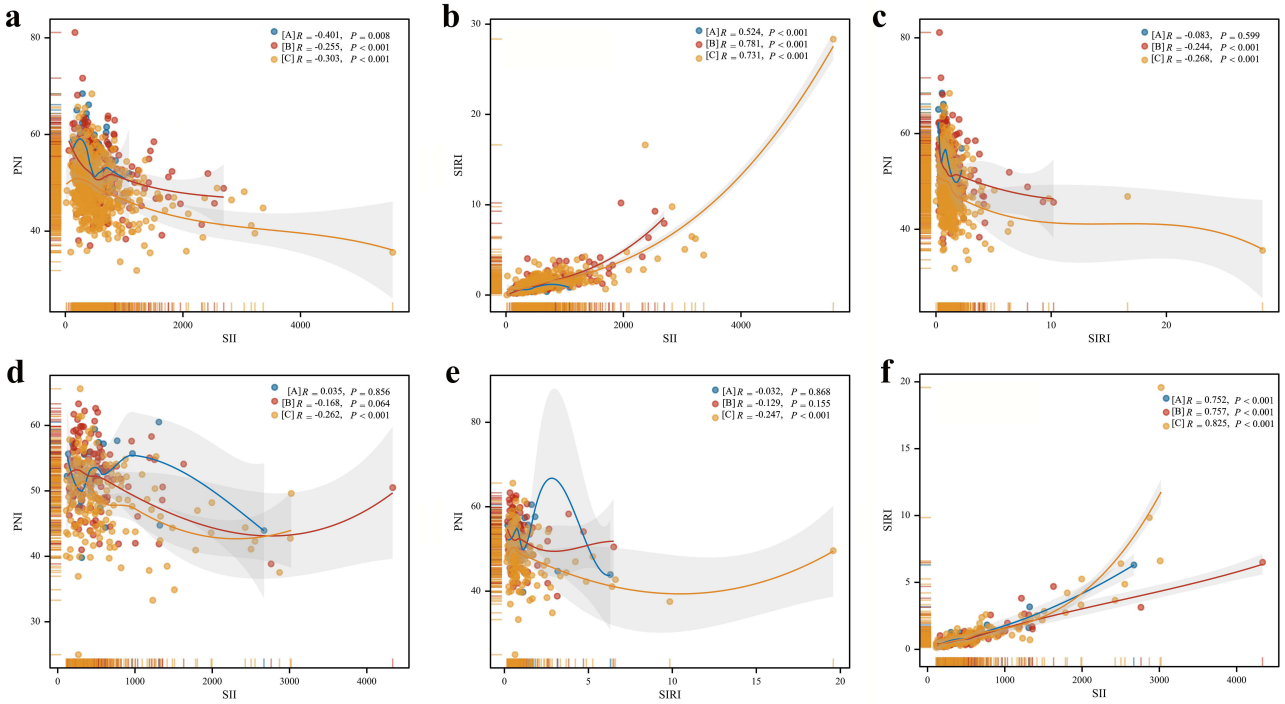

Figure 4 Correlation analysis of hematological indicators within Subgroups in male patients (**a–c**) and female patients (**d–f**). A: 18–44 years old; B: 45–60 years old; C: 61–75 years old.

Abbreviations: SII, systemic immune-inflammation index; PNI, prognostic nutritional index; SIRI, the systemic inflammation response index.

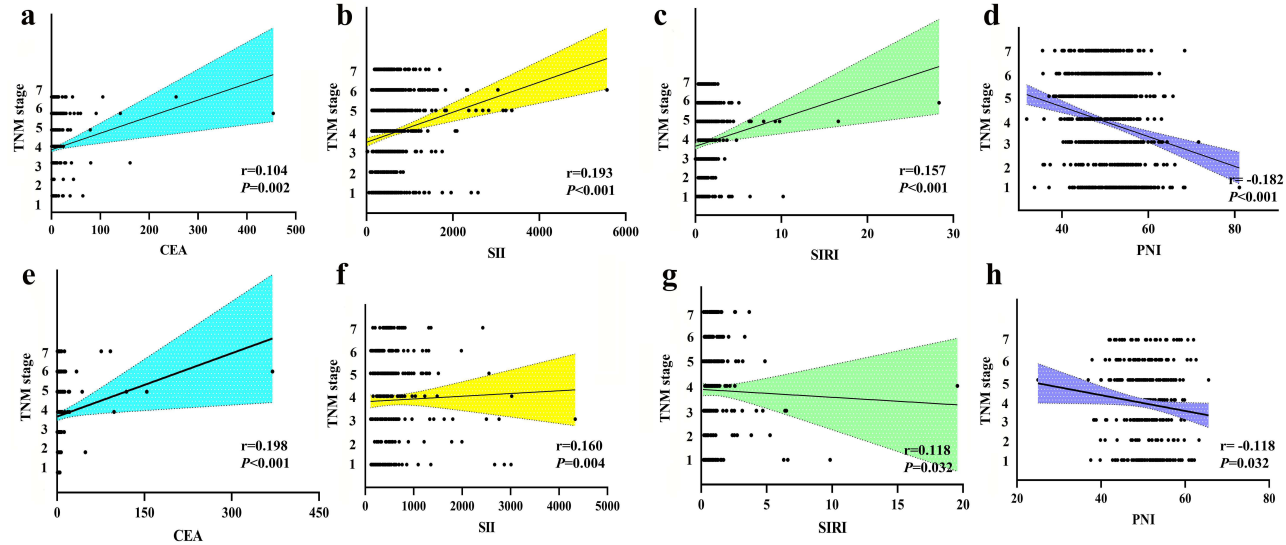

Figure 5 Association between TNM stage and CEA, SII, SIRI and PNI in male cohorts (**a–d**) and female cohorts (**e–h**) using Spearman's analysis. 1: stage Ia, 2: stage Ib, 3: stage IIa, 4: stage IIb, 5: stage IIIa, 6: stage IIIb and 7: stage IIIc.

Abbreviations: SII, systemic immune-inflammation index; PNI, prognostic nutritional index; SIRI, the systemic inflammation response index.

ROC Analysis of the Hematological Indexes in Early and Advanced Stages GC Patients

The stage of the malignancy was further classified as low stage and high stage, where stages I–II were considered early stage and stages III–IV were considered advanced stage.[27] The AUC of CEA, SII, PNI, and SIRI combined for the diagnosis in the early stage of male GC patients was 0.897 (95% CI: 0.875–0.918, sensitivity: 86.57%, specificality: 80.30%, PPV: 76.71%, and NPV: 88.86%) (Figure 6a). The AUC was 0.745 (95% CI, 0.710–0.780), with a sensitivity of

https://doi.org/10.2147/JIR.S496703

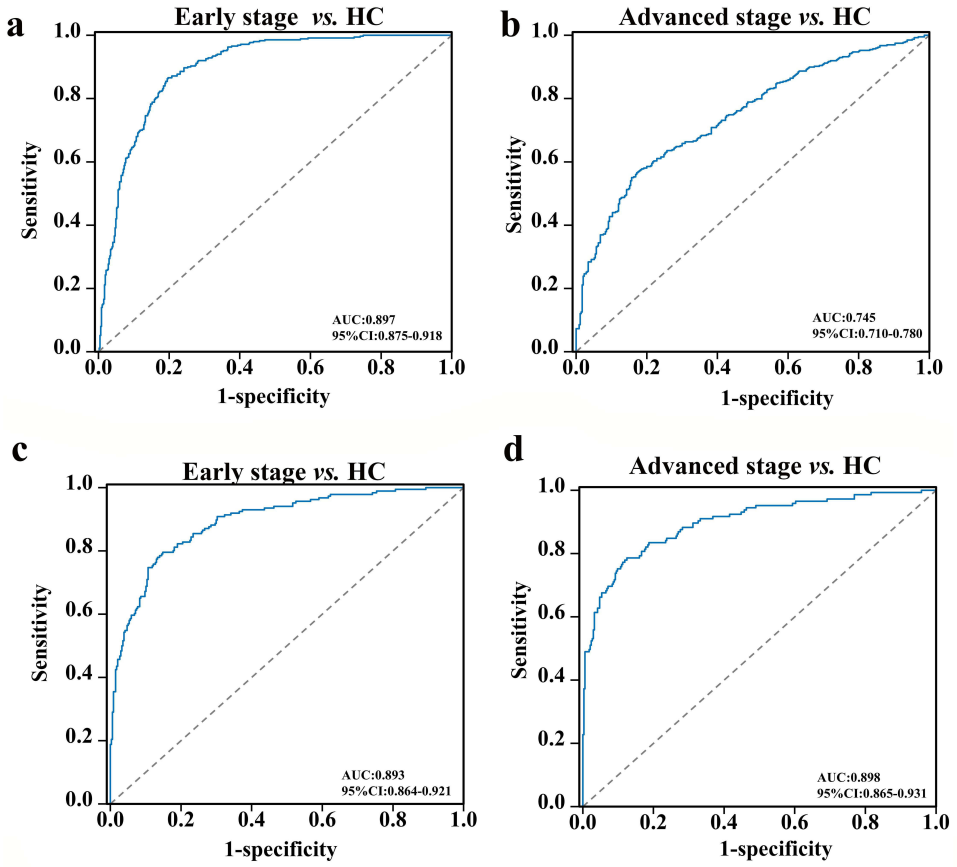

Figure 6 The ROC curves of hematological indicators for differentiating early stages or advanced stages GC from healthy control (**a** and **b**) In male GC cohorts and (**c** and **d**) In female GC cohorts.
Abbreviations: GC, gastric cancer; ROC, receiver-operator characteristic curve; HC, healthy control.

56.53%, a specificity of 82.86%, a PPV of 78.95%, and a NPV of 62.64% in the advanced stage (Figure 6b). In contrast to the male patients, the combination of above 4 indexes in early stage (AUC=0.893, 95% CI: 0.864–0.921, sensitivity: 79.57%, specificity: 85.13%, PPV: 74.75%, and NPV: 88.31%), and advanced stage (AUC=0.898, 95% CI: 0.865–0.931, sensitivity: 78.62%, specificity: 87.54%, PPV: 73.08%, and NPV: 90.49%) showed similar diagnosis effects in the female patient cohort (Figure 6c and d).

Discussion

In China, GC is a prevalent digestive tract tumor and a major cause of cancer mortality.[28] Due to lack of early symptoms in GC patients, most patients are diagnosed at an advanced stage.[29] Gastroscopy is currently the most common and effective guideline method for diagnosing GC, but it is not suitable for mass screening of GC due to its invasiveness, low tolerance, and high cost. In addition, the most common tumor markers CEA, CA72-4, or CA19-9 are not the unique biomarkers for GC diagnosis because of their poor sensitivity and specificity.[30,31] Therefore, it is crucial to identify noninvasive, highly sensitive, specific, and easily accessible indicators. An increasing number of studies have indicated that there is an inflammatory link between tumor, microenvironment, and the systemic response. Different inflammatory markers have been analyzed in many cancers, including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and PNI in thyroid carcinoma,[32] platelet-to-lymphocyte ratio (PLR) and SII in laryngeal squamous cell carcinoma,[33] and SIRI in breast cancer.[34] In view of this, the present study focused on inflammatory markers to determine whether they could become new indicators for assisting the diagnosis of GC.

In the present study, eligible patients and healthy controls were grouped by gender. Compared with the healthy control group, the age, CEA, SII, and SIRI were significantly increased, and PNI was significantly decreased in both male and

female cohorts. These results suggest that the occurrence of GC patients has a certain relationship with hematological indicators. SII and SIRI are new inflammatory markers that are associated with neutrophils, platelets, monocytes, or lymphocytes in peripheral blood. During tumorigenesis, neutrophils can secrete transforming factor-β (TGF-β), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), etc, to promote tumor growth or metastasis.[32,35] Platelets can protect tumor cells from natural killer cell tumor lysis, and escape immune surveillance, thereby leading to angiogenesis and tumor cell survival.[36] Monocytes, especially those differentiated into tumor-associated macrophages (TAMs), are involved in tumorigenesis.[34] Beyond that, lymphocytes play an important role in antitumor immune activity and tumor-associated immune responses.[37] During inflammation, conventional blood indicators such as neutrophil, lymphocyte, monocyte, and platelet counts often show abnormalities, leading to abnormal SII and SIRI results.[8,38] PNI was devised in 1984 as a risk score relating postoperative complications with baseline nutrition, using albumin and lymphocyte counts, which has proven to be a practical tool that accurately and globally assesses the nutritional profile of patients, reflecting the relevance of inflammation and related signaling pathways on nutrition and metabolism.[39,40] Serum albumin levels are an important indicator of body nutrition, immune status, and surgical risk.[41] Low serum albumin is associated with tumor inflammatory response and affects the prognosis of various malignant tumors.[42] Through the ROC-AUC analysis, we have found that the diagnostic ability of PNI was significantly superior to other hematological indicators to predict male GC (AUC=0.908, 95% CI: 0.892–0.925) and female GC (AUC=0.890, 95% CI: 0.865–0.914) compared to control groups. Additionally, the combination of the tumor markers and inflammatory markers is more effective than a single marker in diagnosing patients with GC patients, improving the accuracy of detection (male: 84.77%, female: 82.78%). A previous study has revealed that higher PNI was still significantly associated with better overall survival (HR=0.405; 95% CI 0.253–0.649; $P<0.001$) in GC, and higher-PNI patients had a protective effect regarding postoperative morbidity and mortality.[42] Besides, a high preoperative SII and SIRI were independent risk factors for poor prognosis in GC patients.[43,44] Systemic inflammation markers have been linked to increased cancer risk and mortality in a number of studies. Despite these insights, few studies have estimated pre-diagnostic associations between systemic inflammation markers and cancer risk.[45]

Through multivariate logistic regression analysis, the age, CEA, PNI, and SIRI were independent risk factors for male and female GC patients. Immediately after, we establish a nomogram model for GC patients, and the C statistic of its evaluation was 0.917 for males, with a sensitivity of 83.29% and a specificity of 90.57%, and 0.875 for females, with a sensitivity of 80.06% and a specificity of 85.16%, demonstrating that the model had high accuracy. Unfortunately, SII was not one of the independent risk factors for male GC patients, although it is associated with the development of GC. SII was associated with the platelet counts in peripheral blood. In the male cohort, we found no difference in the platelet count between GC and healthy control ($P=0.645$), which may be the cause of this result.

Considering that age is one of the independent risk factors for GC, we conducted a subgroup analysis stratified by age. Interestingly, in the group of female patients, only PNI was negatively correlated with SII and SIRI in the 61–75 years age group. Moreover, SII was strongly positively correlated with SIRI in the age group of 61–75 years ($r= 0.825$, $P<0.001$). We know that with age, estrogen levels in female decline. Estrogen can down-regulate local inflammatory cytokine levels, reduce the infiltration of inflammatory cells,[46] and inhibit the adhesion and exudation of neutrophils, thereby alleviating local inflammatory reactions.[47] Therefore, the decrease or disruption of estrogen levels is bound to exacerbate inflammation within the body.

Early diagnosis can greatly improve the cure rate and survival rate of GC. We observed that CEA, SII, and SIRI were positively correlated with TNM stage, while PNI was negatively correlated with TNM stage in both male and female patients. Similar findings were reported by Cao et al,[48] Ren et al,[49] and Nogueiro et al,[42] which stated that SII, SIRI, and PNI were related to TNM stage ($P <0.001$) in GC patients, respectively. Importantly, the AUC for CEA, SII, PNI, and SIRI combined in the early diagnosis of male GC patients was 0.897 (95% CI=0.875–0.918, sensitivity: 86.57%, specificity: 80.30%), whereas it was only 0.745 (95% CI, 0.710–0.780, sensitivity: 56.53%, specificity: 82.86%) in the advanced stage. No such results were observed in the female cohort. In other words, the early diagnostic value of inflammatory markers in males is superior to that in females. Similar results were shown in a study done by Fang et al on patients with GC. They reported that systematic inflammatory markers NLR and PLR had higher diagnostic value in male than female patients, although the diagnostic efficiency of NLR and PLR in their study was lower than in the

present study.[50] A partial explanation for the result might be that males are more likely than females to engage in certain unhealthy habits, such as smoking, drinking, or staying up late, which can lead to the male immune system having a stronger response to cancer cells entering the peripheral blood, leading to an increased ratio of neutrophils, lymphocytes, and platelets. Incorporating gender factors into the early diagnosis of GC can supplement previous research and enhance the application value of systemic inflammatory markers. In another study of 125 GC patients, Zhang et al displayed that the preoperative PLR, NLR, and SII could be utilized as diagnostic markers for GC, with an AUC value of 0.843 (95% CI: 0.791–0.885), sensitivity of 66.40%, and specificity of 96.80%, and all three inflammatory indices were notably higher in progressive-stage GC patients than in early-stage GC patients.[51]

Most previous research has examined the role of the SII, SIRI, and PNI in evaluating the survival of GC patients, while few have explored the value of the SII, SIRI, and PNI in diagnosing GC. To our knowledge, this is the first study to examine the diagnostic value of combining the SII, SIRI, PNI and CEA in GC and in early-stage GC. Nevertheless, some limitations of the present study should be noted. Firstly, GC is one of the most widely distributed cancers in different regions, and it is difficult to draw generalized conclusions in a single-center analysis. Secondly, the cut-off value of laboratory data was calculated only by mathematical methods, and the sensitivity and specificity of these data in diagnosing require further verification in multi-center and large cohorts. Thirdly, some other inflammatory indicators associated with cancer progression, such as procalcitonin, interleukin-6, and C-reactive protein, were not included in our study. Despite some limitations of our study, it does not prevent clinical practitioners from applying systemic inflammatory markers for screening and identifying high-risk populations. Importantly, this study is the first to analyze the diagnostic value of combining inflammatory markers with common tumor markers in GC according to gender stratification.

Conclusions

In sum, the study demonstrated that SII, SIRI, and PNI, markers of systemic inflammation, were associated with the diagnosis of GC. The combined CEA, SII, SIRI, and PNI could be used as screening biomarkers in GC, especially in the early stage of male GC patients. The combined biomarkers have good sensitivity and specificity, and are a non-invasive and simple method for screening high-risk groups for GC. In clinical practice, the existing diagnostic methods should be combined with the assessment of systemic inflammatory markers to improve diagnostic efficiency.

Data Sharing Statement

The data that support the results of this study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Clinical Research Ethics Committee of Jiangsu Cancer Hospital (No. KY-2024-012 and No. KY-2024-119). Due to retrospective characteristics of the study, informed consent was waived. All patient data was treated with confidentiality.

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

All authors have no conflicts of interest of declare.

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