Research Square

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Systemic inflammation score as a predictor of efficacy and prognosis of immunotherapy in advanced gastric cancer

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Research Article

Keywords: gastric cancer, immunotherapy, prognostic biomarker, systemic inflammation score, treatment response

Posted Date: September 2nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8693406/v1

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Additional Declarations: No competing interests reported.

Abstract

BACKGROUND

Immunotherapy has become a standard care for patients with advanced gastric cancer (AGC). The inflammatory makers are considered to play a critical role in tumor progression. Individual inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), as well as combined index systemic inflammation score (SIS)—have gained increasing attention. We conducted this study to explore the feasibility of SIS in predicting the efficacy and prognosis of patients with AGC.

METHODS

We enrolled patients who received treatment at Jiangsu Cancer Hospital between May 2022 and January 2025, categorizing them into two groups according to the SIS. The study compared progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR). Receiver operating characteristic curve analyses were performed to identify the optimal cutoff values for LMR. Kaplan-Meier method for PFS were performed to compare the prognostic impact.

RESULTS

Survival analysis showed that patients with an SIS of 0 had better PFS compared to those with an SIS of 1 or 2 ($p < 0.001$). Patients with lower SIS scores exhibited higher ORR and DCR. Multivariate analysis indicated that SIS was an independent prognostic factor.

CONCLUSION

Our study suggested that SIS could be utilized to predict the therapeutic efficacy and prognosis of immunotherapy in patients with AGC. As a predictive biomarker, SIS may refine individual immunotherapy regimens for patients with AGC.

1 Introduction

Gastric cancer (GC), as one of the major global disease burdens, exhibits marked geographical difference in its epidemiological characteristics. According to global cancer statistics, over one million newly diagnosed cases occur annually, ranking fifth in incidence among malignancies worldwide[1]. GC has emerged as a major public health challenge threatening human health[2, 3]. At present, radical surgical resection combined with regional lymph node dissection remains the foundation in the treatment of GC. However, epidemiological studies suggested that most of the patients present with locally advanced or metastatic GC at initial diagnosis[4]. Despite recent innovation in surgical methods, survival rate of patients with advanced gastric cancer (AGC) remains low[5–7]. With the clinical movement of immune checkpoint inhibitor (ICI), immunotherapy has been established as a first-line standard care for metastatic renal cell carcinoma, unresectable melanoma, and programmed death-

ligand 1 (PD-L1) positive non-small cell lung cancer and other solid tumors[8, 9]. The ATTRACTION-4 study showed the efficacy with ICI in AGC where systemic chemotherapy plus a PD-1 inhibitor significantly prolongs PFS[10, 11].

Currently, the assessment of therapeutic efficacy and prognosis for patients with AGC predominantly relies on enhanced CT/MRI, genomic analyses including HER2 status and microsatellite instability testing (MSI), as well as levels of tumor markers including CEA and CA19-9 [12–14]. Nevertheless, these modalities are limited by time consumption, and restricted sensitivity. In view of the substantial heterogeneity in immunotherapy response, the development of new biomarker systems is an urgent need. Biomarkers including tumor mutational burden (TMB) and PD-L1 was validated as paramount indicators for assessing responses to immunotherapy. Neutrophils, the most abundant leukocytes in human immune system, have recently emerged as pivotal players in tumor microenvironment. Neutrophils could be activated to exert anti-tumor functions, including direct phagocytosis of tumor cells, release of cytotoxic granules, and facilitation of immune cell recruitment [15, 16]. Lymphocytes, by contrast, remain central mediators of anti-tumor immunity and are indispensable for orchestrating effective immune responses against cancer[17]**.** T cells, particularly cytotoxic T cells (CD8+ T cells), were reported to recognize and directly damage tumor cells, whereas B cells contribute to the immune response by producing antibodies[18, 19]. Thus, maintaining the balance between neutrophils and lymphocytes is potential for effective cancer immunotherapy[20]. Platelets also play a complex role in tumor biology[21]**.** Platelets could adhere to the surface of tumor cells and form microaggregates, thereby providing a physical shield that protects tumor cells from immune attack[22]. In addition, platelets secrete a variety of bioactive factors, e.g transforming growth factor-β, platelet factor 4, and vascular endothelial growth factor[21]. These molecules were reported to promote tumor proliferation and invasion and contribute to the establishment of an immunosuppressive tumor microenvironment [23]. Previous investigation suggested that monocytes could impose effects on tumor microenvironment through multiple mechanisms, including induction of immune tolerance, enhancement of local immunosuppression, facilitation of tumor cell dissemination, and promotion of tumor angiogenesis [24–26]. Changes in these inflammatory cells and their mediators could be associated with peripheral blood-based indices, e.g. the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR). These composite inflammatory markers were considered as important indicators for assessing treatment response and prognosis in cancer[27–29].

Previous studies mainly focused on the impact of individual peripheral blood inflammatory markers on the prognosis of GC[30, 31]. In recent years, the analysis of combined parameters, by integrating several inflammation-related parameters to construct a prognostic scoring system, is reported to achieve precise stratification and management for patients with GC, thereby more accurately predicting their prognosis[32, 33]. Systemic inflammation score (SIS) is a combined index based on serum albumin (Alb) and LMR. Ma et al. found that a higher SIS was significantly associated with a poorer 5-year OS and DFS in all pStages[34]. Moreover, the time-dependent curves of the SIS score consistently outperformed the NLR in predicting 5-year OS after surgery. Lin et al. proposed a modified systemic inflammation score (mSIS) to assess the prognosis of patients with GC after surgery[35]. The mSIS scoring system sets the

cutoff values for serum albumin and LMR at 3.4 and 40 g/L, respectively, and employs a scoring rule similar to that of the SIS for grouping. The study of Lin et al demonstrated that a high mSIS is significantly related to poor postoperative prognosis in patients with GC, indicating that this scoring system can effectively identify high-risk patients and provides a new, convenient, and potentially valuable tool for clinical prognostic assessment[35]. This scoring system, based on peripheral blood parameters, is more accessible and allows for dynamic monitoring inflammatory status during postoperative follow-up, thereby providing a tool for the development of individualized treatment plans. Our study aims to investigate the correlation between the SIS and the short-term efficacy and long-term prognosis of immunotherapy in patients with AGC, and to assess whether SIS could serve as a marker for guiding GC treatment.

2 Materials and methods

Patient selection

Patients with unresectable advanced gastric cancer who diagnosed at the Jiangsu Cancer Hospital from May 2022 to January 2025 were consecutively collected. The basic information of enrolled patients included demographic characteristics: age, gender, etc.; laboratory parameters: complete blood count (including parameters such as hemoglobin, white blood cell count, and platelet count); pathological features: histological classification (e.g. adenocarcinoma, signet ring cell carcinoma, etc.), and imaging examinations.

All patients included in the study met the following inclusion criteria: 1) histopathologically confirmed gastric adenocarcinoma; 2) stage IV disease according to the 8th edition of AJCC TNM staging system (presence of distant organ/peritoneal metastasis); 3) first-line treatment with an ICI based regimen (either monotherapy or combination therapy); 4) completion of≥2 cycles of systemic therapy; 5) availability of baseline and post-treatment imaging data assess according to RECIST version 1.1. The exclusion criteria were as follows: 1) lack of histological or cytological confirmation; 2) locally confined disease or potentially resectable metastatic lesions; 3) cardiac dysfunction (NYHA class III-IV), active autoimmune disease, or active HIV/HBV infection; 4) occurrence of ≥grade 3 infectious events during treatment; 5) failure to undergo at least one post-treatment imaging assessment; 6) presence of other primary malignancies. The study protocol was approved by the ethic committees of all participating institutions.

Study Design

Before treatment initiation, the feasibility of each regimen was confirmed. All patients received at least two cycles of systemic therapy, with treatment intervals maintained within ±3 days. Patients in the monotherapy group were treated with an ICI alone, whereas those in the combination group received an ICI plus chemotherapy. In addition, patients with HER2-positive disease received concomitant anti-HER2 targeted therapy.

In monotherapy group, patients meeting the eligibility criteria were allocated to receive either nivolumab or sintilimab where patients received nivolumab at a dose of 360 mg administered intravenously once per cycle or administered sintilimab at 200mg per dose once per cycle via intravenous infusion.

Chemotherapy was administrated with the following one option: 1) oxaliplatin 180 mg administered by intravenous infusion combined with tegafur-gimeracil-oteracil (S-1) 50 mg orally twice daily on days 1-14; 2) nab-paclitaxel 200-300 mg administered once per cycle via intravenous infusion; 3) nab-paclitaxel 100 mg administered by intravenous infusion combined with oral S-1 50 mg twice daily on days 1-14; 4) oxaliplatin 180 mg administered by intravenous infusion, in combination with oral capecitabine 1.5 g twice daily on days 1-14; 5) paclitaxel liposome 180 mg administered intravenously, along with oral S-1 50 mg twice daily on days 1-14.

Patients with HER2-positive AGC were assigned to receive trastuzumab at a dose of 4 mg/kg, administered once per cycle via intravenous infusion.

Peripheral blood samples (typically EDTA-K2-anticoagulated venous blood) were collected, with a minimum volume of 2 ml. Samples with evidence of coagulation or hemolysis were discarded and recollected. Anticoagulated samples were gently inverted 5-8 times to ensure adequate mixing with the anticoagulant and to prevent cell aggregation or clotting. For certain assays (e.g. erythrocyte sedimentation rate), plasma or serum was obtained after centrifugation at 3000 r/min for 5-10 minutes. Mixed blood samples were then loaded into the analyzer, which automatically aspirated the specimens for testing. Red blood cell, white blood cell, and platelet counts and volumes were determined using the electrical impedance method. White blood cell differentials (e.g. neutrophils, lymphocytes) were analyzed using optical or radio-frequency methods. Hemoglobin concentration was measured by the cyanmethemoglobin method.

Corresponding parameters were measured before treatment. NLR was calculated as the absolute neutrophil count divided by the lymphocyte count; PLR as the platelet count divided by the lymphocyte count; and the LMR as the lymphocyte count divided by the monocyte count. NLR, PLR, and LMR were collected at the initiation of immunotherapy.

Follow-up

All patients underwent at least three follow-up visits, which included both in-person hospital visits and telephone follow-ups. The follow-up period commenced on the surgery date and extended until January 31, 2025, or loss of follow-up. PFS is the period from the date of the first dose of study treatment to the occurrence of any of the following events:1) radiologically confirmed disease progression (based on the first imaging assessment):2) treatment discontinuation due to severe adverse events, or death from any cause.

Endpoints and definitions

The primary end point of our study was Progression-free survival (PFS), and secondary endpoints were objective response rate (ORR) and disease control rate (DCR).

In this study, target lesions were defined as measurable lesions confirmed by baseline imaging. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Confirmation of the best overall response required radiologic evidence from at least two consecutive assessments separated by an interval of ≥4 weeks. Complete response (CR) was defined as the disappearance of all target lesions, with no appearance of new lesions and no unequivocal progression of non-target lesions and partial response (PR) was defined as at least a 30% decrease in the sum of diameters of target lesions compared with baseline, with no unequivocal progression of non-target lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD; or disappearance of target lesions accompanied by unequivocal progression of non-target lesions, but still meeting criteria for SD. Progressive disease (PD) was defined as the appearance of one or more new lesions; or at least a 20% increase in the sum of diameters of target lesions compared with baseline, with an absolute increase of ≥5 mm; or disappearance of target lesions accompanied by unequivocal progression of non-target lesions, not meeting criteria for SD. The objective response rate (ORR) is the proportion of patients achieving CR or PR and the disease control rate (DCR) is the proportion of patients achieving CR, PR, or SD (with SD maintained for at least 8 weeks).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics, version 27.0. Receiver operating characteristic (ROC) curve analyses were performed to identify the optimal cutoff values for NLR, PLR, and LMR. Categorical variables were analyzed with the Chi-square or Fisher's exact test. Continuous variables with non-normal distributions were analyzed using the Mann-Whitney U test or Kruskal-Wallis H test. Survival analysis utilized the Kaplan-Meier method to plot the survival curve. Comparisons of time-to-event curves for PFS were performed using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for covariates were estimated with the Cox proportional-hazards model.

3 Results

Baseline characteristics

From May 2022 and January 2025, 132 patients were screened for eligibility and met the inclusion criteria. During the course of treatment, 27 patients discontinued treatment due to financial constraints or unacceptable toxicities. Consequently, 105 patients were included in the final analysis. Among the enrolled patients, there were 66 males and 39 females, with ages ranging from 31 to 79 years (mean, 60.4±11.9 years). 96 patients (91.4%) had adenocarcinoma and 9 (8.6%) had signet-ring cell carcinoma based on histopathologic classification. With respect to tumor differentiation, poor differentiation was observed in 64 (60.9%) of patients, whereas 41 (39.1%) had non-poorly differentiated tumors. Regarding treatment regimens, 7 patients (6.7%) received monotherapy, 89 (84.8%) were assigned with immunotherapy plus chemotherapy, and 9 (8.6%) received immunotherapy combined with both

chemotherapy and targeted therapy as first-line immunotherapy. The baseline characteristics of the study population are summarized in Table 1.

Optimal cutoff values

The ROC curves for NLR, PLR, and LMR are shown in Figure 1, Figure 2 and Figure 3. According to image-based analysis, the optimal cutoff values for NLR, PLR, and LMR were 2.8, 194.5, and 3.1, respectively. The areas under the ROC curve (AUCs) for NLR, PLR, and LMR were 0.652, 0.657, and 0.640. These findings indicate that the prognostic performance of the three indices in patients with AGC was comparable.

The optimal cutoff value for the LMR was determined to be 3.1. On the basis of LMR and serum albumin levels, patients were stratified according to the SIS. An SIS score of 0 was defined as LMR≥3.1 and albumin≥40 g/L; patients with LMR≥3.1 or albumin≥40 g/L were allocated a score of 1; and a score of 2 was defined as LMR<3.1 and albumin<40 g/L. Accordingly, patients were categorized into three groups based on SIS scores of 0, 1, or 2.

Survival analysis

Based on the cutoff values derived from inflammatory markers, we utilized Kaplan-Meier survival analyses to stratify patients according to NLR, PLR, and LMR and evaluated their associations with PFS. The corresponding survival curves are presented in Figure 4. As shown in Figure 4A–C, significant differences in progression-free survival (PFS) were observed across the inflammatory indices ($P < 0.001$). Specifically, patients with NLR < 2.8 (Figure 4A), PLR < 194.5 (Figure 4B), or LMR > 3.1 (Figure 4C) exhibited markedly prolonged PFS compared with their respective counterparts. These findings suggest that the stratification based on these cutoff values effectively distinguishes prognostic subgroups, and validates the clinical prognostic utility of thresholds determined by ROC analysis.

A total of 29, 42, and 34 patients were classified into SIS scores of 0, 1, and 2 respectively. The baseline clinical characteristics of patients stratified by SIS score are presented in Table 2. In this study, ROC curves related to the SIS score were generated based on PFS outcomes after two cycles of treatment, yielding an area under the curve (AUC) of 0.706. Among patients with AGC receiving immunotherapy, the SIS score demonstrated superior predictive performance for survival outcomes compared with NLR and PLR (AUC=0.652 and 0.657, respectively). The results are illustrated in Figure 5.

Short-term efficacy assessment

Imaging data collected after two treatment cycles were compared with baseline, and treatment efficacy was evaluated in all patients. It was found that in the SIS = 0 group, 11 patients (37.9%) achieved PR, 17 (58.6%) achieved SD, and 1 (3.4%) experienced PD. For SIS = 1, the distribution was 6 (14.3%) PR, 20 (47.6%) SD, and 16 (38.1%) PD. In the SIS = 2 group, PR was observed in 1 patient (2.9%), while 17 (50.0%) had SD and 16 (47.1%) had PD. Overall, patients with SIS=0 showed better outcomes, characterized by a higher rate of PR and a predominance of SD. The SIS=1 group was mainly stable

disease but also showed an increase in PD. In the SIS=2 group, SD was most common, while PR was almost absent. The ORRs for SIS=0, 1, and 2 were 37.9%, 14.3%, and 2.9%, respectively (P<0.001). The corresponding DCRs were 96.6%, 61.9%, and 52.9% (P<0.001) (Table 3). Collectively, these findings support the potential utility of SIS as a predictor of short-term response to immunotherapy.

Long-term Survival Analysis

The association between SIS classification and PFS was further examined by survival curve analysis (Figure 6). The median PFS was 18 months for patients with SIS=0, 5 months for those with SIS=1, and 3 months for those with SIS=2. Notably, the survival curves demonstrated a distinct separation among the groups as follow-up time increased. Patients classified as SIS=0 exhibited a markedly longer PFS compared with those in the SIS=1 or SIS=2 groups (HR=0.418, 95%CI=0.216-0.809), and the difference was statistically significant (P < 0.001).

Cox Regression Analysis of Prognostic Factors in AGC Patients Receiving Immunotherapy

Univariate Analysis

We use cox proportional hazards regression model to assess the association between PFS and potential predictive factors, including sex, age, pathological type, KPS score, degree of differentiation, HER-2 status, CPS score, treatment regimen, baseline NLR, baseline PLR, and SIS score. CPS score (HR=0.486, 95% CI=0.283-0.815), baseline NLR (HR=0.385, 95% CI=0.223-0.665), baseline PLR (HR=0.442, 95% CI=0.269-0.725), and SIS score (HR=0.319, 95% CI=0.173-0.588) were all significantly associated with PFS (P < 0.05). The results of the univariate analysis are summarized in Table 4.

Multivariate Analysis

Covariates that reached statistical significance in the univariate analysis were entered into the multivariate Cox regression model where CPS score, baseline NLR, baseline PLR, and SIS score were included. The results showed that the SIS score was an independent risk factor for disease progression in AGC patients receiving immunotherapy (HR=0.418, 95% CI=0.216-0.809, P=0.01). Patients with lower SIS scores were less likely to experience disease progression compared with those with higher scores (Table 5).

4 Discussion

In our study, survival analysis showed that patients with LMR≥3.1 had significantly longer PFS compared with those with lower ratios, suggesting that a higher LMR may serve as a favorable prognostic biomarker in GC. This finding is consistent with previous reports [36–38]. Using the cut-off value of 3.1 for LMR combined with serum albumin, we constructed SIS groups based on established scoring system. To evaluate prognosis in AGC patients receiving immunotherapy, we analyzed the predictive value of SIS with PFS as the endpoint. Based on PFS data after two treatment cycles, the AUC reached 0.706, indicating that SIS provides relatively high accuracy in predicting patient outcomes. Peripheral

blood inflammatory markers e.g. NLR and PLR have already been widely investigated and applied in prognostic evaluation for AGC immunotherapy [39–42]. However, our analysis demonstrated that SIS outperformed both NLR (AUC=0.652) and PLR (AUC=0.657) in predicting survival outcomes. Using Kaplan-Meier analysis, we further examined PFS according to SIS grouping. The median PFS was 18 months for patients with SIS 0, 5 months for SIS 1, and 3 months for SIS 2, showing statistically significant differences among the groups. Notably, patients with SIS 0 displayed a markedly better survival curve than those with SIS 1 or 2, with significant separation observed over time. This difference reached statistical significance, highlighting the prognostic value of SIS in AGC patients undergoing immunotherapy.

We analyzed the response rates of AGC patients undergoing immunotherapy, focusing on the association between SIS score and treatment response. Patients with SIS=0 showed higher PR and SD rates, indicating an overall favorable response. In the SIS=1 group, SD was more frequent, but the proportion of PD was also relatively high, suggesting heterogeneity in treatment response. By contrast, the SIS=2 group had very low PR and high PD rates, reflecting poor responsiveness and limited clinical benefit. The ORR in the SIS 0, 1, and 2 groups was 37.9%, 14.3%, and 2.9%, respectively, while the DCR was 96.6%, 61.9%, and 52.9%, with statistically significant differences. These findings further indicate that patients with lower SIS scores achieve higher objective response and disease control rates after immunotherapy, whereas patients with higher SIS scores may require closer clinical monitoring or alternative treatment strategies. In addition, we performed Cox regression analysis to explore the relationship between PFS and potential risk factors in patients treated with immunotherapy. Univariate analysis revealed significant differences in PFS across groups defined by CPS score, baseline NLR, baseline PLR, and SIS score where these variables were included in a multivariate Cox regression model, we identified SIS as an independent risk factor for disease progression (HR=0.418, 95% CI=0.216-0.809, P=0.01). Therefore, patients with lower SIS scores were less likely to experience disease progression compared with those with higher scores.

Although our study yielded valuable findings, there are still several limitations. Firstly, we did not use OS as the primary endpoint but instead selected PFS as the main outcome measure because patient survival has gradually improved with advances in medical technology. Second, given the real-world study design, the results may be affected by the sample size and selection bias. More extensive, since the data were collected from a single center, the generalizability of our conclusions should be interpreted with caution, especially considering potential biases introduced by regional treatment variations and ethnic heterogeneity. This suggests for future multicenter, prospective, randomized controlled trials to validate these findings and to further assess the clinical value of the SIS in predicting the efficacy and prognosis of immunotherapy in cancer patients. In addition, incorporating dynamic changes in NLR, PLR, or LMR during treatment (e.g. ΔNLR or fluctuation range) into the baseline SIS framework may help establish treatment response-based dynamic prognostic models. Combining SIS with other established biomarkers, such as PD-L1, CPS and TMB, to build integrated predictive models could also provide a more comprehensive evaluation of patient outcomes. In conclusion, SIS could be considered to evaluate both efficacy and prognosis in AGC patients receiving immunotherapy. Lower SIS scores are associated

with better treatment responses, while higher scores predict shorter PFS. As an easily accessible predictive indicator, SIS could play a role in optimizing immunotherapy strategies for AGC.

Abbreviations

AGC: advanced gastric cancer; CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; CI: confidence interval; CPS: combined positive score; CR: complete response; DCR: disease control rate; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; GC: gastric cancer; GPS: Glasgow Prognostic Score; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; ICI: immune checkpoint inhibitor; LMR: lymphocyte to monocyte ratio; NLR: neutrophil to lymphocyte ratio; ORR: objective response rate; OS: overall survival; PD: progressive disease; PD-1: programmed cell death-1; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PLR: platelet to lymphocyte ratio; PR: partial response; SD: stable disease; SIS: systemic inflammation score; TMB: tumor mutational burden

Declarations

Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Wenxin Wang, Feiyu Wang and Ying Peng. The first draft of the manuscript was written by Wenxin Wang, Feiyu Wang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding Statement

This work was supported by Jiangsu Commission of Health Medical Research Project (Grant numbers[Z2022019]) and the National Natural Science Foundation of China General Program (Grant numbers[82272671]).

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgments

The authors would like to acknowledge all patients participating in the study. We acknowledge the assistance of the Big Data Center of Jiangsu Cancer Hospital & The Affiliated Cancer Hospital of Nanjing Medical University.

Data availability statement

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request. For access to the shared data, please contact huangxinen06@163.com.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Medical Ethical Committee of Jiangsu Cancer Hospital.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1 Characteristics of the Patients at Baseline

Variables	n (%)
Gender	
Male	66 (62.9%)
Female	39 (37.1%)
Age (years)	60.4±11.9
KPS score	
90-100	74 (70.5%)
70-80	31 (29.5%)
Histological type	
Adenocarcinoma	96 (91.4%)
Signet-ring cell carcinoma	9 (8.6%)
Grade	
Moderately differentiated	17 (16.2%)
Moderately to Poorly differentiated	24 (22.9%)
Poorly differentiated	64 (60.9%)
HER2 status	
Positive	9 (8.6%)
Negative	96 (91.4%)
CPS score	
1	31 (29.5%)
≥1	36 (34.3%)
≥5	24 (22.9%)
≥10	14 (13.3%)
Therapy	
Monotherapy	7 (6.7%)
Immunotherapy plus chemotherapy	89 (84.8%)
Immunotherapy combined with both chemotherapy and targeted therapy	9 (8.6%)

Note: Data are n (%) unless otherwise noted.

Abbreviations: KPS□karnofsky performance status; CPS, combined positive score; HER2, human epidermal growth factor receptor 2.

Table 2 Baseline Clinical Characteristics of Patients Stratified by SIS Score

Variables	SIS score			*P* value
	0	1	2	
Number	29	42	34	
Gender				0.777
Male	18 (62.1%)	28 (66.7%)	20 (58.8%)	
Female	11 (37.9%)	14 (33.3%)	14 (41.2%)	
Age (years)	59.2±12.8	60.2±13.9	61.6±7.9	0.768
KPS score				0.222
90-100	24 (82.8%)	27 (64.3%)	23 (67.6%)	
70-80	5 (17.2%)	15 (35.7%)	11 (32.4%)	
Histological type				0.193
Adenocarcinoma	24 (82.8%)	40 (95.2%)	32 (94.1%)	
Signet-ring cell carcinoma	5 (17.2%)	2 (4.8%)	2 (5.9%)	
Grade				0.944
Moderately differentiated	4 (13.8%)	6 (14.3%)	7 (20.6%)	
Moderately to Poorly differentiated	7 (24.1%)	10 (23.8%)	7 (20.6%)	
Poorly differentiated	18 (62.1%)	26 (61.9%)	20 (58.8%)	
HER-2				0.339
Positive	2 (6.9%)	2 (4.8%)	5 (14.7%)	
Negative	27 (93.1%)	40 (95.2%)	29 (85.3%)	
CPS score				0.322
1	6 (20.7%)	11 (26.2%)	14 (41.2%)	
≥1	10 (34.5%)	14 (33.3%)	12 (35.3%)	

≥5	10 (34.5%)	9 (21.4%)	5 (14.7%)	
≥10	3 (10.3%)	8 (19.1%)	3 (8.8%)	
Therapy				0.510
Monotherapy	3 (10.3%)	2 (4.8%)	2 (5.9%)	
Immunotherapy plus chemotherapy	24 (82.8%)	38 (92.4%)	27 (79.4%)	
Immunotherapy combined with both chemotherapy and targeted therapy	2 (6.9%)	2 (4.8%)	5 (14.7%)	

Note: Data are n (%) unless otherwise noted.

Abbreviations: CPS, combined positive score; HER2: human epidermal growth factor receptor 2; KPS karnofsky performance status.

Table 3 Correlation of the SIS score with treatment response

Treatment Assessment	Stratification by SIS Score			*P value*
	0	1	2	
CR	0 (0%)	0 (0%)	0 (0%)	
PR	11 (37.9%)	6 (14.3%)	1 (2.9%)	
SD	17 (58.6%)	20 (47.6%)	17 (50.0%)	
PD	1 (3.4%)	16 (38.1%)	16 (47.1%)	
CR+PR	11 (37.9%)	6 (14.3%)	1 (2.9%)	
CR+PR+SD	28 (96.6%)	26 (61.9%)	18 (52.9%)	
ORR	37.9%	14.3%	2.9%	<0.001
DCR	96.6%	61.9%	52.9%	<0.001

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SIS, systemic inflammation score.

Table 4 Univariate Cox Regression Analysis of covariates for PFS

	HR	95% CI	P value
Gender (Male vs Female)	0.996	0.611-1.623	0.987
Age (<60 vs ≥60)	0.839	0.520-1.354	0.472
KPS Score (90-100 vs 70-80)	1.280	0.771-2.126	0.340
Histological type (adenocarcinoma vs signet-ring cell carcinoma)	0.600	0.240-1.504	0.276
Grade (moderately/Well differentiation vs poorly differentiation)	1.035	0.637-1.684	0.889
HER-2 status (positive vs negative)	0.975	0.443-2.145	0.950
CPS Score (≥5 vs <5)	0.486	0.283-0.815	0.007
Therapy (combination regimen vs single-agent treatment)	0.336	0.103-1.089	0.069
NLR (<2.8 vs ≥2.)	0.385	0.223-0.665	<0.001
PLR (<194.5 vs ≥194.5)	0.442	0.269-0.725	0.001
SIS Score (0 vs 1-2)	0.319	0.173-0.588	<0.001

Abbreviations: CI, confidence interval; CPS, combined positive score; HER2: human epidermal growth factor receptor 2; HR, hazard ratio; KPS, karnofsky performance status; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SIS, systemic inflammation score.

Table 5 Multivariate Cox Regression Analysis for PFS

	HR	95% CI	P value
CPS Score (≥5 vs.<5)	0.607	0.344-1.072	0.085
NLR (<2.8 vs.≥2.8)	0.640	0.351-1.167	0.145
PLR (<194.5 vs.≥194.5)	0.711	0.419-1.206	0.206
SIS Score (0 vs.1-2)	0.418	0.216-0.809	0.010

Abbreviations: CPS, combined positive score; NLR, neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SIS, systemic inflammation score.

Figures

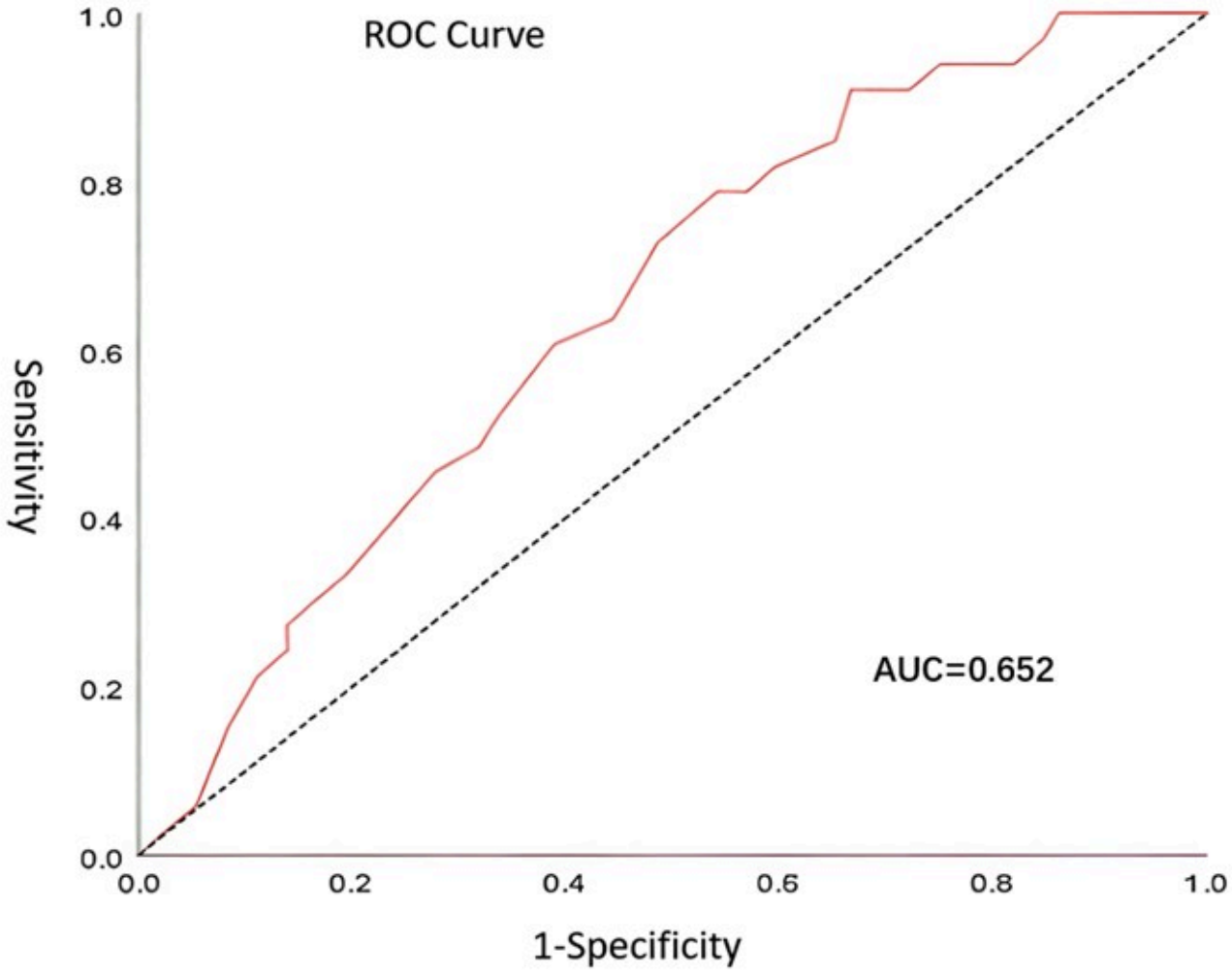


Figure 1

Receiver operating characteristic curve for predicting progression-free survival using NLR. NLR, neutrophil to lymphocyte ratio; AUC, area under the curve

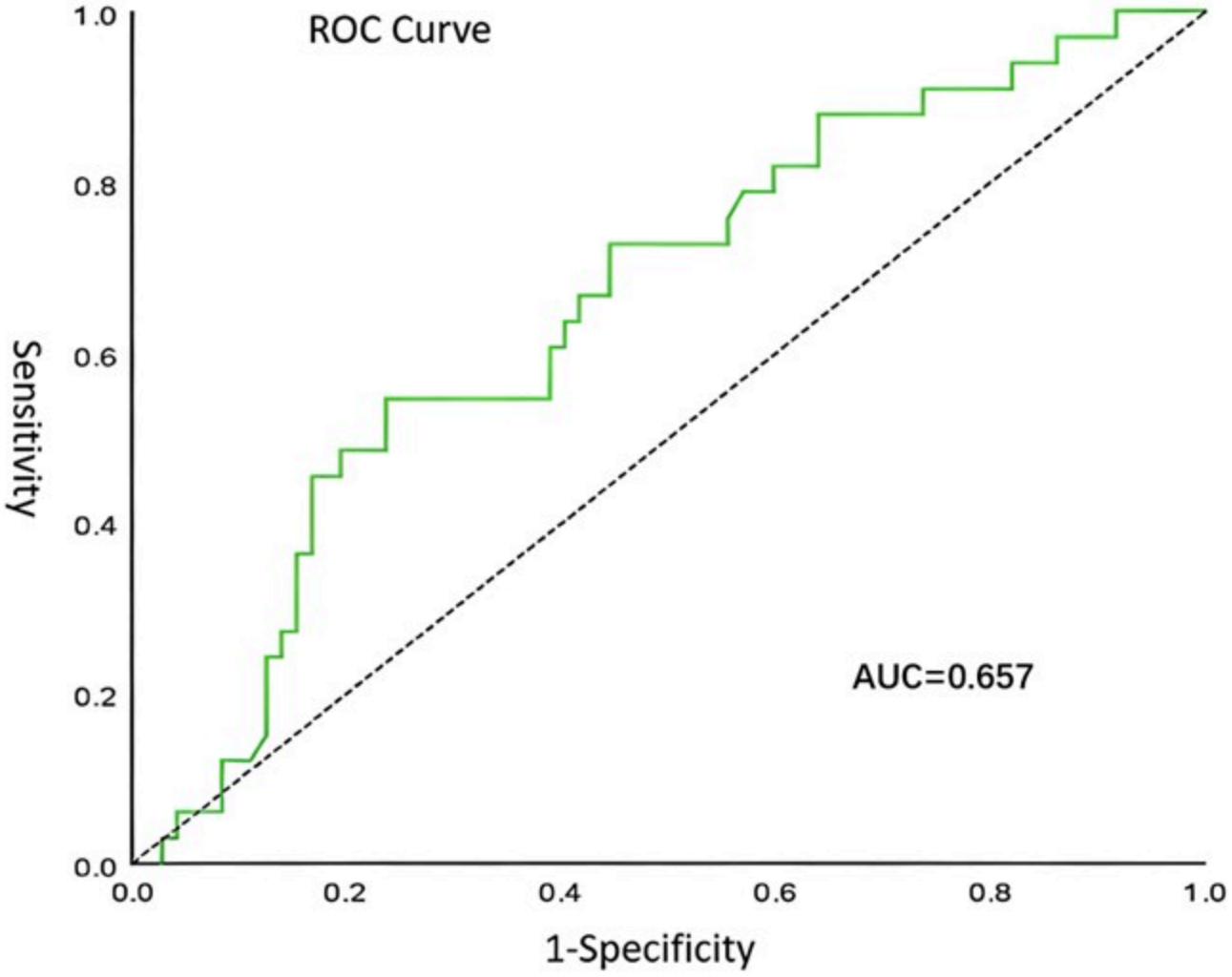


Figure 2

Receiver operating characteristic curve for predicting progression-free survival using PLR. PLR: platelet to lymphocyte ratio.

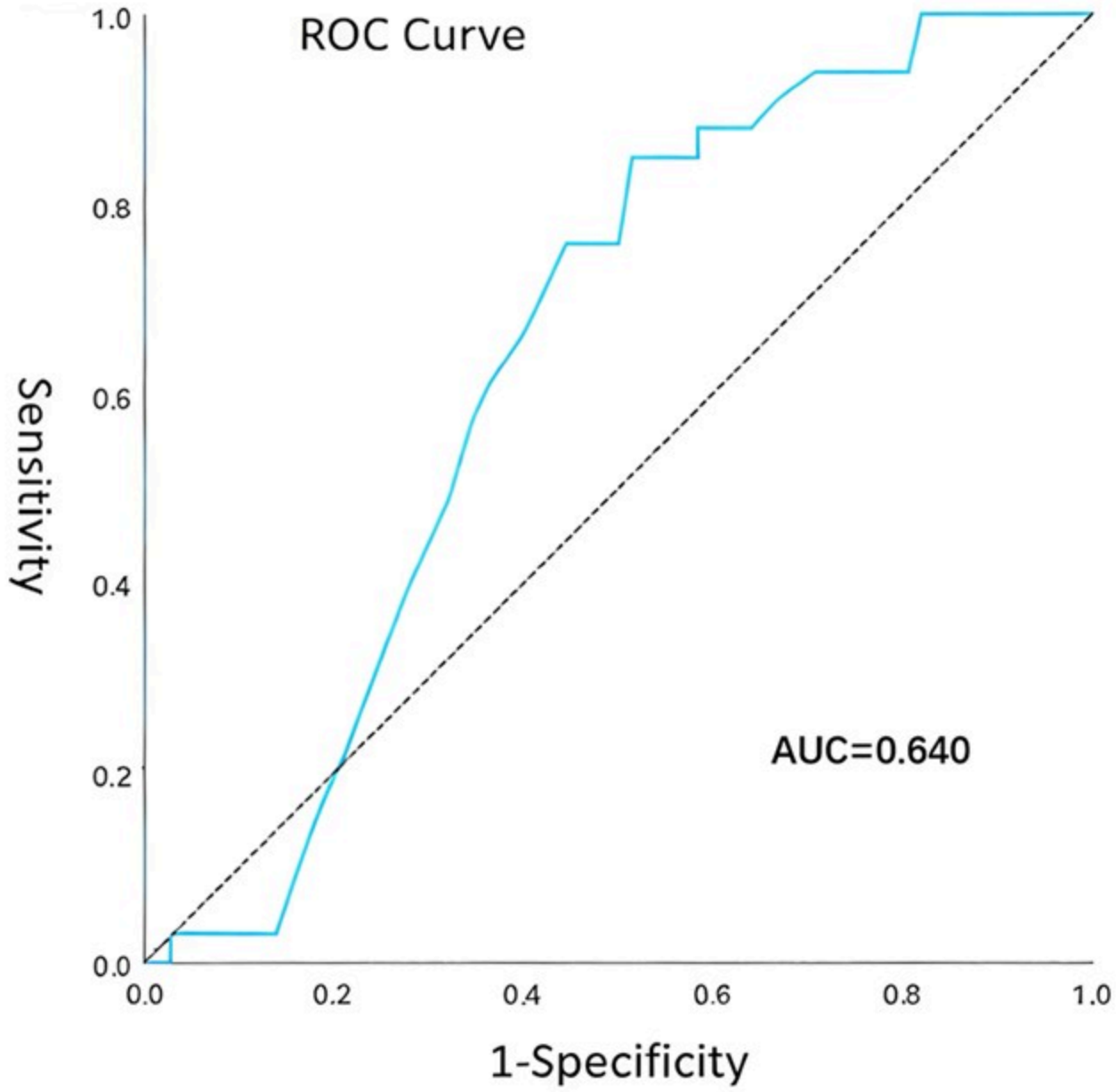


Figure 3

Receiver operating characteristic curve for predicting progression-free survival using LMR. LMR, lymphocyte to monocyte ratio.

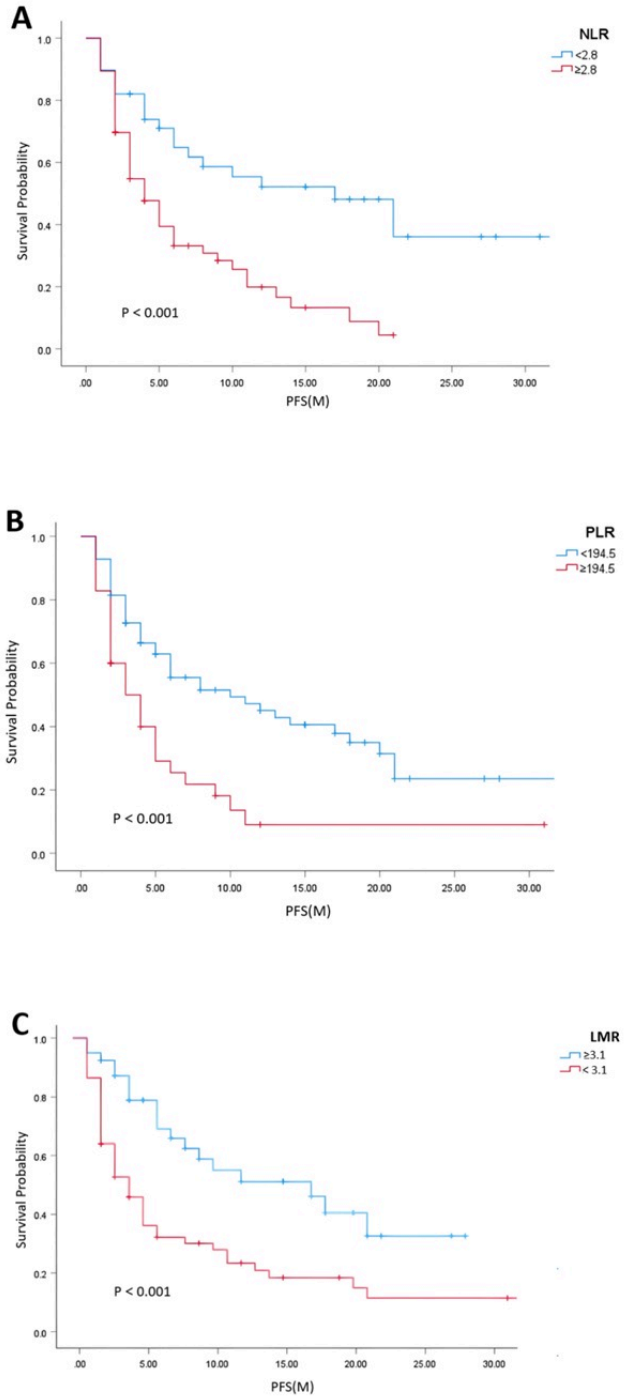


Figure 4

Kaplan-Meier curves for progression-free survival: (A) comparison by NLR; (B) comparison by PLR; (C) comparison by LMR. LMR, lymphocyte to monocyte ratio; M, month; NLR, neutrophil to lymphocyte ratio, PFS, progression-free survival; PLR: platelet to lymphocyte ratio.

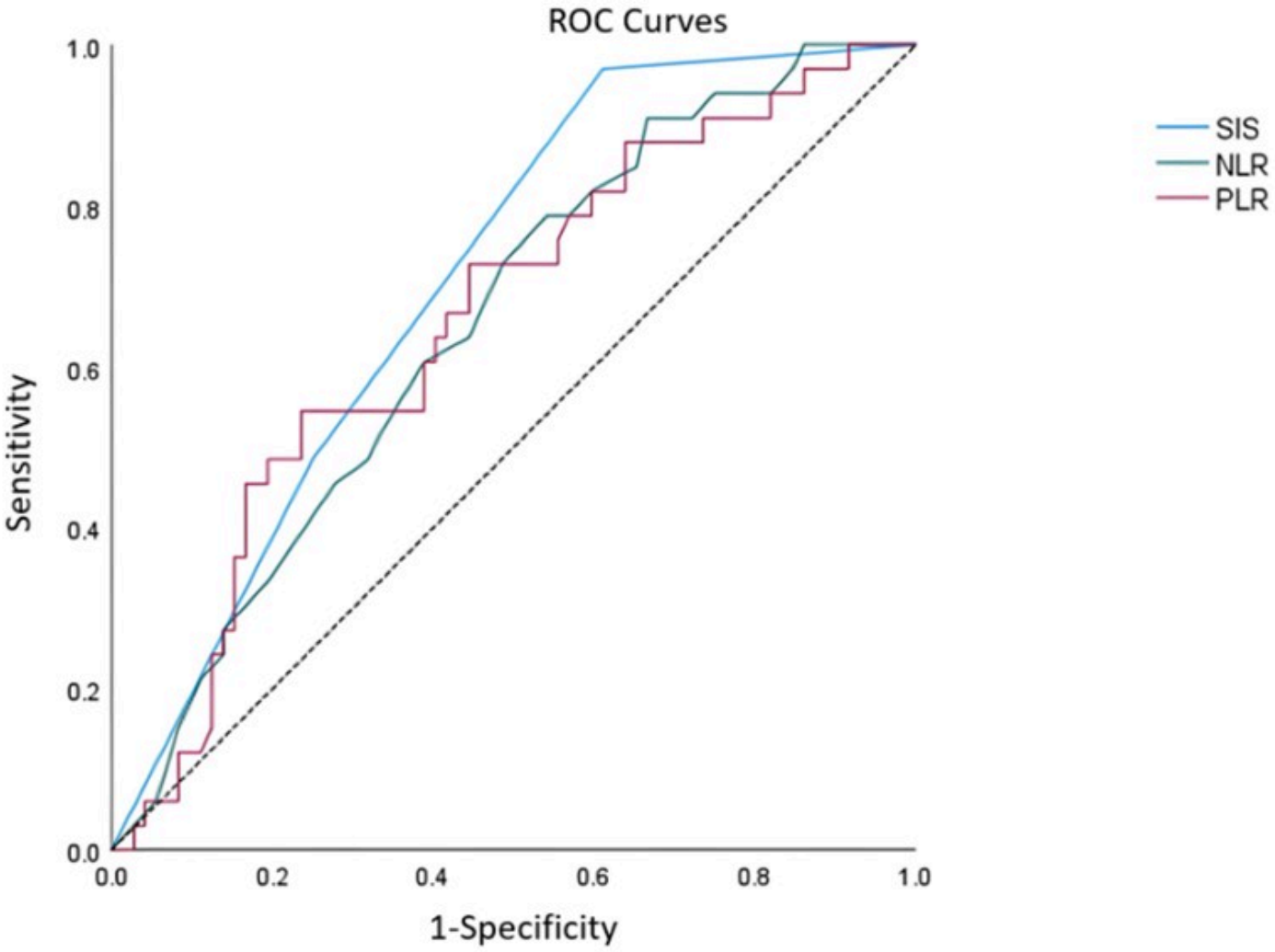


Figure 5

Receiver Operating Characteristic Curves of Different Peripheral Blood Parameters for Predicting Progression-free Survival. NLR, neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SIS, systemic inflammation score.

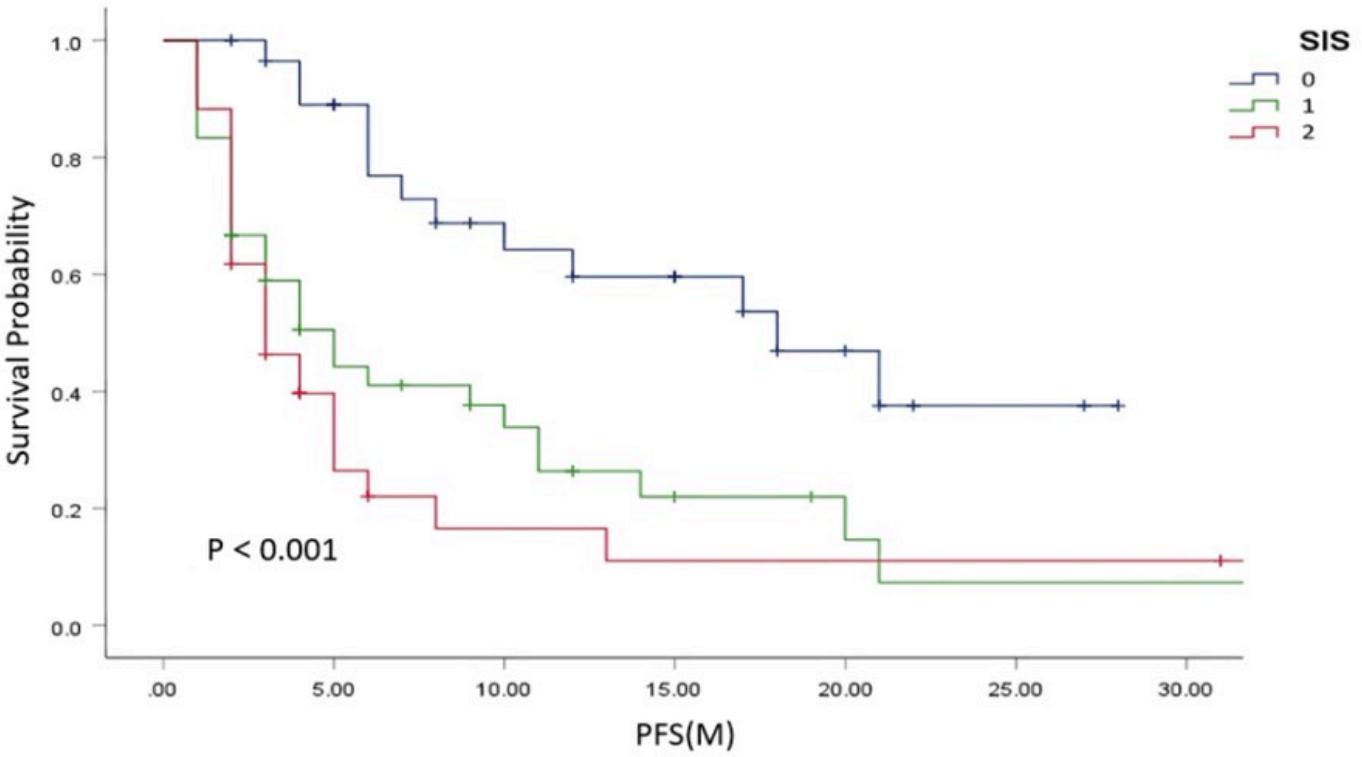


Figure 6

Progression-free survivalAnalysis Stratified by Systemic Inflammation Score. M, month; SIS, systemic inflammation score.