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A Combined Immune-Inflammatory Score for Predicting Treatment Response and Survival in Advanced Gastric Cancer Receiving Chemoimmunotherapy

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ABSTRACT

Effective biomarkers are urgently needed to guide chemoimmunotherapy in advanced gastric cancer (AGC) and improve clinical outcomes. This study aimed to explore a blood-based immune score for predicting outcomes in patients with AGC receiving chemoimmunotherapy.

In this retrospective analysis, patients with AGC receiving chemoimmunotherapy were included. Treatment response was assessed by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Peripheral blood immune-inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and C-reactive protein-to-albumin ratio (CAR), and immune cell subsets, including $CD4^+$, $CD8^+$, and natural killer (NK) cells, were measured pre- and post-treatment. Receiver operating characteristic (ROC) analysis determined optimal cutoffs. Logistic regression identified independent predictors of objective response rate (ORR), and a combined immune-inflammatory score was constructed. Progression-free survival (PFS) was estimated using the Kaplan–Meier method, with risk stratification based on the score. Bootstrap resampling was used for internal validation.

Among 100 patients, the ORR was 46.0%. Multivariate analysis confirmed NLR ≤ 2.5 (adjusted odds ratio [aOR]=0.333), $CD8^+$ T cells≥30% (aOR=3.439), and SII ≤ 600 (aOR=0.386) as independent predictors of ORR. The combined score (range 0–3) achieved an area under the curve (AUC) of 0.874 for ORR prediction. During a median follow-up of 15.3 months, patients with a score≥2 (favorable immune profile group) had significantly longer PFS than those with a score≤1 (unfavorable immune profile group) (median PFS: 15.6 vs 7.8 months). Bootstrap internal validation confirmed the stability of the score (concordance index [C-index]=0.814).

The NLR/SII/$CD8^+$ T-cell score was associated with treatment response and survival among patients with AGC receiving chemoimmunotherapy, suggesting that it is a hypothesis-generating tool requiring external validation and is not ready for clinical use.

Keywords: Antineoplastic combined chemotherapy protocols; Biomarkers; CD8-positive T-lymphocytes; Immunotherapy; Stomach neoplasms; Treatment outcome

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INTRODUCTION

Globally, gastric cancer is a prevalent and serious digestive system malignancy. Patients with advanced gastric cancer (AGC), often ineligible for curative surgery, typically face a poor prognosis. Chemotherapy has been the main systemic treatment method for this condition, but its efficacy has reached a plateau, and the objective response rate (ORR) and survival remain suboptimal.[1,2] Immunotherapy has recently introduced transformative advances in advanced gastric cancer treatment. In particular, immunotherapy combined with chemotherapy has been shown in multiple clinical studies to significantly improve treatment response and survival and is now a key first-line option for advanced gastric cancer.[3–6]

However, clinical practice reveals substantial variability in patient responses to chemoimmunotherapy. Some patients have poor responses and even experience rapid disease progression, which may increase the medical burden and delay the optimal timing of treatment.[7–9] Therefore, identifying clinical indicators that accurately predict treatment response and facilitate individualized treatment planning is clinically vital for improving the prognosis of patients with advanced gastric cancer.[10]

Based on the above clinical background, this study retrospectively reviewed data from patients with AGC treated with chemoimmunotherapy, evaluated treatment response, screened potential predictive factors for objective response, and constructed a simple combined immune-inflammatory score (0–3). We examined whether pretreatment levels of blood-based immune-inflammatory markers (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], systemic immune-inflammation index [SII], C-reactive protein-to-albumin ratio [CAR]) and immune cell subsets ($CD8^+$ T cells, natural killer [NK] cells) were associated with treatment response to chemoimmunotherapy, and whether this score outperformed any single biomarker in this cohort. In addition, we explored whether this score was associated with progression-free survival (PFS) and could stratify patients into different risk groups, with the aim of providing a potential tool for response prediction and survival risk stratification that requires further validation.

Study Design

Clinical data were retrospectively obtained from AGC patients who received combined immunotherapy and chemotherapy from 3 departments at our hospital, including Oncology, Gastroenterology, and Gastrointestinal Surgery, between September 1, 2023, and September 1, 2024. A total of 122 patients were initially screened. After applying the inclusion and exclusion criteria, 22 patients were excluded for the following reasons: regimen inconsistency or interruption (n = 6), missing key data (n = 9), severe comorbidities (n = 3), and other reasons (n = 4). The remaining 100 patients were included in the final analysis. Using the hospital's electronic records, patients were grouped into response (CR + PR) or non-response (SD + PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).[11] By comparing clinical profiles and immune-related indicators between the two groups, the study aimed to identify immunological predictors of treatment response to chemoimmunotherapy in advanced gastric cancer. The study design is summarized in Figure 1. Follow-up data for survival analysis were updated as of June 30, 2025.

Ethics Statement

Approval was granted by the 900th Hospital of PLA Joint Logistic Support Force ethics board (Approval No. 2023XKZL03), and all procedures followed the Declaration of Helsinki.[12] Informed consent was waived by the ethics committee due to the retrospective use of archived clinical data. All participant data were fully anonymized to protect privacy.

Inclusion and Exclusion Criteria

Inclusion criteria:[13,14] (1) aged 18 to 75 years, inclusive, irrespective of gender; (2) advanced gastric cancer (stage IIIB/IIIC/IV) confirmed by histology or imaging; (3) no prior immunotherapy and planned treatment with combined immunotherapy and chemotherapy; (4) the presence of a tumor that can be evaluated for treatment response using RECIST 1.1, that had not previously received local treatment; (5) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and expected survival ≥ 12 months; (6) organ function requirements included: hemoglobin > 9 g/dL, platelets $\geq 80 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L; creatinine clearance > 50 mL/min; alanine aminotransferase/aspartate aminotransferase $\leq 2.5 \times$ upper limit of normal (ULN); total bilirubin ≤ 1.5 mg/dL; creatinine ≤ 1.5 mg/dL; international normalized

ratio (INR), partial thromboplastin time/prothrombin time $\leq 1.5 \times$ ULN; (7) the clinical, laboratory, and follow-up data were complete.

Exclusion criteria:[15,16] (1) double or triple primary tumors; (2) known allergy to any component of the drug used in the study; (3) use of systemic immunomodulators (e.g., interferon, interleukin 2, tumor necrosis factor [TNF]) within 4 weeks before treatment or within 5 drug half-lives, whichever was longer; (4) severe infection (Common Terminology Criteria for Adverse Events grade > 2) within 4 weeks before the first dose; recent digestive surgery (< 1 month) or incomplete recovery; (5) antibiotic use within 4 weeks; history of stroke, transient ischemic attack (TIA), acute myocardial infarction, New York Heart Association (NYHA) class II–IV heart failure, or coronary interventions (e.g., angioplasty, stenting) before screening; (6) pregnant or lactating women; (7) human immunodeficiency virus (HIV) positivity; severe coagulation disorders; active tuberculosis (confirmed or suspected cases requiring chest X-ray/sputum evaluation for exclusion); (8) untreated chronic hepatitis B, hepatitis B virus deoxyribonucleic acid > 500 IU/mL, or active hepatitis C. Inclusion allowed: inactive hepatitis B surface antigen carriers, stable treated HBV (DNA < 500 IU/mL), cured hepatitis C, or hepatitis C virus antibody-positive with undetectable RNA; (9) history of substance, alcohol, or drug abuse.

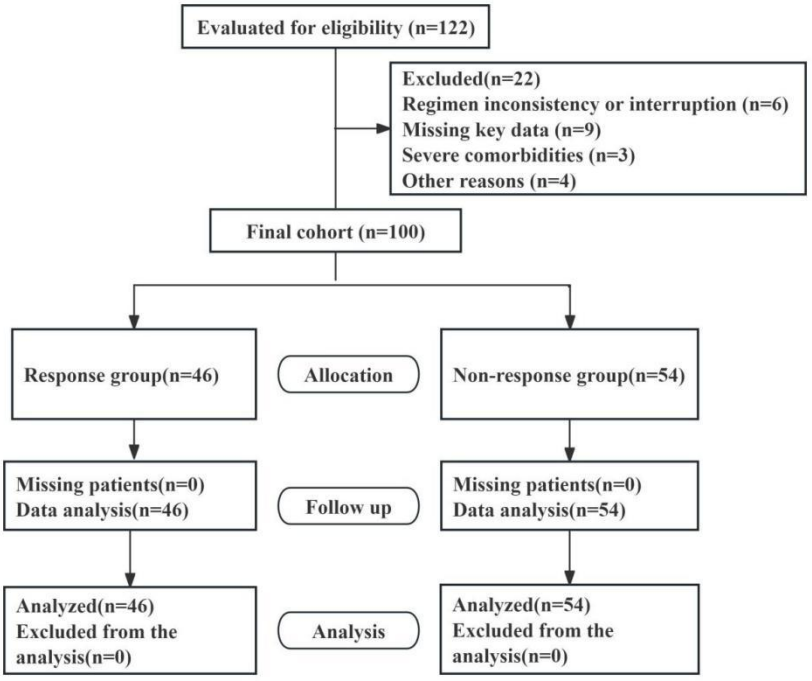

Figure 1. Design flow chart. A total of 122 patients were screened; 22 were excluded due to regimen inconsistency/interruption (n = 6), missing key data (n = 9), severe comorbidities (n = 3), and other reasons (n = 4). The final analytic cohort comprised 100 patients.

Sample Size Calculation

Sample size was determined using PASS 15.0 software, with ORR as the primary endpoint, and calculated to meet the requirements of multivariate logistic regression. Based on prior immunotherapy studies,[17] an ORR of 45% was assumed, with $\alpha = 0.05$ (two-sided) and $\beta = 0.2$ (power 80%). The minimum required sample size was 89. To account for possible missing data, the sample size was increased by 12%, and 100 patients were included to meet the power requirement.

Treatment Options

Patient data were retrospectively collected from medical records. According to the medical record, all patients were treated per the CSCO Gastric Cancer Guidelines 2021.[18] The immunotherapeutic agents were programmed cell death protein 1 (PD-1) inhibitors,

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including sintilimab (200 mg, day 1, every 3 weeks; marketed as TYVYT; Innovent Biologics, Suzhou, China) in 62 patients, tislelizumab (200 mg, day 1, every 3 weeks; BeiGene, Beijing, China) in 24 patients, and camrelizumab (200 mg, day 1, every 2 weeks; marketed as AiRuiKa; Jiangsu Hengrui Pharmaceuticals Co., Ltd., Lianyungang, China) in 14 patients. All PD-1 inhibitors were administered intravenously. Chemotherapy backbones were selected ''at the physician's discretion and according to the patient's condition: XELOX regimen (48 patients): oxaliplatin 130 mg/m^2, day 1 (Eloxatin; Sanofi-Aventis, Paris, France), plus capecitabine 1000 mg/m^2 twice daily, days 1–14 (Xeloda; Roche Products Ltd., Basel, Switzerland), every 3 weeks. SOX regimen (32 patients): oxaliplatin 130 mg/m^2, day 1 (Eloxatin; Sanofi-Aventis, Paris, France), S-1 40–60 mg twice daily, days 1–14 (Teysuno; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan), every 3 weeks. FOLFOX regimen (12 patients): oxaliplatin 85 mg/m^2, day 1 (Eloxatin; Sanofi-Aventis, Paris, France), leucovorin 400 mg/m^2, day 1 (Fresenius Kabi, Bad Homburg, Germany), 5-fluorouracil 400 mg/m^2 bolus then 2400 mg/m^2 continuous infusion over 46 hours (Fresenius Kabi, Bad Homburg, Germany), every 2 weeks. Other platinum-fluoropyrimidine doublets (8 patients). Treatment cycles were repeated every 2 or 3 weeks for 6 to 8 cycles, followed by maintenance with PD-1 inhibitor alone until disease progression or unacceptable toxicity. Dose reductions or treatment delays were applied according to standard clinical practice.

Evaluation Indicators

Data on the baseline, efficacy, and immune-related evaluation indicators were retrospectively extracted and retrieved from the hospital's electronic records.

Baseline Data

Patient baseline data were obtained from electronic medical records, including: age, gender, ECOG score, primary tumor site, degree of differentiation, Lauren classification, clinical stage, number of metastatic sites, specific metastatic sites (liver, lung, peritoneum, distant lymph nodes), and number of previous systemic treatment lines.

Efficacy Evaluation Indicators

The primary endpoint, ORR, was evaluated according to RECIST 1.1. Computed tomography (CT) or magnetic resonance imaging (MRI) reports and images were collected and compared at baseline and approximately every 2 months after chemoimmunotherapy. Two physicians independently assessed response (CR, PR, SD, PD). ORR was defined as the proportion of patients with CR or PR.[19] Based on initial response, patients were categorized into response (CR + PR) and non-response (SD + PD). The secondary endpoint was PFS, defined as the time from initiation of chemoimmunotherapy to the first documented radiographic disease progression (per RECIST 1.1) or death from any cause, whichever occurred first. Surviving patients without progression were censored at the date of last contact. The follow-up data were updated as of June 30, 2025.

Immune-Related Evaluation Indicators

Immune-related laboratory data were retrospectively obtained for all patients. The time points that were collected corresponded to the results of completed fasting peripheral-venous-blood tests recorded in the medical record at baseline before treatment and at approximately 1 and 2 months after the initiation of treatment.

(1) Immune-inflammatory indices: Neutrophil, lymphocyte, and platelet counts were obtained from automated analyzers to calculate NLR, PLR, and SII (neutrophils×platelets / lymphocytes).[20] Serum CRP and albumin (ALB) levels at the same time point were extracted from biochemical test records, and CAR was calculated.

(2) Immune cell subsets: Peripheral blood samples (2 mL) were collected in ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes at baseline, 1 month, and 2 months post-treatment. Flow cytometry was performed using a Navios flow cytometer (Beckman Coulter, Brea, CA, USA). The following fluorescently labeled monoclonal antibodies (BD Biosciences, San Jose, CA, USA) were used: fluorescein isothiocyanate (FITC) anti-CD3, phycoerythrin (PE) anti-CD4, allophycocyanin (APC) anti-CD8, and phycoerythrin-Cy7 (PE-Cy7) anti-CD56. The gating strategy was as follows: lymphocytes were first identified by forward scatter (FSC) versus side scatter (SSC) gating. From the lymphocyte population, CD3$^+$ T cells were gated, followed by CD4$^+$ and CD8$^+$ subsets. NK cells were defined as CD3$^-$CD56$^+$ cells within the lymphocyte gate. A minimum of 10 000 events were acquired per sample. Daily quality control was performed using Flow Check Pro beads (Beckman Coulter) to verify instrument performance. Data were analyzed using

Kaluza software (Beckman Coulter), with the $CD4^+/CD8^+$ ratio calculated accordingly.

(3) Timing of blood collection and corticosteroid control: Peripheral blood samples were collected at 3 time points: baseline (within 3 days before the first dose of chemoimmunotherapy) to reflect the pretreatment immune-inflammatory status; 1 month after treatment initiation (day 1 of cycle 2, 21–28 days after the first dose, just before the next infusion) to capture early immune changes; and 2 months after treatment initiation (day 1 of cycle 3 or 4, 56–70 days after the first dose, before the infusion) to assess sustained immune modulation. All samples were collected before administration of chemotherapy or PD-1 inhibitor on scheduled treatment days to avoid acute drug effects. Regarding corticosteroid control, patients who had received systemic corticosteroids (equivalent to prednisone≥ 10 mg/day) within 14 days prior to any scheduled blood draw were excluded from the analysis at that time point, according to the inclusion/exclusion criteria of this study. No such exclusions occurred in the final cohort, confirming that none of the 100 included patients had corticosteroid exposure within the prespecified window.

Statistical Analysis

All analyses were performed using SPSS 26.0 and R 4.2.0. Normality was tested using the Shapiro–Wilk test. Normally distributed data are presented as mean ± SD and compared by independent-samples t tests; non-normally distributed data are presented as median (IQR) and compared by Mann–Whitney U test. Categorical variables are expressed as n (%) and compared by chi-square or Fisher's exact test. ROC curves were used to determine the optimal cutoff values of pretreatment immune indices for predicting ORR based on the Youden index. AUC, sensitivity, and specificity were calculated. Univariate logistic regression was performed using the dichotomized variables. Variables with $p<0.10$ were entered into multivariate logistic regression with forward stepwise selection (entry $p<0.05$, removal $p>0.10$). Adjusted odds ratios (aORs) with 95% CI were calculated. To mitigate overfitting given the sample size (n = 100), we used: (1) prescreening based on univariate $p<0.10$; (2) stepwise selection with strict thresholds; (3) bootstrap internal validation (1000 iterations) to compute optimism-corrected C-index. Calibration was assessed using a calibration plot and the Hosmer–Lemeshow test. A combined prediction model was built using the independent predictors. Model performance was compared using ROC analysis with the DeLong test. Decision curve analysis (DCA) evaluated clinical net benefit. PFS was estimated using the Kaplan–Meier method with log-rank tests. Univariate and multivariate Cox proportional hazards regression (forward stepwise) identified independent prognostic factors. The proportional hazards assumption was formally tested using Schoenfeld residuals. Patients were stratified into favorable immune profile (score≥2) and unfavorable immune profile (score≤1) groups based on the combined score (0–3). Bootstrap resampling (1000 iterations) was used to calculate the optimism-corrected C-index for PFS prediction. OS was not formally analyzed because the data were immature; only PFS was used as the primary survival endpoint. For immune parameters measured at baseline, 1 month, and 2 months, we used repeated-measures ANOVA with time as the within-subject factor and response group as the between-subject factor. The sphericity assumption was tested using Mauchly's test; the Greenhouse–Geisser correction was applied when violated. Post hoc pairwise comparisons were adjusted using Bonferroni correction. Non-normally distributed data were log-transformed before analysis. This approach replaced the original multiple pairwise comparisons. All included patients (n=100) had complete key data at baseline and follow-up time points, as patients with any missing data were excluded during screening. Therefore, no imputation methods were applied. All tests were two-sided, and $p<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics and Treatment Response

A total of 100 patients with advanced gastric cancer receiving chemoimmunotherapy were included. According to RECIST 1.1 criteria, the ORR was 46.0% (46/100), including 4 complete responses (CR, 4.0%) and 42 partial responses (PR, 42.0%). Stable disease (SD) occurred in 32 patients (32.0%) and progressive disease (PD) in 22 patients (22.0%), yielding a disease control rate (DCR) of 78.0% (Table 1). Baseline demographic, clinical, and pathological characteristics were well balanced between the response group (n = 46) and non-response group (n = 54), with no significant differences in age, sex, ECOG performance status, primary tumor site, differentiation grade, Lauren classification, clinical stage, metastatic burden, or prior treatment lines (all $p>0.05$) (Table 2).

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Comparison of Immune Parameters

Pretreatment levels of systemic inflammatory markers (NLR, PLR, SII, CAR) were significantly lower in the response group than in the non-response group (all $p<0.001$), while the proportions of $CD8^+$ T cells and NK cells were significantly higher (both $p<0.001$). The $CD4^+/CD8^+$ ratio was lower in responders ($p<0.001$). During treatment, responders showed a progressive decline in NLR, PLR, SII, and CAR, as well as a significant increase in $CD8^+$ T cells and NK cells at 2 months post-treatment (all $p<0.001$). In contrast, non-responders exhibited no significant changes in any of these parameters (all $p>0.05$) (Tables 3 and 4).

Table 1. Treatment response to chemoimmunotherapy in advanced gastric cancer

Response Category (RECIST 1.1)	Number of Patients (n)	Proportion (%)
Complete Response (CR)	4	4.0%
Partial Response (PR)	42	42.0%
Stable Disease (SD)	32	32.0%
Progressive Disease (PD)	22	22.0%
Objective Response Rate (ORR)	46	46.0%
Disease Control Rate (DCR)	78	78.0%

This table summarizes the objective response rate (ORR) and disease control rate (DCR) according to RECIST 1.1 criteria in 100 patients with advanced gastric cancer receiving chemoimmunotherapy. ORR = complete response (CR) + partial response (PR); DCR=CR + PR + stable disease (SD). Progressive disease (PD) indicates no response. CR: complete response; DCR: disease control rate; ORR: objective response rate; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

Table 2. Comparison of baseline characteristics between response group and non-response group

Baseline Characteristics Demographics	Response Group (n=46)	Non-response Group (n=54)	Statistic	*p*
Age [years, M (Q1, Q3)]	61 (54, 67)	63 (56, 70)	Z = 1.32	0.187
Sex [n (%)]			$\chi^2 = 0.15$	0.699
Male	31 (67.4)	34 (63.0)		
Female	15 (32.6)	20 (37.0)		
Performance Status				
ECOG Score [n (%)]			$\chi^2 = 0.09$	0.764
0	20 (43.5)	21 (38.9)		
1	26 (56.5)	33 (61.1)		
Primary Tumor Features				
Primary Site [n (%)]			$\chi^2 = 0.28$	0.597
Gastric Body/Antrum	34 (73.9)	37 (68.5)		
Gastroesophageal Junction/Cardia	12 (26.1)	17 (31.5)		
Differentiation Grade [n (%)]			$\chi^2 = 0.55$	0.459
Well/Moderate	19 (41.3)	19 (35.2)		
Poor/Undifferentiated	27 (58.7)	35 (64.8)		
Lauren Classification [n (%)]			$\chi^2 = 0.12$	0.729
Intestinal	23 (50.0)	24 (44.4)		
Diffuse/Mixed	23 (50.0)	30 (55.6)		

Table 2. Continued...

Baseline Characteristics Demographics	Response Group (n=46)	Non-response Group (n=54)	Statistic	*p*
Disease Stage and Burden				
Clinical Stage [n (%)]			$\chi^2 = 0.27$	0.603
IIIB/IIIC	11 (23.9)	11 (20.4)		
IV	35 (76.1)	43 (79.6)		
Number of Metastatic Sites [M (Q1, Q3)]	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	Z = 0.48	0.631
Common Metastatic Sites [n (%)]				
Liver Metastasis	17 (37.0)	23 (42.6)	$\chi^2 = 0.33$	0.566
Lung Metastasis	10 (21.7)	15 (27.8)	$\chi^2 = 0.50$	0.479
Peritoneal Metastasis	14 (30.4)	19 (35.2)	$\chi^2 = 0.26$	0.610
Distant Lymph Node Metastasis	24 (52.2)	24 (44.4)	$\chi^2 = 0.60$	0.439
Prior Treatment				
Line of Therapy [n (%)]			$\chi^2 = 0.05$	0.823
First-Line	37 (80.4)	45 (83.3)		
Second-Line or Beyond	9 (19.6)	9 (16.7)		

Continuous variables were compared using the Mann–Whitney U test (Z value); categorical variables using the chi-square test (χ^2).
ECOG: Eastern Cooperative Oncology Group; M: median; Q1: first quartile; Q3: third quartile.

Table 3. Comparison of peripheral blood immune-inflammatory indices between groups before and after treatment [M(Q1, Q3)]

Indicator	Group	Baseline	1 Month Post-Treatment	2 Months Post-Treatment	*p* (Group)	*p* (Time)	*p* (Group×Time)
NLR	Response group	2.1 (1.6, 2.4)	1.7 (1.3, 2.0)	1.4 (1.1, 1.8)	<0.001	<0.001	<0.001
	Non-response group	3.2 (2.7, 3.8)	3.1 (2.6, 3.7)	3.0 (2.5, 3.6)			
PLR	Response group	152 (131, 172)	135 (118, 156)	121 (105, 142)	<0.001	<0.001	<0.001
	Non-response group	215 (192, 241)	210 (188, 236)	206 (185, 232)			
SII	Response group	486 (412, 553)	392 (328, 457)	315 (262, 371)	<0.001	<0.001	<0.001
	Non-response group	721 (654, 793)	708 (642, 781)	695 (630, 768)			
CAR	Response group	0.15 (0.11, 0.18)	0.12 (0.09, 0.15)	0.09 (0.07, 0.12)	<0.001	<0.001	<0.001
	Non-response group	0.28 (0.23, 0.34)	0.27 (0.22, 0.33)	0.26 (0.21, 0.32)			

Data are presented as median (interquartile range, IQR). P values for group, time, and group×time interaction were derived from repeated measures ANOVA performed on log-transformed values to approximate normality. Post hoc pairwise comparisons were adjusted using Bonferroni correction. In the response group, all time-point comparisons were statistically significant for each indicator (adjusted $P < 0.05$); no significant changes were observed in the non-response group.
CAR: C-reactive protein-to-albumin ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index.

Table 4. Comparison of immune cell subsets between groups before and after treatment [mean±SD]

Indicator	Group	Baseline	1 Month Post-Treatment	2 Months Post-Treatment	*p* (Group)	*p* (Time)	*p* (Group×Time)
$CD3^+$ T cells	Response group	68.2±7.5	72.5±8.1	76.3±8.4	0.002	<0.001	<0.001
	Non-response group	62.1±7.2	62.8±7.4	63.5±7.6			
$CD4^+$ T cells	Response group	32.5±5.8	33.1±6.1	33.8±6.3	0.315	0.172	0.684
	Non-response group	33.7±6.2	34.2±6.3	34.6±6.5			
$CD8^+$ T cells	Response group	32.8±6.4	37.2±6.8	41.5±7.2	<0.001	<0.001	<0.001
	Non-response group	24.6±5.9	25.1±6.1	25.7±6.3			
NK cells	Response group	16.8±4.2	19.3±4.5	22.1±4.8	<0.001	<0.001	<0.001
	Non-response group	12.3±3.8	12.7±3.9	13.1±4.1			
$CD4^+/CD8^+$ T cell ratio	Response group	1.02±0.21	0.90±0.18	0.82±0.16	<0.001	<0.001	<0.001
	Non-response group	1.42±0.28	1.39±0.27	1.36±0.26			

ata are mean ± SD. *p* values for group, time, and interaction from repeated measures ANOVA with Bonferroni correction. In responders, $CD8^+$ T cells, NK cells, and $CD4^+/CD8^+$ ratio changed significantly between all time points (adjusted $P < 0.05$); nonresponders showed no significant changes. CD: cluster of differentiation; NK: natural killer; SD: standard deviation.

ROC Curve Analysis for Cut-off Values

ROC curve analysis determined optimal cutoff values for pretreatment immune indices: NLR≤2.5, SII≤600, $CD8^+$ T cells≥30%, PLR≤180, CAR≤0.2, NK cells≥15%, and $CD4^+/CD8^+$ ratio≤1.4. All indices showed significant predictive value for ORR (all $P<0.05$), with SII having the highest AUC (0.854) (Table 5).

Logistic Regression Analysis for ORR

Univariate and multivariate logistic regression analyses were performed to identify independent predictors of ORR. In univariate analysis, NLR ≤ 2.5, SII ≤ 600, and $CD8^+$ T cells ≥ 30% were associated with higher ORR (all $p\leq0.001$). Multivariate analysis identified these three as independent predictors (adjusted OR = 0.333, 0.386, and 3.439, respectively; all $p<0.05$). PLR ≤ 180 showed a borderline association in univariate analysis ($p=0.075$) but did not retain significance in the multivariate model ($p=0.340$) (Table 6).

Table 5. ROC curve analysis of pretreatment immune indices for predicting treatment response

Predictive Index	AUC	95% CI	Optimal Cutoff Value	Sensitivity (%)	Specificity (%)	*p*
SII	0.854	0.774–0.928	≤ 600	84.8	83.3	<0.001
NLR	0.834	0.765–0.923	≤ 2.5	82.6	81.5	<0.001
$CD8^+$ T Cells	0.739	0.714–0.888	≥ 30%	73.9	75.9	<0.001
PLR	0.823	0.740–0.906	≤ 180	78.3	79.6	<0.001
CAR	0.805	0.720–0.890	≤ 0.2	76.1	77.8	<0.001
NK Cells	0.722	0.658–0.846	≥ 15%	71.7	74.1	<0.001
$CD4^+/CD8^+$	0.691	0.590–0.792	≤ 1.4	67.4	70.4	0.001

Optimal cutoff values were determined by maximizing the Youden index. Sensitivity and specificity are reported as percentages. *p* values were derived from the ROC curve analysis testing the null hypothesis that AUC = 0.5.
AUC: area under the curve; CAR: C-reactive protein-to-albumin ratio; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; ROC: receiver operating characteristic; SII: systemic immune-inflammation index.

Table 6. Univariate and multivariate logistic regression analysis for ORR

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
NLR ≤ 2.5 (vs >2.5)	0.267 (0.122–0.584)	0.001	0.333 (0.142–0.782)	0.011
SII ≤ 600 (vs >600)	0.244 (0.110–0.539)	<0.001	0.386 (0.171–0.872)	0.022
$CD8^+$ T cells ≥ 30% (vs <30%)	3.337 (1.592–6.993)	0.001	3.439 (1.585–7.464)	0.002
PLR ≤ 180 (vs >180)	0.522 (0.255–1.067)	0.075	0.670 (0.294–1.525)	0.340
CAR ≤ 0.2 (vs >0.2)	0.560 (0.276–1.134)	0.107	NA	NA
NK cells ≥ 15% (vs <15%)	1.682 (0.838–3.376)	0.143	NA	NA
$CD4^+/CD8^+$ ≤ 1.4 (vs >1.4)	0.657 (0.331–1.304)	0.230	NA	NA

Variables with univariate P < 0.10 (NLR, SII, $CD8^+$ T cells, PLR) were entered into multivariate logistic regression using forward stepwise selection (entry P < 0.05, removal P > 0.10). CAR: C-reactive protein-to-albumin ratio; CI: confidence interval; NA: not applicable; NK: natural killer; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; ORR: objective response rate; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index.

Combined Predictive Model Performance

A combined model incorporating independent predictors was developed and its performance was compared with individual indicators. The combined model demonstrated superior discrimination (AUC=0.874, 95% CI, 0.792–0.936) compared to individual markers (NLR: 0.834; SII: 0.854; $CD8^+$ T cells: 0.739). The DeLong test 'showed that the combined model's AUC was significantly greater than that of each single indicator (all P<0.05) (Table 7). In addition, the model showed a balance between sensitivity (86.9%) and specificity (85.2%), and the Youden index was the highest (0.721). As shown in Figure 2, the combined model's ROC curve surpassed that of each single predictor, further illustrating the synergistic value of combining systemic inflammatory markers with cellular immune parameters in predicting treatment response.

Decision Curve Analysis

Decision curve analysis was performed to evaluate the clinical net benefit of the combined score for predicting ORR. As shown in Figure 3, the combined score (red solid line) provided a positive net benefit across threshold probabilities ranging from approximately 0.1 to 0.4, which was superior to both the "treat all" and "treat none" strategies. This suggests that the combined score may offer net clinical benefit within this threshold range.

Survival Analysis and Risk Stratification

The median follow-up duration was 15.3 months (IQR, 12.5–21.8). During follow-up, 57 patients (57.0%) progressed or died, and the median PFS for the whole cohort was 7.8 months (95% CI: 6.5–9.1). Univariate and multivariate Cox regression analyses were performed to identify prognostic factors for PFS.

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In univariate analysis, NLR≤2.5, SII≤600, and $CD8^+$ T cells≥30% were associated with longer PFS (all $p<0.05$). Multivariate analysis confirmed these three as independent protective factors (adjusted HR=0.422, 0.468, and 0.558, respectively; all $p<0.05$) (Table 8).

Based on the combined score (0–3), patients were stratified into a favorable immune profile group (score≥2, n=48, 48.0%) and an unfavorable immune profile group (score≤1, n=52, 52.0%) (Table 9). A higher combined score (≥2) indicates more favorable immune-inflammatory profiles and was therefore defined as low risk, while a lower score (≤1) was defined as high risk. Kaplan–Meier analysis showed that the favorable immune profile group had longer PFS than the unfavorable immune profile group, with median PFS of 15.6 months (95% CI: 12.146–19.054) versus 7.8 months (95% CI: 6.334–9.266) (log-rank $p<0.001$) (Figure 4). The 12-month PFS rates were 70.8% and 23.0%, respectively. OS data were immature (median follow-up 15.3 months); the median OS was not reached. The 12-month landmark OS rate for the entire cohort was 60.0%. Formal OS analysis was not performed due to limited events and follow-up duration.

Internal Validation

Internal validation using bootstrap resampling (1000 iterations) yielded an optimism-corrected C-index of 0.814 (95% CI: 0.762–0.866) for the combined score in predicting PFS, suggesting acceptable discriminative ability and limited overfitting.

Table 7. Performance comparison of individual indicators and the combined prediction model

Predictor / Model	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Youden Index	*p* for AUC Comparison vs Combined Model
NLR (≤2.5)	0.834 (0.765–0.923)	82.6	81.5	0.641	0.039
$CD8^+$ T Cells (≥30%)	0.739 (0.714–0.888)	73.9	75.9	0.498	0.005
SII (≤600)	0.854 (0.774–0.928)	84.8	83.3	0.681	0.028
Combined Prediction Model	0.874 (0.792–0.936)	86.9	85.2	0.721	—

The combined prediction model was constructed via logistic regression using the three independent predictors identified by multivariate analysis (NLR ≤2.5, $CD8^+$ T cells ≥30%, and SII ≤600). The DeLong test was used to compare AUCs between the combined model and each single indicator. AUC: area under the curve; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune-inflammation index.

Table 8. Univariate and multivariate Cox regression analysis for progression-free survival

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
NLR ≤ 2.5 (vs >2.5)	0.395 (0.234–0.668)	0.001	0.422 (0.245–0.727)	0.002
SII ≤ 600 (vs >600)	0.428 (0.255–0.718)	0.002	0.468 (0.272–0.805)	0.006
$CD8^+$ T cells ≥ 30% (vs <30%)	0.512 (0.303–0.866)	0.013	0.558 (0.321–0.970)	0.039
PLR ≤ 180 (vs >180)	0.608 (0.361–1.023)	0.062	NA	NA
CAR ≤ 0.2 (vs >0.2)	0.715 (0.423–1.209)	0.210	NA	NA
NK cells ≥ 15% (vs <15%)	0.768 (0.452–1.305)	0.329	NA	NA
$CD4^+/CD8^+$ ≤ 1.4 (vs >1.4)	0.821 (0.482–1.398)	0.464	NA	NA

Variables with univariate $p<0.10$ (NLR, SII, $CD8^+$ T cells, PLR) were entered into multivariate Cox regression using forward stepwise selection. The final model retained NLR, SII, and $CD8^+$ T cells. The proportional hazards assumption was tested using Schoenfeld residuals; no significant violation was detected (global test $p=0.274$). CAR: C-reactive protein-to-albumin ratio; CI: confidence interval; HR: hazard ratio; NA: not applicable; NK: natural killer; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index.

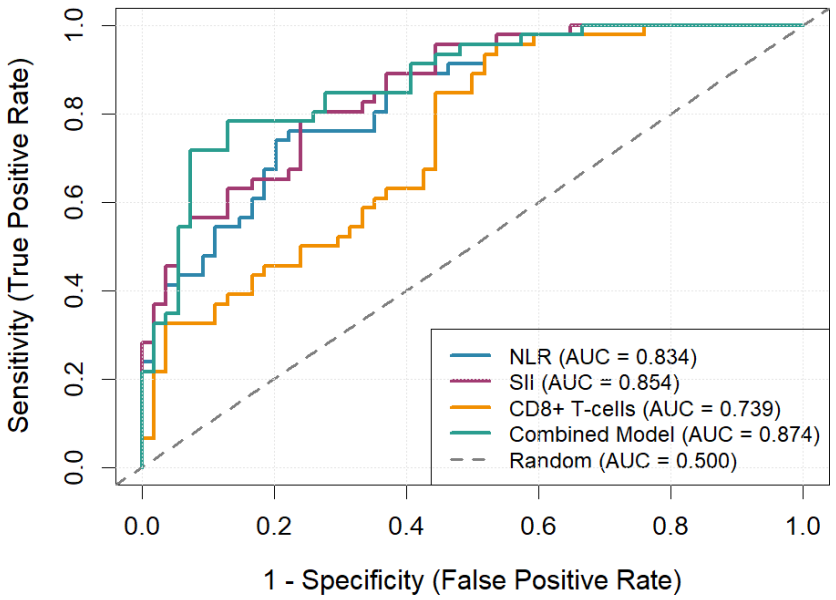

Figure 2. ROC curves for predicting treatment response. The receiver operating characteristic (ROC) curves show the performance of individual biomarkers (NLR, SII, $CD8^+$ T cells) and the combined model for predicting objective response to chemoimmunotherapy. The area under the curve (AUC) with 95% confidence intervals (in parentheses) is displayed in the legend: NLR 0.834 (0.765–0.923), SII 0.854 (0.774–0.928), $CD8^+$ T cells 0.739 (0.714–0.888), and combined model 0.874 (0.792–0.936). The diagonal dashed line represents the reference line (AUC = 0.5). The combined model outperformed each individual marker (DeLong test, all $P < 0.05$).

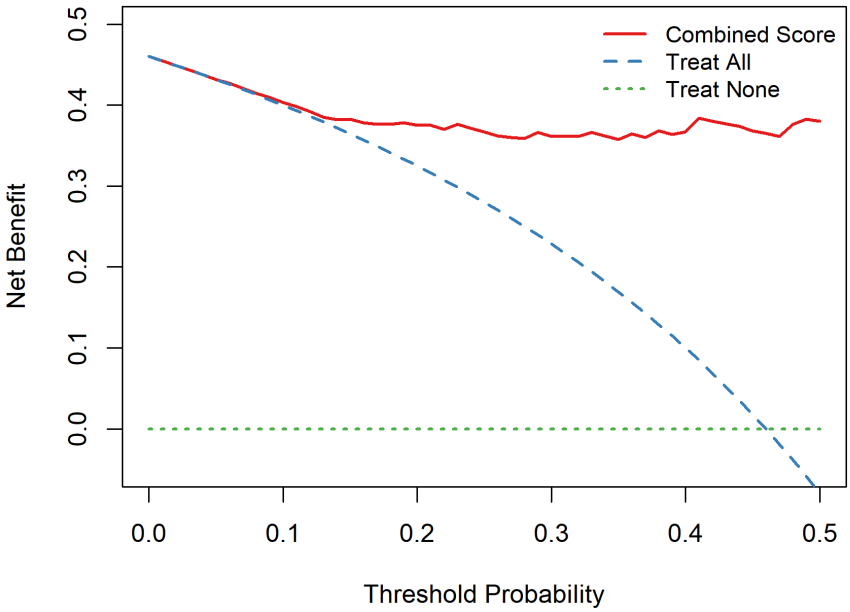

Figure 3. Decision curve analysis for the combined immune-inflammatory score. The y-axis shows net benefit, and the x-axis shows threshold probability. The combined score (red solid line) is compared with two extreme strategies: "treat all" (blue dashed line) and "treat none" (green dotted line). The combined score provides a positive net benefit across threshold probabilities of approximately 0.1 to 0.4, indicating clinical utility.

Table 9. Risk stratification and progression-free survival outcomes

Immune Profile Group	n (%)	Median PFS (months, 95% CI)	12-month PFS Rate (%)	Log-rank *p*
favorable immune profile (score ≥ 2)	48 (48.0)	15.6 (12.146–19.054)	70.8	<0.001
unfavorable immune profile (score ≤ 1)	52 (52.0)	7.8 (6.334–9.266)	23.0	

The combined score (0–3) counts favorable features: NLR≤2.5, SII ≤ 600, and $CD8^+$ T cells≥30%. A score≥2 defines the favorable immune profile group; a score≤1 defines the unfavorable immune profile group. The log-rank test was used to compare PFS between the two groups. P values are two-sided. CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; PFS: progression-free survival; SII: systemic immune-inflammation index.

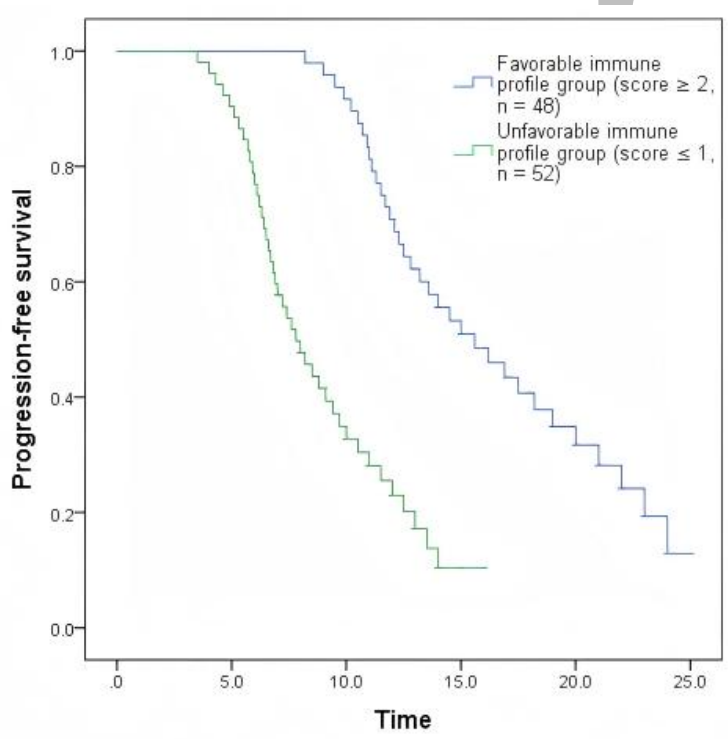

Figure 4. Kaplan-Meier curves for progression-free survival (PFS) according to immune profile groups. Favorable immune profile group (score ≥ 2, n = 48) vs unfavorable immune profile group (score ≤ 1, n = 52). The median PFS was 15.6 months (95% CI: 12.146–19.054) in the favorable group and 7.8 months (95% CI: 6.334–9.266) in the unfavorable group (log-rank $p < 0.001$). .

DISCUSSION

This retrospective analysis of 100 advanced gastric cancer patients treated with chemoimmunotherapy evaluated peripheral blood immune-inflammatory markers and cell subsets in relation to treatment response and survival. The main observations were as follows: First, low pretreatment levels of systemic immune-inflammatory markers (NLR ≤ 2.5 and SII ≤ 600) and a high proportion of $CD8^+$ T cells (≥ 30%) were associated with objective response. A combined model integrating these 3 indicators showed an AUC of 0.874 for ORR, which was higher than that of any single marker. Second, these baseline markers were also associated with longer PFS in multivariate Cox regression (adjusted HR = 0.422, 0.468, and 0.558, respectively; all $p<0.05$). Third, a simple combined score (0–3) based on these markers stratified patients into favorable (score ≥ 2) and unfavorable (score ≤ 1) groups; the 2 groups differed in median PFS (15.6 vs 7.8 months, log-rank $p<0.001$), and the bootstrap-corrected C-index was 0.814. These findings suggest that this

score may have potential as a research tool for hypothesis generation, but it is not yet ready for clinical implementation. The lack of external validation substantially limits the robustness and generalizability of the model. Therefore, the score should be considered exploratory, and independent external validation in larger, multicenter cohorts is mandatory before any claim of clinical applicability can be made.

The optimal cutoffs identified in this study—NLR ≤ 2.5, SII ≤ 600, and $CD8^+$ T cells ≥ 30%—are not only statistically discriminative but also biologically meaningful. NLR ≤ 2.5 and SII ≤ 600 reflect a state of low systemic inflammation, characterized by reduced neutrophil- and platelet-mediated immunosuppression, which has been shown to preserve $CD8^+$ T cell function. A $CD8^+$ T cell proportion ≥ 30% in peripheral blood indicates a relatively robust adaptive immune reserve, which is essential for mounting an effective antitumor response upon PD-1 blockade. These thresholds align with previously reported ranges in gastric cancer studies (e.g., NLR cutoff 2–3, SII cutoff 500–600), supporting their potential relevance beyond our single-center cohort.[21] The strong predictive power of NLR and SII in this study is consistent with previous studies of the tumor immune microenvironment. Systemic inflammatory response can inhibit T cell function, promote angiogenesis and tumor metastasis by releasing a variety of cytokines and growth factors, thereby weakening the efficacy of immunotherapy.[22,23] Our study confirms that low NLR and low SII at baseline are favorable factors for immunotherapy benefit, not only for objective response but also for longer PFS. This aligns with findings from a meta-analysis by Rugambwa et al,[24] which synthesized 17 studies involving immunotherapy for a variety of cancers, including gastric cancer, and found that elevated baseline NLR significantly correlates with poorer objective response. Our study not only supported this finding, but also determined the specific cutoff values of NLR and SII (2.5 and 600, respectively) for the advanced gastric cancer population in our center by ROC analysis. These cutoffs, however, require external validation before any clinical application can be considered, and should currently be viewed as hypothesis-generating rather than practice-changing. SII showed the highest predictive performance among individual indices (AUC = 0.854) in this study. SII integrates the parameters of neutrophils, platelets, and lymphocytes, and theoretically can more comprehensively reflect the complex interactions of the "inflammation-coagulation-immunity" network. Although this study did not directly compare the three indicators, the excellent performance of SII suggests that compared with NLR or PLR, it may be a more robust indicator to comprehensively evaluate the immunosuppressive state of the body, aligning with trends observed in other cancers, such as hepatocellular carcinoma and NSCLC.[25] On the other hand, the baseline level of peripheral blood $CD8^+$ T cells, which are core effector cells in adaptive immunity, was shown to be a strong predictor in the present study independent of inflammatory markers. This finding has important clinical implications. Although tumor-infiltrating $CD8^+$ T cell density is the gold standard "immune-inflamed" phenotype marker, its assessment relies on an invasive tissue biopsy that is not readily repeatable.[26] Recent studies have increasingly examined the role of peripheral blood lymphocyte subsets. For instance, studies by Kievit et al[27] and Tietze et al[28] and NSCLC have linked higher pretreatment peripheral $CD8^+$ T cells to improved immunotherapy response. This study validates this association in advanced gastric cancer and provides strong evidence for the use of a convenient and reproducible peripheral blood test to assess a patient's "immune reserve," or systemic immune status. This is especially applicable to patients in whom tissue samples cannot be obtained or undergo repeat biopsy, achieving an effective, noninvasive complement to histological markers. The predictive synergy between low NLR/SII and high $CD8^+$ T cells can be explained by the dual impact of systemic inflammation on antitumor immunity. Elevated NLR reflects expanded neutrophil populations that directly suppress $CD8^+$ T cell function, as recently demonstrated in gastric cancer where *P2RX1*-deficient neutrophils induce $CD8^+$ T cell dysfunction and *BFAR* promotes neutrophil infiltration via the *S100A8/S100A9-BFAR-PRP19-YBX1* axis to restore $CD8^+$ T cell function.[29,30] Similarly, elevated platelet counts (reflected by higher SII) contribute to immunosuppression, with PD-L1-positive platelets inducing $CD8^+$ T cell exhaustion.[31] Thus, high NLR/SII indicates an immunosuppressive myeloid landscape that blunts $CD8^+$ T cell effector function. Conversely, a high baseline $CD8^+$ T cell proportion reflects the host's T cell repertoire and functional reserve, which is essential for response to PD-1 blockade. In gastric cancer, responders show early expansion of activated $CD8^+$ T cells with increased granzyme B and CXCL10, whereas non-responders exhibit T cell exhaustion driven by pathways

such as the m1A-*SFRP2*-*NFAT*/*TOX* axis, which operates independently of PD-L1 expression.[32,33] Notably, PD-1$^+$ CD8$^+$ T cells in the tumor microenvironment have been identified as a potential biomarker of resistance to chemoimmunotherapy, indicating that even when CD8$^+$ T cells are present, their functional impairment dictates treatment outcomes.[34] Therefore, low systemic inflammation (low NLR, low SII) reduces myeloid suppression on CD8$^+$ T cells, while high baseline CD8$^+$ T cells provide the effector pool for PD-1 blockade. The combined score captures these 2 complementary dimensions, explaining its superior predictive performance.

Tumor-infiltrating CD8$^+$ T cells (CD8$^+$ TILs) are established prognostic biomarkers in gastric cancer, with higher densities associated with favorable survival. However, tissue-based TIL assessment requires invasive biopsy, provides only a static snapshot, and cannot be repeated longitudinally.[35] In contrast, peripheral blood CD8$^+$ T cell measurement is minimally invasive, readily repeatable, and allows dynamic monitoring during treatment. Our study demonstrates that baseline peripheral blood CD8$^+$ T cell proportion ($\geq$30%) independently predicts treatment response and PFS, consistent with prior studies in gastric cancer.[27] Thus, while TIL density remains the gold standard for intratumoral immune assessment, peripheral blood CD8$^+$ T cell measurement serves as a practical, noninvasive surrogate—particularly when tumor tissue is unavailable or repeat biopsy is not feasible. Future studies should explore the additive value of combining both approaches.

At present, clinical practice mainly relies on PD-L1 CPS for decision-making, but its predictive efficacy is limited.[36,37] The combined model constructed in this study integrates the 2 dimensions of systemic inflammation (NLR/SII) and cellular immunity (CD8$^+$ T cells), and outperformed each individual marker in this cohort. Moreover, a simple additive score based on these 3 markers successfully stratified patients into favorable (score $\geq$ 2) and unfavorable (score $\leq$ 1) groups, with a marked difference in median PFS (15.6 vs 7.8 months, log-rank P<0.001) and a bootstrap-corrected C-index of 0.814, indicating good discriminative ability for survival prediction. Decision curve analysis further supported the clinical value of the combined score, demonstrating a positive net benefit across a range of threshold probabilities (0.1–0.4). This is in line with the current trend of biomarker research from "single target" to "systematic evaluation." For example, the Glasgow Prognostic Score (GPS) or its modified version (mGPS), which combines CRP and albumin and is used to assess systemic inflammatory response and nutritional status, has established prognostic value across multiple cancer types.[38] Our model is similar but goes a step further by taking a broader view of the host immune state and simultaneously assessing the level of systemic inflammation that is detrimental to the immune response and the CD8$^+$ T-cell reserve that mediates antitumor activity. A patient with both "low inflammation" and "high immunity" features is significantly more likely to benefit from immunotherapy plus chemotherapy and to have a longer PFS.

Another important result of this study is the characterization of dynamic trajectories of immune indicators. Responders exhibited a divergent pattern: declining NLR/SII alongside rising CD8$^+$/NK cells, whereas non-responders showed relatively stable indices. Although most studies have focused on the predictive role of baseline values, few studies have supported the value of serial monitoring. For example, Xia et al[39] demonstrated in lung cancer immunotherapy that a decrease in NLR at an early stage, such as within 6 weeks of treatment, was associated with longer survival. Similar early dynamic changes were observed in gastric cancer in the present study. From a biologic point of view, this suggests that effective combination immunotherapy may help systematically improve the immune landscape, that is, suppress excessive, tumor-promoting systemic inflammation, while successfully activating and expanding antitumor effector immune cells. From the perspective of clinical practice, these findings provide a potential reference index for early efficacy prediction and dynamic monitoring that warrants prospective validation.

These findings hold potential for clinical translation. Immunotherapy combined with chemotherapy is expensive and associated with some toxicity. This model is based on routine blood tests and may, after prospective validation, serve as a supportive tool to complement PD-L1 testing—particularly when PD-L1 results are unavailable or inconclusive—in identifying patients who are more likely to benefit from chemoimmunotherapy. Such an approach could potentially help avoid ineffective treatment in low-benefit individuals and reduce unnecessary healthcare costs, but these possibilities require confirmation in future studies before any clinical translation can be considered. The tests relied on by the model can be carried out in hospitals at all levels and do

not rely on complex gene sequencing or immunohistochemistry platforms, which greatly improve accessibility and scalability, and help to narrow the gap in precision medical practice between different levels of medical institutions. Patients in the unfavorable immune profile group (high inflammation and low $CD8^+$ T cells) may have primary resistance to current chemoimmunotherapy regimens. This provides ideas for the design of new clinical studies, such as exploring the combination of chemoimmunotherapy with drugs that target inflammatory pathways (such as IL-6 inhibitors) or enhance T-cell priming to overcome baseline immune resistance in such patients.

Several limitations of this study warrant consideration. First, the cohort size was relatively small; although the prespecified sample size was met, prospective multicenter validation is required. Second, due to limited follow-up (median 15.3 months), overall survival data were immature and not formally analyzed; longer follow-up is needed to confirm whether the score predicts OS. Third, this study lacked external validation. Bootstrap internal validation alone is insufficient to establish generalizability; the optimal cutoffs and model performance may be center-specific. The score should therefore be viewed as exploratory pending rigorous external validation in independent cohorts. Fourth, we did not compare our score with PD-L1 CPS, MSI, or EBV status because these data were not uniformly available (PD-L1 testing was not routine; MSI and EBV status were available in fewer than 20% of patients). Their omission limits biological interpretation, and it remains unknown whether our score adds independent value beyond these established biomarkers. Fifth, although we described treatment regimens in detail, heterogeneity of PD-1 inhibitors and chemotherapy backbones may have influenced outcomes; the sample size precluded subgroup analyses by specific regimen. Sixth, we did not apply penalized regression (e.g., least absolute shrinkage and selection operator (LASSO)). However, stepwise selection was conservative (entry $P<0.05$), and the bootstrap-corrected C-index (0.814) suggests acceptable discriminative ability. Seventh, several important confounders (HER2 status, nutritional condition, cachexia, comorbidities) were not evaluated due to retrospective design and incomplete records, potentially introducing residual bias. Corticosteroid exposure was not included as an unmeasured confounder because it was systematically assessed per protocol, and no patient in the final cohort had corticosteroid use within the prespecified window. Eighth, the ROC-derived cutoffs (NLR≤2.5, SII ≤600, $CD8^+$ T cells≥30%) were internally optimized and may lack generalizability across populations, laboratory platforms, or ethnic groups; external validation is needed. Finally, future research should integrate this hematological model with tissue biomarkers (PD-L1, EBV, genomics) and radiomics using machine learning, and explore its predictive value in neoadjuvant and adjuvant settings.

CONCLUSION

In summary, this retrospective single-center study found that a simple combined immune-inflammatory score was associated with treatment response and PFS in advanced gastric cancer receiving chemoimmunotherapy. However, the absence of external validation, along with the retrospective design and small sample size, precludes any conclusion about clinical utility or generalizability. The score should be considered exploratory and hypothesis-generating only. Independent external validation in prospective, multicenter cohorts is mandatory before any future clinical application can be considered. At present, this score is not yet ready for clinical decision-making. Future studies that integrate multidimensional biomarkers may help validate and extend these observations.

SIGNIFICANCE AND INNOVATION

This retrospective study developed a simple combined immune-inflammatory score based on routine blood tests (NLR, SII, $CD8^+$ T cells). The score was associated with both objective response and progression-free survival in advanced gastric cancer, with a higher AUC than individual biomarkers. It also distinguished favorable versus unfavorable immune profile groups with different survival outcomes. Pending prospective validation, this score could be considered a hypothesis-generating tool for exploratory patient selection and monitoring, but it is not yet ready for routine clinical use.

STATEMENT OF ETHICS

Approval was granted by the 900th Hospital of PLA Joint Logistic Support Force ethics board (Approval No. 2023XKZL03).

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and institutional data protection policies. However, anonymized data may be obtained from the corresponding author upon reasonable request and with the approval of the hospital's ethics committee.

AI ASSISTANCE DISCLOSURE

No artificial intelligence (AI) tools were used in the preparation of this manuscript, including the writing, data analysis, or figure creation. All work was performed by the authors.

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