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Original Article

Efficacy of immune checkpoint inhibitors combined with chemotherapy for advanced gastric cancer

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Abstract: Objective: To investigate the effects and safety of immune checkpoint inhibitors (ICIs) combined with chemotherapy for advanced gastric cancer, and to evaluate the predictive value of pretreatment peripheral blood inflammatory markers and tumor markers for progression-free survival (PFS). Methods: A retrospective analysis was performed on 89 patients with advanced gastric cancer who received ICI-based treatment. All patients completed at least three cycles of ICI-based treatment. Pretreatment peripheral blood inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and serum carbohydrate antigen 19-9 (CA19-9) levels were collected. Treatment regimens consisted of ICIs combined with chemotherapy, with or without targeted therapy. Tumor response was assessed using contrast-enhanced CT or MRI according to RECIST version 1.1. PFS was analyzed using the Kaplan-Meier method and Cox proportional hazards regression model. ROC curve analysis was conducted to explore the prognostic efficacy of the above biomarkers. Results: No patient achieved complete response. Among all cases, 17 patients achieved partial response, 51 had stable disease, and 21 experienced progressive disease. The overall objective response rate (ORR) and disease control rate (DCR) were 19.10% and 76.40%, respectively, with no significant difference between the two treatment groups in ORR or DCR (P=0.930 and P=0.954, respectively). Compared to baseline levels, NLR, PLR, SII, and CA19-9 levels were significantly decreased after treatment (all P<0.05), suggesting improved systemic inflammatory status in patients. Kaplan-Meier analysis demonstrated that patients with elevated baseline NLR, PLR, SII, and CA19-9 levels had significantly shorter PFS (P=0.002, P<0.001, P<0.001, and P=0.002, respectively). Univariate Cox regression analysis revealed that poor histologic differentiation (P=0.009), lymph node metastasis (P=0.036), high NLR (P=0.002), high PLR (P=0.001), high SII (P<0.001), and high CA19-9 levels (P=0.002) were correlated with shortened PFS. Multivariate Cox regression analysis further identified poor histologic differentiation (P<0.001), elevated SII (P=0.001), and high CA19-9 levels (P=0.003) as independent adverse prognostic factors for shorter PFS. Most treatment-related adverse events were manageable, and no new safety signals were observed in this cohort. Conclusion: ICI combined chemotherapy yields favorable disease control and acceptable safety in patients with advanced gastric cancer. Pretreatment elevated peripheral blood inflammatory markers and CA19-9 levels are associated with poor prognosis, among which SII and CA19-9 were independent risk factors for shortened PFS. Dynamic monitoring of these biomarkers can facilitate clinical risk stratification and individualized treatment decision-making for advanced gastric cancer patients receiving ICI-based therapy.

Keywords: Advanced gastric cancer, immune checkpoint inhibitors, inflammatory markers, carbohydrate antigen 19-9, progression-free survival, real-world study

Introduction

Gastric cancer is a prevalent malignant tumor and ranks as the most common digestive tract malignancy in China [1, 2]. According to the latest data from the National Cancer Center of China, there were approximately 358,700 new stomach cancer cases and 260,400 stomach cancer-related deaths in China in 2022 [3]. Gastric cancer ranks fifth in the incidence of all malignant tumors and third in mortality nationwide [3]. Due to the absence of typical early clinical symptoms and imperfect early screening systems in China, most patients are diagnosed with advanced unresectable gastric cancer at the time of initial consultation, for whom

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radical surgical treatment is no longer feasible. Consequently, non-surgical comprehensive therapies, including radiotherapy, chemotherapy, and molecular targeted therapy, have become the mainstay of clinical treatment. With the rapid advancement of tumor immunotherapy, immune checkpoint inhibitors (ICIs) have shown promising application prospects in the treatment of advanced gastric cancer [4, 5]. However, accurate prediction of ICI treatment efficacy, precise patient screening, and reversal of tumor immune tolerance still require further clinical verification.

Carbohydrate antigen 19-9 (CA19-9) is a classic serologic biomarker for digestive tract malignancies, and its elevation indicates a high risk of tumor occurrence and progression [6, 7]. Previous studies have confirmed that elevated serum CA19-9 levels in gastric cancer patients are closely correlated with advanced tumor progression and poor clinical prognosis [7]. Systemic inflammatory response is also a key component of the tumor immune microenvironment. Peripheral blood inflammatory cells promote tumor cell proliferation and metastasis, disrupt host immune surveillance, and accelerate tumor progression by secreting cytokines and chemokines [8]. The widespread clinical application of ICIs has driven the exploration of tumor predictive biomarkers. Inflammation-related indicators including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been validated as valuable prognostic biomarkers for multiple malignant tumors, such as non-small cell lung cancer and esophageal cancer [9-11]. Systemic Immune-inflammation Index (SII), a novel composite index calculated based on peripheral blood neutrophil, lymphocyte and platelet counts, has also been proven effective for prognostic evaluation of immunotherapy in advanced malignancies [12]. Elevated SII levels were found to be closely associated with shortened overall survival (OS) and progression-free survival (PFS), making SII a reliable indicator for predicting immunotherapy outcomes in advanced tumor patients [13]. Nevertheless, the predictive value of NLR, PLR, SII and CA19-9 for ICI treatment response in advanced gastric cancer remains insufficiently clarified. Therefore, this study aimed to analyze the correlation between the above inflammatory biomarkers, CA19-9 levels, and the efficacy of ICI-based therapy in advanced gastric cancer, so as to provide evidence for individualized clinical treatment.

Materials and methods

Research subjects

A total of 89 patients with advanced gastric cancer who received ICI-based therapy at Shijiazhuang People's Hospital from September 2021 to December 2023 were enrolled in this retrospective study.

Inclusion Criteria: aged ≥18 years; pathologically confirmed gastric cancer; received at least three cycles of ICI-based treatment; complete pretreatment hematologic and tumor marker detection data.

Exclusion criteria: (1) history of hematologic diseases or acute severe infection; (2) complicated with autoimmune diseases or severe organ dysfunction; (3) inability to complete postoperative imaging follow-up after ICI treatment.

All patients received regular follow-up via outpatient review and telephone interview, with the final follow-up deadline set as May 31, 2025. This study was approved by the Medical Ethics Committee of Shijiazhuang People's Hospital (Approval No. [2024]059).

Follow-up was terminated upon disease progression, patient death, or the final follow-up date. All statistical analyses including ROC curve analysis, Kaplan-Meier survival analysis and Cox regression analysis were performed based on the full cohort of 89 patients.

Treatment regimens

The treatment regimens in this study included ICIs combined with chemotherapy and ICIs combined with chemotherapy plus targeted therapy. The administered ICI drugs and standard doses per treatment cycle were as follows: 200 mg sintilimab, toripalimab, camrelizumab or pembrolizumab; 240 mg tislelizumab; and 3 mg/kg nivolumab. Chemotherapy regimens were based on platinum, taxane or fluorouracil agents. Targeted drugs included apatinib and trastuzumab. All treatment regimens were formulated individually based on patients' specific

clinical conditions. Imaging evaluation by CT or MRI was performed every two treatment cycles to assess tumor response.

Outcome measures

The primary endpoint of this study was PFS, defined as the interval from the initiation of ICI-based treatment to confirmed disease progression or all-cause death. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), changes in pretreatment and post-treatment inflammatory markers and CA19-9 levels, and the incidence of treatment-related adverse events. ORR was defined as the proportion of patients achieving complete response (CR) or partial response (PR), and DCR referred to the proportion of patients achieving CR, PR, or stable disease (SD).

Clinical baseline data of enrolled patients were extracted from the hospital electronic medical record system, including age, gender, body mass index (BMI), metastasis status (liver metastasis, lymph node metastasis), tumor TNM stage, histological differentiation grade, tumor size and specific treatment regimens. Peripheral blood samples were collected before the first cycle of ICI treatment to detect neutrophil, lymphocyte and platelet counts as well as serum CA19-9 levels. NLR, PLR and SII were calculated accordingly, and the SII calculation formula was as follows: SII = platelet count × neutrophil count/lymphocyte count. Tumor response was evaluated strictly in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1.

Statistical analysis

SPSS 27.0 software was used for all statistical analyses. Categorical variables were expressed as frequencies and percentages, and intergroup differences were compared using the chi-square test. Continuous variables conforming to normal distribution were presented as mean ± standard deviation ($\bar{x}$±SD), and independent samples t-test was used for intergroup comparison. ROC curve analysis was performed to determine the optimal cut-off values of NLR, PLR, SII, and CA19-9 for predicting disease progression after ICI treatment. Kaplan-Meier survival curves were plotted, and the Log-rank test was used to compare intergroup survival differences.

Variables with P<0.05 by univariate analysis were included in the multivariate Cox proportional hazards regression model. To avoid multicollinearity, NLR, PLR, and SII were not incorporated into the multivariate model simultaneously. SII was selected as the representative systemic inflammatory marker for subsequent multivariate analysis due to its comprehensive inclusion of neutrophil, platelet, and lymphocyte values. Bootstrap resampling with 1,000 repetitions was performed for internal validation of the predictive model. Calibration curves for 2-month, 6-month and 12-month PFS were plotted to evaluate the calibration degree of the model, and Brier scores were calculated to assess prediction error. The C-index was used to evaluate the discriminatory ability of the model. A *P* value of <0.05 was considered significant.

Results

Comparison of baseline characteristics

Baseline characteristics were generally comparable between the two treatment groups, with no statistically significant differences in demographic characteristics, clinicopathologic features, or treatment-related variables (all *P*>0.05; **Table 1**).

Comparison of treatment efficacy

In the ICIs combined with chemotherapy plus targeted therapy group (28 cases), no patients achieved CR, 6 cases achieved PR, 16 cases had SD, and 6 cases developed PD. In the ICIs combined with chemotherapy alone group (61 cases), no patients achieved CR, 11 cases achieved PR, 35 cases had SD, and 15 cases developed PD. The ORR was 21.43% in ICI combined with chemotherapy plus targeted therapy and 18.03% in the ICI combined with chemotherapy while the DCR was 78.57% and 75.41%, respectively. There were no significant inter-group differences in ORR (χ^2=0.008, *P*=0.930) and DCR (χ^2=0.003, *P*=0.954, **Table 2**).

Comparison of laboratory indicators

Pretreatment NLR, PLR, SII and CA19-9 levels showed no significant differences between the two groups (all *P*>0.05). After treatment, the ICI combined with chemotherapy plus targeted therapy exhibited significantly lower NLR, SII

Table 1. Comparison of baseline characteristics

Variable	ICI combined with chemotherapy plus targeted therapy (n=28)	ICIs combined with chemotherapy (n=61)	*P*
Age, years			0.248
<65	11 (39.3)	32 (52.5)	
≥65	17 (60.7)	29 (47.5)	
Male sex	17 (60.7)	42 (68.9)	0.451
BMI <18.5 kg/m^2	7 (25.0)	12 (19.7)	0.569
Liver metastasis	7 (25.0)	13 (21.3)	0.699
Lymph node metastasis	10 (35.7)	28 (45.9)	0.367
Stage IV disease	19 (67.9)	48 (78.7)	0.271
Poor differentiation	15 (53.6)	37 (60.7)	0.529
Previous surgery history	12 (42.9)	22 (36.1)	0.540
ICI agent type	-	-	0.367

Note: Data are presented as n (%) or mean ± standard deviation. ICIs, immune checkpoint inhibitors; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9.

Table 2. Comparison of the therapeutic effects

RECIST	ICI combined with chemotherapy plus targeted therapy (n=28)	ICI combined with chemotherapy (n=61)	χ^2	P
CR	0	0		
PR	6	11		
SD	16	35		
PD	6	15		
ORR (%)	21.43	18.03	0.008	0.930
DCR (%)	78.57	75.41	0.003	0.954

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

and CA19-9 levels than ICI combined with chemotherapy (all *P*<0.05), while no significant difference in post-treatment PLR levels was observed between the two groups (*P*>0.05; **Table 3**).

Comparison of general data from different prognosis groups

All 89 patients were divided into the non-progression group (25 cases) and the progression/death group (64 cases) according to the occurrence of PFS events. There were no significant differences in age, gender, BMI, liver metastasis, lymph node metastasis, tumor stage, differentiation degree, surgical history, treatment regimen and ICI agent type between the two groups (all *P*>0.05). The progression/death group had significantly higher baseline PLR (P=0.005) and SII (*P*<0.001) levels than the non-progression group, while baseline NLR and CA19-9 levels showed no significant inter-group differences (*P*>0.05; **Table 4**).

ROC curve analysis of inflammatory markers and CA19-9

ROC curves were plotted with PFS events as the endpoint to evaluate the predictive efficacy of each biomarker. The optimal cut-off values of NLR, PLR, SII, and CA19-9 were 4.54, 108.10, 311.36 and 22.53 U/mL, respectively. According to these thresholds, patients were divided into high and low level subgroups: 36 high-NLR and 53 low-NLR patients, 50 high-PLR and 39 low-PLR patients, 41 high-SII, and 48 low-SII patients, 49 high-CA19-9 and 40 low-CA19-9 patients.

ROC analysis results showed that the AUC of NLR, PLR, SII, and CA19-9 for predicting prognosis of advanced gastric cancer patients

Table 3. Comparison of laboratory indicators

Variable	ICI combined with chemotherapy plus targeted therapy (n=28)		ICI combined with chemotherapy (n=61)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
NLR	4.39±1.28	2.09±0.97*	4.24±1.38	2.73±1.02*,#
PLR	140.73±69.77	108.72±35.44*	121.13±59.83	112.72±30.62*
SII	318.88±132.64	231.09±82.35*	329.76±135.74	291.22±87.42*,#
CA19-9	24.49±11.20	13.09±9.87*	26.38±11.49	19.55±9.66*,#

Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9. *P<0.05 compared to before treatment in the same group; #P<0.05 compared to the ICIs plus chemotherapy plus targeted therapy group after treatment.

Table 4. Comparison of general data different prognosis groups

Variable		Non-progression group (n=25)	Progression-or-death group (n=64)	t/χ^2	P
Age (%)	<65	12 (48.0)	31 (48.4)	0.001	0.970
	≥65	13 (52.0)	33 (51.6)		
gender (%)	Female	6 (24.0)	24 (37.5)	1.466	0.226
	Male	19 (76.0)	40 (62.5)		
BMI (%)	≥18.5	17 (68.0)	53 (82.8)	2.349	0.125
	<18.5	8 (32.0)	11 (17.2)		
liver_meta (%)	No	21 (84.0)	48 (75.0)	0.836	0.361
	Yes	4 (16.0)	16 (25.0)		
LN_meta (%)	No	19 (76.0)	41 (64.1)	1.166	0.280
	Yes	6 (24.0)	23 (35.9)		
stage (%)	III	4 (16.0)	18 (28.1)	1.420	0.233
	IV	21 (84.0)	46 (71.9)		
differentiation (%)	Moderate/High Differentiation	15 (60.0)	26 (40.6)	2.716	0.099
	Poor Differentiation	10 (40.0)	38 (59.4)		
surgery (%)	No	18 (72.0)	37 (57.8)	1.533	0.216
	Yes	7 (28.0)	27 (42.2)		
treatment (%)	ICI + Chemotherapy + Targeted	10 (40.0)	18 (28.1)	1.176	0.278
	ICI + Chemotherapy	15 (60.0)	46 (71.9)		
ICI agent type (%)	Other ICIs	14 (56.0)	24 (37.5)	2.515	0.113
	Sintilimab	11 (44.0)	40 (62.5)		
NLR		3.87±1.00	4.45±1.43	-1.856	0.067
PLR		85.07±33.48	112.70±43.15	-2.877	0.005
SII ($\times 10^9$/L)		232.02±99.45	343.76±129.79	-3.878	<0.001
CA19-9 (U/mL)		22.52±10.89	27.06±11.38	-1.714	0.090

Note: BMI, body mass index; ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9.

receiving ICI therapy was 0.627 (95% CI: 0.508-0.745, P=0.065), 0.742 (95% CI: 0.614-0.870, P<0.001), 0.722 (95% CI: 0.611-0.834, P=0.001) and 0.608 (95% CI: 0.478-0.738, *P*=0.114), respectively. PLR and SII exhibited significant predictive value, whereas NLR and CA19-9 did not (**Table 5** and **Figure 1**). Therefore, the cut-off values of NLR and CA19-9 were exploratory and should be interpreted cautiously.

Kaplan-Meier PFS analysis of inflammatory markers and CA19-9

Kaplan-Meier survival analysis confirmed that baseline levels of all biomarkers were signifi-

Table 5. ROC curve analysis of inflammatory markers and CA19-9

Variable	AUC	SE	*P*	95% CI	Cut-off Value	Sensitivity (%)	Specificity (%)	Youden Index
NLR	0.627	0.060	0.065	0.508-0.745	4.54	48.44	80.00	28.44
PLR	0.742	0.065	<0.001	0.614-0.870	108.10	70.31	80.00	50.31
SII	0.722	0.057	0.001	0.611-0.834	311.36	57.81	84.00	41.81
CA19-9	0.608	0.066	0.114	0.478-0.738	22.53	60.53	59.45	19.98

Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9.

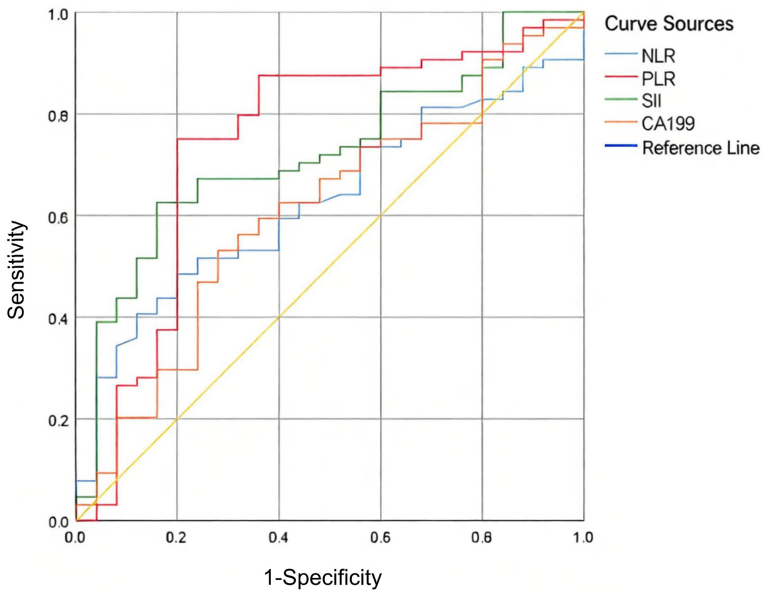

Figure 1. Receiver operating characteristic (ROC) curves for the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and carbohydrate antigen 19-9 (CA19-9).

cantly correlated with patients' PFS. The median PFS was 6.60 months in the high-NLR (≥4.54) group and 9.90 months in the low-NLR (<4.54) group (Log-rank χ^2=10.033, *P*=0.002). The median PFS was 5.80 months in the high-PLR (≥108.10) group and 9.90 months in the low-PLR (<108.10) group (χ^2=11.549, *P*<0.001). For SII subgroups, the median PFS was 5.50 months in the high-SII (≥311.36) group and 10.50 months in the low-SII (<311.36) group (χ^2=16.239, *P*<0.001). The median PFS was 7.00 months in the high-CA19-9 (≥22.53 U/mL) group and 12.10 months in the low-CA19-9 (<22.53 U/mL) group (χ^2=9.809, *P*=0.002; **Table 6** and **Figure 2**).

Although NLR and CA19-9 failed to show significant discriminatory ability in ROC analysis, their high and low level subgroups presented significant PFS differences by survival analysis. This discrepancy is attributed to the different analytical purposes: ROC analysis evaluates binary classification efficacy, while Kaplan-Meier and Log-rank analyses assess time-to-event survival differences. Notably, all cut-off values were derived from the same retrospective cohort, so the survival stratification results of NLR and CA19-9 need further external validation.

Univariate Cox regression analysis

Univariate Cox regression analysis indicated that low BMI, lymph node metastasis, poor histological differentiation, elevated NLR, PLR, SII and CA19-9 levels were significant risk factors for poor prognosis (all P<0.05). The detailed hazard ratios (HR) and 95% confidence intervals (CI) were as follows: BMI (HR=0.503, 95% CI: 0.262-0.965, *P*=0.039), lymph node metastasis (HR=1.700, 95% CI: 1.038-2.785, *P*=0.036), poor histological differentiation (HR=1.341, 95% CI: 1.039-1.696, *P*=0.009), NLR (HR=2.253, 95% CI: 1.342-3.782, *P*=0.002), PLR (HR=2.327, 95% CI: 1.407-3.849, *P*=0.001), SII (HR=2.733, 95% CI: 1.640-4.553, *P*<0.001), CA19-9 (HR=2.315, 95% CI: 1.346-3.982, *P*=0.002). In contrast, age, gender, liver metastasis, tumor stage, surgical history, treatment regimen and ICI agent type were not correlated with patients' prognosis (all P>0.05, **Table 7**).

Multivariate Cox regression analysis

Variables with statistical significance by univariate analysis were considered for inclusion in the multivariate Cox regression model. To avoid overfitting and multicollinearity, NLR and PLR were excluded, and SII was selected as the representative systemic inflammatory marker. The

Table 6. Kaplan-Meier PFS curves based on inflammatory markers and CA19-9 levels

Variable	Kaplan-Meier Survival Analysis				Log-Rank Test	
	Cut-off Value Grouping	PFS	SE	95% CI	χ^2	*P*
NLR	≥4.54	6.60	1.133	4.379-8.821	10.033	0.002
	<4.54	9.90	2.584	4.835-14.965		
PLR	≥108.10	5.80	0.796	4.239-7.361	11.549	0.001
	<108.10	9.90	0.823	8.287-11.513		
SII	≥311.36	5.50	0.767	3.996-7.004	16.239	<0.001
	<311.36	10.50	2.825	4.963-16.037		
CA19-9	≥22.53	7.00	1.295	4.462-9.538	9.809	0.002
	<22.53	12.10	3.227	5.776-18.424		

Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9; PFS, progression-free survival; SE, standard error; CI, confidence interval.

results showed that poor histologic differentiation, elevated SII and high CA19-9 levels were independent adverse prognostic factors for shortened PFS. Specifically, poor histologic differentiation increased the risk of disease progression or death (HR=3.236, 95% CI: 1.674-6.255, P<0.001). Elevated SII (HR=3.166, 95% CI: 1.808-5.546, *P*=0.001) and high CA19-9 level (HR=2.396, 95% CI: 1.358-4.227, *P*= 0.003; **Table 8**) were also independent risk factors for poor prognosis.

Calibration and discrimination verification of the predictive model

Internal validation using 1,000 bootstrap resampling was performed to verify the stability of the predictive model. The 2-month, 6-month, and 12-month PFS calibration curves showed high consistency between predicted and actual observed probabilities. The Brier scores for the three time points were 0.103, 0.201 and 0.156, respectively. The C-index of the model was 0.727 (95% CI: 0.658-0.792), indicating favorable discriminatory ability and predictive stability of the model (**Figure 3**).

Discussion

Gastric cancer is a common malignant tumor with high morbidity and mortality, imposing a heavy socioeconomic burden worldwide. According to GLOBOCAN 2022, there were approximately 968,784 new stomach cancer cases and 660,175 related deaths worldwide, with Asia accounting for 71.4% of new cases and 70.1% of deaths [14]. The current 5-year survival rate of gastric cancer is only 35.1%, which is significantly lower than the average survival level of common malignancies. In recent years, immunotherapy has achieved remarkable breakthroughs in the treatment of unresectable and metastatic advanced gastric cancer, fundamentally optimizing the clinical treatment [15, 16]. Multiple landmark clinical trials, including ATTRACTION-2, CheckMate 649, KEYNOTE-811 and ORIENT-16, have confirmed that PD-1 inhibitors can significantly improve OS and PFS in advanced gastric cancer patients, establishing ICI-based therapy as a first-line standard treatment for advanced gastric cancer [17-19].

Nevertheless, ICI treatment still has limitations in clinical application. Not all gastric cancer patients can benefit from immunotherapy, and approximately 2%-4% of patients may develop severe TRAEs. Moreover, there is currently no rapid and convenient biomarker for accurate prediction of ICI treatment efficacy. Traditional predictive biomarkers such as PD-L1 expression, tumor mutational burden and microsatellite instability are widely recognized for their predictive value, but their clinical application is restricted by cumbersome detection procedures, high costs and inconsistent diagnostic criteria [20-22]. Therefore, it is urgent to identify simple, economical and easily accessible peripheral blood biomarkers to improve the accuracy of immunotherapy prognosis prediction.

Accumulating studies have confirmed that systemic inflammatory response is closely correlated with tumor occurrence, progression and immune status. Peripheral blood inflammatory markers including NLR, PLR and lymphocyte-to-monocyte ratio can indirectly reflect the

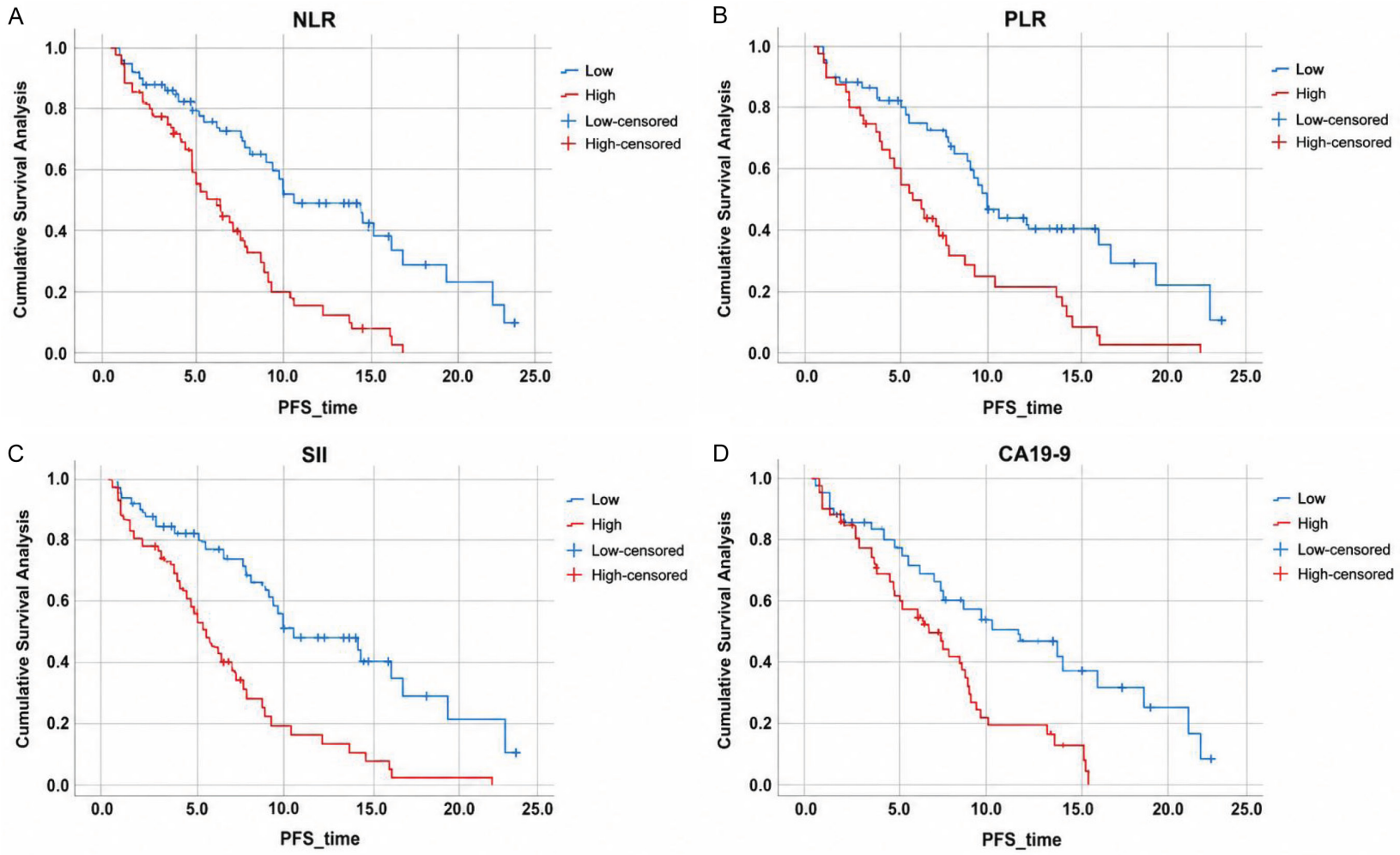

Figure 2. Kaplan-Meier PFS analysis of inflammatory markers and CA19-9. Note: PFS was estimated using the Kaplan-Meier method. (A) Neutrophil-to-lymphocyte ratio (NLR); (B) platelet-to-lymphocyte ratio (PLR); (C) systemic immune-inflammation index (SII); and (D) carbohydrate antigen 19-9 (CA19-9). The blue line indicates the low-level group, and the red line indicates the high-level group.

Table 7. Univariate Cox regression analysis

Variable	Univariate		
	HR (95% CI)	Wald χ^2	*P*-value
Age	0.722 (0.440-1.184)	1.67	0.196
Gender	0.698 (0.413-1.181)	1.80	0.180
BMI	0.503 (0.262-0.965)	4.27	0.039
Liver Metastasis	0.993 (0.562-1.753)	0.06	0.980
Lymph Node Metastasis	1.700 (1.038-2.785)	4.44	0.036
Stage	0.679 (0.373-1.236)	0.03	0.205
Differentiation Degree	1.341 (1.039-1.696)	6.74	0.009
Surgical History	0.831 (0.479-1.440)	0.44	0.509
Treatment Plan	1.422 (0.820-2.465)	1.57	0.21
ICI agent type	0.979 (0.583-1.644)	0.01	0.936
NLR	2.253 (1.342-3.781)	9.45	0.002
PLR	2.327 (1.407-3.849)	10.81	0.001
SII	2.733 (1.640-4.553)	15.17	<0.001
CA19-9	2.315 (1.346-3.982)	7.21	0.002

Note: BMI, body mass index; ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9.

Table 8. Multivariate Cox regression analysis

Variable	Multivariate		
	HR (95% CI)	Wald χ^2	*P*-value
Lymph Node Metastasis	1.067 (0.604-1.885)	0.056	0.824
Differentiation Degree	3.236 (1.674-6.255)	12.19	<0.001
High SII	3.166 (1.808-5.546)	16.24	0.001
High CA19-9	2.396 (1.358-4.227)	9.10	0.003

Note: SII, systemic immune-inflammation index; CA19-9, carbohydrate antigen 19-9.

tumor immune microenvironment and serve as effective indicators for tumor prognosis evaluation and treatment response monitoring. Muangto et al. found that elevated NLR and PLR were positively correlated with the depth of myometrial invasion in endometrial cancer, which could assist in evaluating tumor invasion degree [23]. Knetki-Wróblewska et al. demonstrated that low NLR and PLR levels were associated with prolonged PFS and OS in patients with non-small cell lung cancer [9]. Consistent with previous studies, our research further verified the prognostic value of systemic inflammatory markers and CA19-9 in gastric cancer immunotherapy.

Our ROC curve analysis, Kaplan-Meier survival analysis, and Cox regression analysis systematically confirmed that elevated pretreatment NLR, PLR, SII, and CA19-9 levels were correlated with poor prognosis in advanced gastric cancer patients receiving ICI therapy. The median PFS of patients with high levels of the four biomarkers was significantly shorter than that of patients with low levels. Multivariate analysis further screened out poor histologic differentiation, high SII, and high CA19-9 as independent adverse prognostic factors.

Poorly differentiated gastric cancer is characterized by severe cellular atypia, strong tumor heterogeneity and weak immunogenicity, which easily induces tumor immune escape and forms an immunosuppressive “cold tumor” microenvironment, resulting in poor immunotherapy efficacy. Elevated SII reflects an excessive systemic inflammatory state; activated neutrophils and platelets secrete a large number of pro-inflammatory cytokines, which promote tumor angiogenesis, proliferation, and metastasis, and inhibit anti-tumor immune responses. CA19-9 is closely associated with

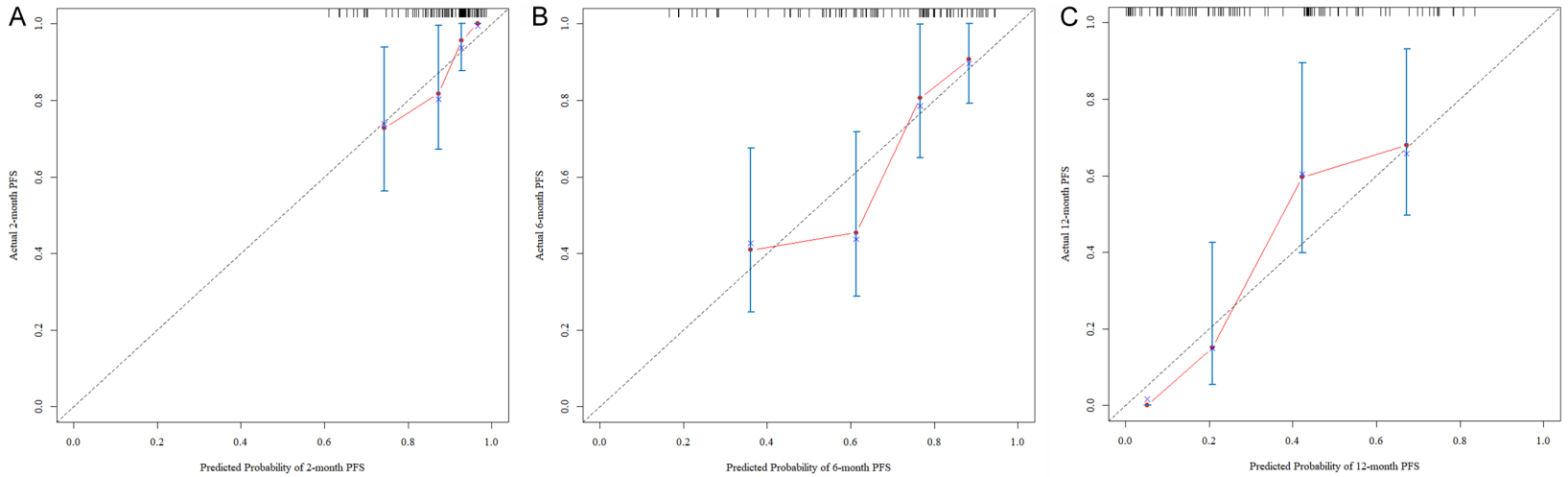

Figure 3. Calibration and discrimination verification of the predictive model. Note: A-C. These images are the calibration curve of 2-, 6- and 12-month PFS respectively. The abscissa is the predicted probability and the ordinate is the observed probability. The dotted line is an ideal state (45-degree diagonal), and among other things, red shows the curve after model correction. The blue error bars show the 95% confidence intervals for each group. The closer the calibration curve is to the reference line, the better it fits the predicted and observed data.

tumor burden, peritoneal metastasis and clinical stage; its persistent elevation indicates uncontrolled tumor progression and severe immune escape, thereby shortening patient survival.

The predictive model constructed in this study exhibited favorable calibration and discriminatory ability verified by internal bootstrap validation, with a C-index of 0.727, confirming its good predictive performance for immunotherapy prognosis.

However, this study also has several limitations. First, this was a single-center retrospective study with inherent selection bias, and the enrolled patient population was relatively homogeneous. Second, although internal validation was performed, external validation based on multi-center, large-sample prospective cohorts is still required to verify the generalizability and robustness of the model. Third, some clinically important variables, such as Eastern Cooperative Oncology Group performance status, human epidermal growth factor receptor 2 status, PD-L1 combined positive score and prior treatment lines, were not completely recorded in the retrospective medical data, which may affect the comprehensiveness of baseline balance assessment. In addition, all cut-off values were derived from the study cohort, which may cause data-driven bias and model overfitting. Therefore, the exploratory cut-off values of NLR and CA19-9 need further external validation before clinical application.

In conclusion, pretreatment peripheral blood inflammatory markers (NLR, PLR, SII) and CA19-9 levels are closely correlated with PFS in advanced gastric cancer patients receiving ICI-based therapy. Among these biomarkers, SII and CA19-9 are simple, economical and effective independent predictive indicators for immunotherapy efficacy and prognosis, which have great potential to guide clinical individualized treatment and risk stratification.

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Disclosure of conflict of interest

None.

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References

[1] Lin JL, Lin JX, Lin GT, Huang CM, Zheng CH, Xie JW, Wang JB, Lu J, Chen QY and Li P. Global incidence and mortality trends of gastric cancer and predicted mortality of gastric cancer by 2035. BMC Public Health 2024; 24: 1763.

[2] Cheng J, Cai M and Wang G. Association of different autoimmune diseases with gastric cancer incidence and risk: a global population-based analysis. Int J Surg 2026; 112: 5006-5013.

[3] Han B, Zheng R, Zeng H, Wang S, Sun K, Chen R, Li L, Wei W and He J. Cancer incidence and mortality in China, 2022. J Natl Cancer Cent 2024; 4: 47-53.

[4] Sundaram ME. Vaccine safety for individuals receiving immune checkpoint inhibitor therapy: a narrative review of current literature and recommendations for future research. Hum Vaccin Immunother 2026; 22: 2607893.

[5] Liu P, Li N, Guo J, Zhao GT, Wang J, Mou Z and Mao J. Immune checkpoint inhibitor therapy for gastric cancer: current status, therapeutic challenges, and future prospects. Front Immunol 2026; 17: 1716934.

[6] Schraps N, Menz A, Viehweger F, Büyücek S, Dum D, Schlichter R, Hinsch A, Fraune C, Bernreuther C, Kluth M, Hube-Magg C, Möller K, Reiswich V, Luebke AM, Lebok P, Weidemann S, Sauter G, Lennartz M, Jacobsen F, Clauditz TS, Marx AH, Simon R, Steurer S, Mercanoglu B, Melling N, Hackert T, Burandt E, Gorbokon N, Minner S, Krech T, Lutz F and Freytag M. Pattern and clinical significance of CA19-9 expression in human cancer: a tissue microarray study on 14,966 tumors. Cancer Med 2026; 15: e71710.

[7] Sun A, Chen H, Shi X, Shang Z and Zhang J. Diagnostic value of joint detection of serum TK1, TSGF, CA199, and CA724 for gastric cancer and its relationship with clinicopathologic features and prognosis. Am Surg 2025; 91: 570-578.

[8] Tan Z, Sheng B, Chen L, Dong H, Deng Y, Li Y, Liu C, Wang H, Yang Z, Xie T and Huang Y. Inflammation-driven mechanisms in endometrial cancer: pathways from inflammatory microenvironment remodeling to immune escape. Front Immunol 2025; 16: 1689114.

[9] Knetki-Wróblewska M, Grzywna A, Krawczyk P, Wojas-Krawczyk K, Chmielewska I, Jankowski T, Milanowski J and Krzakowski M. Prognostic

significance of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in second-line immunotherapy for patients with non-small cell lung cancer. Transl Lung Cancer Res 2025; 14: 749-760.

[10] Liu N, Mao J, Tao P, Chi H, Jia W and Dong C. The relationship between NLR/PLR/LMR levels and survival prognosis in patients with non-small cell lung carcinoma treated with immune checkpoint inhibitors. Medicine (Baltimore) 2022; 101: e28617.

[11] Aoyama T, Ju M, Komori K, Tamagawa H, Tamagawa A, Onodera A, Morita J, Hashimoto I, Ishiguro T, Endo K, Cho H, Onuma S, Fukuda M, Oshima T, Yukawa N and Rino Y. The platelet-to-lymphocyte ratio is an independent prognostic factor for patients with esophageal cancer who receive curative treatment. In Vivo 2022; 36: 1916-1922.

[12] Meng L, Yang Y, Hu X, Zhang R and Li X. Prognostic value of the pretreatment systemic immune-inflammation index in patients with prostate cancer: a systematic review and meta-analysis. J Transl Med 2023; 21: 79.

[13] Menyhart O, Fekete JT and Győrffy B. Inflammation and colorectal cancer: a meta-analysis of the prognostic significance of the systemic immune-inflammation index (SII) and the systemic inflammation response index (SIRI). Int J Mol Sci 2024; 25: 8441.

[14] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[15] Liu K, Yuan S, Wang C and Zhu H. Resistance to immune checkpoint inhibitors in gastric cancer. Front Pharmacol 2023; 14: 1285343.

[16] Li W, Xu M, Cheng M, Wei J, Zhu L, Deng Y, Guo F, Bi F and Liu M. Current advances and future directions for sensitizing gastric cancer to immune checkpoint inhibitors. Cancer Med 2025; 14: e71065.

[17] Liu T, Bai Y, Lin X, Li W, Wang J, Zhang X, Pan H, Bai C, Bai L, Cheng Y, Zhang J, Zhong H, Ba Y, Hu W, Xu R, Guo W, Qin S, Yang N, Lu J, Shitara K, Lei M, Li M, Bao N, Chen T and Shen L. First-line nivolumab plus chemotherapy vs chemotherapy in patients with advanced gastric, gastroesophageal junction and esophageal adenocarcinoma: checkmate 649 Chinese subgroup analysis. Int J Cancer 2023; 152: 749-760.

[18] Hindson J. KEYNOTE-811: pembrolizumab in advanced HER2+ gastric cancer. Nat Rev Gastroenterol Hepatol 2022; 19: 79.

[19] Xu J, Jiang H, Pan Y, Gu K, Cang S, Han L, Shu Y, Li J, Zhao J, Pan H, Luo S, Qin Y, Guo Q, Bai Y, Ling Y, Guo Y, Chen Y, Wang Y and Zhou H. Abstract CT078: first-line treatment with sintilimab (sin) vs placebo in combination with chemotherapy (chemo) in patients (pts) with unresectable gastric or gastroesophageal junction (G/GEJ) cancer: final overall survival (OS) results from the randomized, phase III ORIENT-16 trial. Cancer Res 2023; 83 Supple 8: CT078.

[20] Di Federico A, Alden SL, Smithy JW, Ricciuti B, Alessi JV, Wang X, Pecci F, Lamberti G, Gandhi MM, Vaz VR, Spurr LF, Sholl LM, Pfaff KL, Rodig SJ, Li YY, Cherniack AD, Nishino M, Johnson BE and Awad MM. Intrapatient variation in PD-L1 expression and tumor mutational burden and the impact on outcomes to immune checkpoint inhibitor therapy in patients with non-small-cell lung cancer. Ann Oncol 2024; 35: 902-913.

[21] Moeckel C, Bakhl K, Georgakopoulos-Soares I and Zaravinos A. The efficacy of tumor mutation burden as a biomarker of response to immune checkpoint inhibitors. Int J Mol Sci 2023; 24: 6710.

[22] Kavun A, Veselovsky E, Lebedeva A, Belova E, Kuznetsova O, Yakushina V, Grigoreva T, Mileyko V, Fedyanin M and Ivanov M. Microsatellite instability: a review of molecular epidemiology and implications for immune checkpoint inhibitor therapy. Cancers (Basel) 2023; 15: 2288.

[23] Muangto T, Maireang K, Poomtavorn Y, Thaweekul Y, Punyashthira A, Chantawong N, Wisarnsirirak P, Pattaraarchachai J and Suwannarurk K. Study on preoperative neutrophil/lymphocyte (NLR) and platelet/lymphocyte ratio (PLR) as a predictive factor in endometrial cancer. Asian Pac J Cancer Prev 2022; 23: 3317-3322.