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Systemic Immune-Inflammation Index and Systemic Inflammation Response Index Predict Response to Neoadjuvant Therapy in Locally Advanced Esophageal Squamous Cell Carcinoma

Zhonghua Zhang
Nanjing Medical University
Lijun Zhu
Nanjing University of Chinese Medicine
Xiaodong You
Nanjing Medical University
Wen Jiang
Nanjing Medical University
Chengan Zhang
Nanjing Medical University
Ting Wang
Nanjing Medical University
Yanhong Gu
guyhphd@163.com
Nanjing Medical University

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Abstract

Background

Assessment of systemic and local immune responses is critical for determining the efficacy of cancer interventions. Our findings indicate that baseline systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) are strongly and independently correlated with treatment response following neoadjuvant chemoimmunotherapy in patients with locally advanced esophageal squamous cell carcinoma (ESCC).

Methods

This study aimed to evaluate the predictive value of baseline SII and SIRI for the efficacy of neoadjuvant chemoimmunotherapy in locally advanced ESCC. From January 2021 to December 2024, this retrospective study enrolled 126 patients with ESCC, all of whom received 2–4 cycles of standard-dose immunotherapy combined with platinum-based chemotherapy (without radiotherapy) and underwent curative surgery within 4–6 weeks after the last neoadjuvant treatment. SII and SIRI were calculated based on the complete blood count results before the first treatment. The primary endpoint of this study was tumor regression grade (TRG), and secondary endpoints included tumor response assessment, residual tumor proportion (RTP), disease-free survival (DFS) and overall survival (OS). Ordinal logistic regression analysis was used to assess the association between these indicators and TRG. Receiver operating characteristic (ROC) curves were utilized to assess their predictive ability for poor tumor regression of patients with ESCC who received neoadjuvant chemoimmunotherapy.

Results

Increased SII and SIRI were significantly associated with a higher pathological TRG. Radiological assessment further revealed markedly lower objective response rates in patients with elevated SII or SIRI. ROC curves demonstrated SII and SIRI had a good predictive ability for poor tumor regression (SII: AUC = 0.769 and SIRI: AUC = 0.695, respectively).

Conclusion

Baseline SII and SIRI serve as independent and valuable biomarkers for predicting neoadjuvant therapy response in patients with locally advanced ESCC.

Introduction

Esophageal cancer (EC) is a highly prevalent and deadly form of cancer, ranking seventh in incidence and sixth in mortality among malignant tumors worldwide [1, 2]. China, a country with a high incidence of EC, accounts for nearly 50% of the total number of morbidity and mortality cases worldwide [3]. Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype. Despite advances in treatment, most patients are diagnosed at a locally advanced or metastatic stage. While neoadjuvant chemoimmunotherapy has improved outcomes for some patients with locally advanced ESCC [4], predicting individual treatment response remains a major clinical challenge due to significant heterogeneity. Finding and validating other potential prognostic markers is crucial because it not only helps to identify the clinical characteristics of patients with poor treatment response, but also enables more precise individualized treatment planning for patients, which can further optimize the therapeutic efficacy and improve the patient's prognosis.

Beyond intrinsic tumor factors, cancer progression is driven by complex systemic processes [5], with persistent inflammation serving as a well-established driver of tumorigenesis across diverse cancer types [6, 7]. The systemic inflammatory state is often reflected in the peripheral blood. Circulating immune cells, such as neutrophils, lymphocytes, and monocytes, are not only participants in inflammation but also key modulators of tumor progression. Consequently, biomarkers derived from these cells-particularly composite indices like the Systemic Immune-Inflammation Index (SII) and the Systemic Inflammation Response Index (SIRI) have emerged as valuable tools for quantifying the host's inflammatory and immune status. By integrating counts of multiple cell types, SII and SIRI provide a more holistic measure than single parameters and have proven to be robust predictors of survival and treatment response across various solid tumors [8–13]. However, the value of SII and SIRI in assessing the efficacy of neoadjuvant therapy for locally advanced ESCC remains to be elucidated [14, 15].

Given the established prognostic value of SII and SIRI in other cancers [9, 16, 17] and the urgent need for reliable response predictors in locally advanced ESCC, we hypothesized that these baseline inflammatory indices could effectively stratify patients based on their likelihood of responding to neoadjuvant chemoimmunotherapy. We therefore conducted a retrospective study of 126 patients with locally advanced ESCC who received neoadjuvant chemoimmunotherapy (without radiotherapy) followed by curative surgery. Using tumor regression grade (TRG) as

the primary endpoint, and radiological response, residual tumor proportion (RTP), disease-free survival (DFS), and overall survival (OS) as secondary endpoints, we employed ordinal logistic regression [18] and receiver operating characteristic (ROC) curve analysis to quantify the associations between SII/SIRI and treatment outcomes, and to validate their predictive potential as accessible, cost-effective tools for individualized ESCC treatment decision-making. This study aimed to provide a practical predictive tool to guide individualized neoadjuvant therapy selection for locally advanced ESCC.

Materials and Methods

Patients and Study Design

A review of the medical records from the Jiangsu Provincial People's Hospital was conducted to identify patients with locally advanced ESCC who received neoadjuvant therapy. The study's flowchart is depicted in Fig. 1. The patient population included individuals between the ages of 18 and 80 years, with an Eastern Cooperative Oncology Group (ECOG) performance status ranging from 0 to 1, and complete clinical information available. The patients were diagnosed with ESCC based on pathological examination of biopsy specimens from the primary tumor site. Patients with mid-to-lower esophageal tumors (> 18 cm from the incisor teeth) were considered potentially resectable after imaging and endoscopy and were scheduled for neoadjuvant therapy. All patients were confirmed cM0 (no distant metastasis) at enrollment. Following diagnosis, patients received neoadjuvant therapy with immunotherapy combined with platinum-based chemotherapy (without radiotherapy) between January 2021 and December 2024, and underwent curative surgery within 4–6 weeks following the final neoadjuvant therapy session. All patients underwent a standardized, minimally invasive (thoracoscopic and laparoscopic) three-incision esophagectomy with gastric conduit reconstruction. Two patients had microscopic residual tumor (R1) on final pathology (both classified as TRG 2 and TRG 3); all others achieved R0 resection. Lymphadenectomy was performed principally as an extended two-field dissection, with a three-field dissection applied in select cases. The thoracic dissection meticulously covered the bilateral recurrent laryngeal nerve chains and the subcarinal area. The abdominal dissection involved a systematic clearance of the lympho-adipose tissues surrounding the left gastric artery, common hepatic artery, and celiac trunk. Patients who received systemic hormone therapy or antibiotic therapy within three months prior to neoadjuvant therapy, a conservative criterion adopted from oncological studies to allow for the stabilization of immune cell counts after potential modulation, had other malignant tumors within the past two years that were not cured, had other major diseases affecting survival or immune function (such as cardiovascular or cerebrovascular diseases, liver failure or kidney failure, active autoimmune diseases, immune deficiencies, etc.), were pregnant or breastfeeding, or had other conditions deemed unsuitable by the investigator were excluded from the study. The Institutional Review Board of The First Affiliated Hospital of Nanjing Medical University has approved this protocol, which adheres to the principles of the Declaration of Helsinki.

Data Collection and Definition

This retrospective study enrolled 126 patients with locally advanced ESCC who received 2–4 cycles of standard-dose immunotherapy combined with platinum-based chemotherapy. Comprehensive baseline data were collected at admission via a standardized electronic case-report form, including age, height, weight, body-mass index (BMI), smoking and alcohol exposure, and documented comorbidities (hypertension and diabetes mellitus), and liver and kidney function. The clinical characteristics that were taken into consideration in this study included pre-neoadjuvant blood test results, type of immune checkpoint inhibitor, type of platinum-based drug, distance of the tumor from the incisor, degree of tumor differentiation, imaging test results, and postoperative pathological results. Furthermore, data on DFS and OS were also retrieved to evaluate long-term outcomes.

Imaging assessments of patients were conducted before and after neoadjuvant therapy. The assessment methods that were typically employed included computed tomography [19] scans and/or positron emission tomography (PET) scans. The clinical physicians responsible for evaluating treatment efficacy employed the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) to assess response categories, which included complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD). In addition, the pathological results of patients following esophageal cancer radical surgery were assessed. All surgical specimens were processed according to a standardized protocol. Two gastrointestinal pathologists, unaware of imaging findings, independently graded tumor regression according to the tumor regression grade criteria recommended by the Chinese Society of Clinical Oncology (CSCO) guidelines for esophageal cancer (2024 edition): Grade 0 (complete response, no viable tumor cells), Grade 1 (moderate response, < 10% viable cells), Grade 2 (mild response, 10–50% viable cells), Grade 3 (poor response, > 50% viable cells). Additionally, RTP was determined by post-operative pathological examination of the surgical specimen. It was defined as the percentage of residual viable tumor cells relative to the total tumor bed area, as assessed by two independent pathologists. The study endpoints were defined as follows: the primary endpoint was TRG. the secondary endpoints included radiological tumor response assessment, RTP, as well as long-term survival outcomes (DFS and OS). DFS was defined as the time from the date of surgery to disease recurrence or death from any cause, whichever occurred first. OS was defined as the time from the date of surgery to death from any cause.

The baseline complete blood count (CBC) results were obtained within 7 days prior to the first cycle of neoadjuvant therapy. All patients were afebrile (body temperature < 37.3°C) and without clinical signs of active infection at the time of blood draw. In the present study, the SII and SIRI were calculated as follows: SII = (neutrophil count × platelet count) / lymphocyte count, whereas SIRI was calculated as (neutrophil count × monocyte count) / lymphocyte count.

Statistical analysis

The normality of continuous variables was determined using the Shapiro-Wilk test. Continuous variables with normal distribution are expressed as mean and standard deviation, while others are expressed as median and interquartile range (IQR). Categorical variables are presented as counts (%). Kruskal-Wallis test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. The percentage of missing values was calculated and abnormal values were detected for all continuous variables to minimize bias. We used random forest imputation to address missing values for variables with missing values less than 20%.

To investigate the relationship of SII and SIRI with TRG of patients with ESCC who received neoadjuvant chemoimmunotherapy, ordinal logistic regression was used and parallel line test was conducted to assess the ordinal logistic regression models. Patients were categorized into three distinct groups based on tertiles of SII and SIRI levels. Additionally, we conducted multivariable logistic regression to investigate the association between SII and SIRI and radiological tumor response assessment. Then, the relationship of SII and SIRI with RTP was explored using Analysis of Variance and restricted cubic spline (RCS) analysis. Furthermore, ROC curves were employed to assess their predictive ability for poor tumor regression of patients with ESCC who received neoadjuvant chemoimmunotherapy.

A two-sided P-value < 0.05 was considered statistically significant. All analyses were conducted using R software (version 4.3.3).

Results

1. **Patient characteristics**

This study included 126 patients with locally advanced ESCC who underwent neoadjuvant therapy. Based on the postoperative pathological assessment of TRG, the patients were divided into four groups: TRG 0 (complete response, n = 26), TRG 1 (moderate response, n = 38), TRG 2 (mild response, n = 39), and TRG 3 (poor response, n = 23). A comprehensive comparison of patient baseline characteristics is presented in Table 1 and Supplementary Table 1. In the study population, 94 cases were male (74.6%) and 32 cases were female (25.4%), with a median age of 68 years. Comparative analysis showed that the groups were well-balanced in terms of most baseline characteristics, including age, gender, BMI, and clinical stage (cT, cN). However, significant differences were observed in systemic inflammation indices (SII and SIRI) levels across the TRG groups.

Table 1. Comparison of baseline characteristics of patients with different TRG.

	Tumor regression grade					*P*-value
Characteristics	Overall	0	1	2	3	
	N = 126	N = 26	N = 38	N = 39	N = 23	
SII, median (IQR)	513 (456)	411 (203)	445 (451)	538 (356)	813 (529)	0.002
SIRI, median (IQR)	1.17 (1.38)	0.82 (0.78)	1.00 (1.40)	1.23 (1.43)	1.91 (1.20)	0.014
Age, median (IQR)	68 (8)	69 (9)	69 (8)	69 (6)	67 (8)	0.931
Gender						0.038
Male, n (%)	94 (74.6%)	15 (57.7%)	32 (84.2%)	33 (84.6%)	14 (60.9%)	
Female, n (%)	32 (25.4%)	11 (42.3%)	6 (15.8%)	6 (15.4%)	9 (39.1%)	
BMI, median (IQR)	22.4 (4.2)	22.2 (4.0)	21.9 (4.6)	22.6 (3.8)	22.8 (3.7)	0.852
Smoking, n (%)	58 (46.0%)	10 (38.5%)	19 (50.0%)	18 (46.2%)	11 (47.8%)	0.85
Alcohol, n (%)	52 (41.3%)	9 (34.6%)	17 (44.7%)	17 (43.6%)	9 (39.1%)	0.795
Hypertension, n (%)	38 (30.2%)	3 (11.5%)	11 (28.9%)	17 (43.6%)	7 (30.4%)	0.105
Diabetes, n (%)	12 (9.5%)	3 (11.5%)	5 (13.2%)	2 (5.1%)	2 (8.7%)	0.809
Distance from incisor, median (IQR)	28.0 (4.00)	29.0 (3.75)	28.0 (5.00)	29.0 (3.00)	27.0 (5.00)	0.452
Tumor differentiation grade						0.511
High, n (%)	21 (16.7%)	6 (23.1%)	2 (5.3%)	7 (17.9%)	6 (26.1%)	
Medium, n (%)	72 (57.1%)	15 (57.7%)	26 (68.4%)	21 (53.8%)	10 (43.5%)	
Low, n (%)	33 (26.2%)	5 (19.2%)	10 (26.3%)	11 (28.2%)	7 (30.4%)	
cT						0.223
cT2, n (%)	20(15.9%)	4(15.4%)	4(10.5%)	8(20.5%)	4(17.4%)	
cT3, n (%)	83(65.9%)	20(76.9%)	27(71.1%)	25(64.1%)	11(47.8%)	
cT4, n (%)	23(18.2%)	2(7.7%)	7(18.4%)	6(15.4%)	8(34.8%)	
cN						0.885
cN0, n (%)	87(69.0%)	18(69.2%)	24(63.2%)	30(76.9%)	15(65.2%)	
cN1, n (%)	31(24.6%)	7(26.9%)	11(28.9%)	7(17.9%)	6(26.1%)	
cN2, n (%)	8(6.4%)	1(3.9%)	3(7.9%)	2(5.2%)	2(8.7%)	
ypTNM staging						< 0.001
□, n (%)	26 (20.6%)	26 (100%)	0 (0%)	0 (0%)	0 (0%)	
□, n (%)	23 (18.3%)	0 (0%)	20 (52.6%)	2 (5.1%)	1 (4.3%)	
□A, n (%)	36 (28.6%)	0 (0%)	16 (42.1%)	13 (33.3%)	7 (30.4%)	
□B, n (%)	40 (31.7%)	0 (0%)	2 (5.3%)	23 (59.0%)	15 (65.2%)	
□A, n (%)	1 (0.8%)	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)	
Macroscopic Classification						0.860
Medullary, n (%)	66 (52.4%)	17 (65.4%)	21 (55.3%)	17 (43.6%)	11 (47.8%)	
Ulcerative, n (%)	28 (22.2%)	5 (19.2%)	7 (18.4%)	8 (20.5%)	8 (34.8%)	
Intraluminal, n (%)	8 (6.3%)	2 (7.7%)	2 (5.3%)	4 (10.3%)	0 (0%)	
Stricturing, n (%)	9 (7.1%)	1 (3.8%)	4 (10.5%)	3 (7.7%)	1 (4.3%)	
Fungating, n (%)	15 (11.9%)	1 (3.8%)	4 (10.5%)	7 (17.9%)	3 (13.0%)	
Residual tumor proportion (RTP), median (IQR)	0.500 (0.675)	0 (0)	0.200 (0.175)	0.800 (0.100)	1.00 (0.0500)	< 0.001

Radiological tumor response assessment						< 0.001
CR, n (%)	27 (21.4%)	26 (100%)	1 (2.6%)	0 (0%)	0 (0%)	
PR, n (%)	40 (31.7%)	0 (0%)	37 (97.4%)	3 (7.7%)	0 (0%)	
SD, n (%)	53 (42.1%)	0 (0%)	0 (0%)	36 (92.3%)	17 (73.9%)	
PD, n (%)	6 (4.8%)	0 (0%)	0 (0%)	0 (0%)	6 (26.1%)	
OS, median (IQR)	950 (887)	1150 (726)	947 (962)	980 (1090)	756 (433)	0.126
DFS, median (IQR)	852 (896)	1150 (726)	866 (872)	900 (1100)	600 (320)	0.012
Duration of follow-up, median (IQR)	950 (887)	1150 (726)	947 (931)	980 (1090)	756 (433)	0.126

Note: One case was classified as stage ⅡA after pathological evaluation.

Prior to the initial treatment, a complete blood count and biochemical testing were performed on all patients. A statistically significant difference in serum creatinine (Scr) levels was observed between the groups. However, other indicators of liver and kidney function did not demonstrate statistical significance. With regard to the selection of pharmaceutical agents for the neoadjuvant therapy regimen, PD-1 inhibitors were predominantly sintilimab (64.3%), with no statistically significant disparities in drug selection preferences observed between the groups. The utilization of platinum-based medications (carboplatin, cisplatin, and nedaplatin) exhibited homogeneity across the study groups. Statistically significant differences were not observed between groups with respect to the distance from the primary tumor to the incisor or the differentiation grade.

All patients underwent imaging assessments before and after neoadjuvant therapy. Imaging assessments demonstrated a CR rate of 100% in the TRG 0 group, while the PD rate reached 26.1% in the TRG 3 group. All patients underwent a three-incision esophagectomy involving the neck, chest, and abdomen, followed by a partial gastrectomy with esophagogastric anastomosis. The pathological TNM staging was conducted in accordance with the 8th edition of the AJCC Staging Manual. The TNM staging system demonstrated a robust correlation with the TRG grouping. Within the TRG 3 group, 65.2% of cases were classified as stage III, and RTP identified by pathological examination of the surgical specimen exhibited a notable increase, rising from 0% in the TRG 0 group to 100% in the TRG 3 group.

After a median follow-up of 950 days, survival analysis showed that the TRG 3 group had the shortest median overall survival (OS, 756 days) and disease-free survival (DFS, 600 days). The difference in DFS among the groups was statistically significant (P = 0.012), whereas the difference in OS was not (P = 0.126). No perioperative deaths were recorded.

2. **Higher SII and SIRI could be associated with poor treatment response in ESCC**

As TRG increases from complete response (TRG Grade 0) to no response (TRG Grade 3), the median SII shows a significant increase, rising from 411 to 813. SIRI also increases at the same time, from 0.82 to 1.91 (Table 1). Ordinal logistic regression analyses indicated that higher levels of SII and SIRI were significant predictors of elevated TRG. As shown in Table 2, in the unadjusted Model 1, compared to the low SII group, the medium and high SII groups had odds ratios (ORs) of 2.24 (95% CI 1.04–4.91, P = 0.041) and 3.80 (95% CI 1.72–8.61, P = 0.001), respectively, for achieving a higher TRG. This association remained significant and stable in Model 2 (adjusted for age, gender, and BMI) and Model 3 (further adjusted for smoking, alcohol, hypertension, and diabetes), with ORs for the medium SII group ranging from 2.52 to 2.54 (P < 0.05) and for the high SII group from 3.94 to 4.33 (P ≤ 0.001). SIRI showed a similar trend: in the fully adjusted Model 3, the medium and high SIRI groups had ORs of 2.36 (95% CI 1.05–5.35, P = 0.038) and 3.70 (95% CI 1.58–8.82, P = 0.003), respectively, compared to the low SIRI group. The parallel line test confirmed that all models met the requirements of ordinal logistic regression (P > 0.05, Supplementary Table 2), supporting the validity of the ordinal logistic regression models used.

Table 2. Univariable and multivariable ordinal logistic regression analysis for tumor regression grade.

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P-value*
SII						
Low (< 404)	Ref		Ref		Ref	
Medium (404–700)	2.24 (1.04–4.91)	0.041	2.54 (1.16–5.68)	0.021	2.52 (1.13–5.67)	0.024
High (> 700)	3.80 (1.72–8.61)	0.001	4.33 (1.90–10.10)	< 0.001	3.94 (1.71–9.30)	0.001
SIRI						
Low (< 0.83)	Ref		Ref		Ref	
Medium (0.83–1.89)	2.17 (1.00–4.77)	0.052	2.22 (1.01–4.96)	0.048	2.36 (1.05–5.35)	0.038
High (> 1.89)	3.50 (1.59–7.87)	< 0.001	3.68 (1.62–8.49)	0.002	3.70 (1.58–8.82)	0.003

Model 1: unadjusted.

Model 2: adjusted for age, gender and BMI.

Model 3: adjusted for age, gender, BMI, smoking, alcohol, hypertension, and diabetes.

It is noteworthy that although SII/SIRI levels were significantly associated with treatment response, the distributions of the types of PD-1 inhibitors (Fig. 2 A, B), types of platinum-based drugs (Fig. 2 C, D), and the number of treatment cycles received (Fig. 2 E, F) showed no statistically significant differences (all P > 0.05) among the high, medium, and low tertiles, indicating comparable treatment backgrounds across groups and strengthening the reliability of the observed associations. The risk estimates for SII and SIRI remained stable as more confounders were added to the models, further suggesting that their predictive ability for treatment response is independent of common clinical confounding factors.

Concurrently, analogous patterns were identified in preoperative imaging-based tumor response assessment. Multivariate regression analysis revealed a significant association between SII/SIRI levels and preoperative radiological tumor response assessment (based on RECIST 1.1 criteria) (Fig. 3). The forest plots (Fig. 3A and 3B) present the odds ratios (ORs) and 95% confidence intervals (CIs) derived from three sequential models: the unadjusted model (Model 1), the model adjusted for demographic factors (Model 2), and the fully adjusted model incorporating clinical confounders (Model 3). In the analysis for SII, patients with a moderate level exhibited a non-significant trend towards an increased probability of achieving an objective radiographic response (Objective Response Rate, ORR = CR + PR) compared to the low-level group (OR ranging from 2.09 to 2.54 across models). Conversely, a high SII level was consistently and significantly associated with disease control failure (SD/PD), with adjusted ORs of 4.09 (Model 1), 4.54 (Model 2), and 4.07 (Model 3); all confidence intervals excluded the null value of 1. An identical analytical framework was applied to SIRI (Fig. 3B). The results indicated that a high SIRI level was robustly associated with poorer imaging outcomes, with ORs of 3.71, 3.80, and 3.73 in Models 1, 2, and 3, respectively. Notably, the strength of association for a moderate SIRI level increased following multivariable adjustment in Model 3. Critically, the visualization confirms a dose-response relationship, wherein the point estimates (ORs) increase progressively from the low to the high-level groups for both inflammatory indices. Furthermore, the stability of these associations is evidenced by the fact that the 95% CIs for all medium and high-level groups across both SII and SIRI analyses do not intersect the line of no effect (OR = 1) in any of the three statistical models.

Furthermore, data regarding the RTP, determined by pathological examination of the surgical specimen, were collected and analyzed. The findings indicated a substantial correlation between SII and SIRI, as well as RTP (Fig. 4). As SII levels increased, RTP demonstrated a stepwise increase, with the high SII group exhibiting a significantly higher RTP compared to the moderate and low-level groups (Fig. 4A and B). A substantial positive correlation between SIRI and RTP was demonstrated, with the residual tumor extent in the high SIRI group exhibiting comparability to that in the high SII group (Fig. 4C and D), which validates the synergistic predictive effect of inflammatory markers. Patients exhibiting concurrent elevations of both inflammatory markers (defined by the optimal cutoff values derived from ROC analysis, see below) were associated with the higher RTP burden.

Subsequently, ROC curves were employed to assess the predictive value of systemic immune-inflammatory markers (Fig. 5). The pathological response was defined by tumor regression grade (TRG), which was classified into two grades for analysis: low TRG (TRG0 and TRG1), indicating good tumor regression, and high TRG (TRG2 and TRG3), indicating poor regression. The ROC analysis specifically evaluated the ability of the markers to predict high TRG. Among all indices, SII exhibited the highest discriminatory accuracy, with an area under the curve [22] of 0.769. The AUC of SII was significantly superior to that of neutrophils (P = 0.005) and lymphocytes (P = 0.042), although the difference compared to platelets did not reach statistical significance (P = 0.163, Supplementary Table 3). The SII curve was closest to the upper left

corner, indicating the best balance between sensitivity and specificity (Fig. 5A). The optimal cutoff value for SII was determined to be 547 (Fig. 5A), which yielded a sensitivity of 86.4% and a specificity of 60.6%. Additionally, SIRI, with an AUC of 0.695, was significantly higher than that of monocytes (P < 0.05) though not statistically different from neutrophils or lymphocytes (P > 0.05, Supplementary Table 4). The optimal cutoff value for SIRI was 1.42 (Fig. 5B), corresponding to a sensitivity of 77.3% and a specificity of 66.3%. At these validated cutoffs, the positive predictive value (PPV) and negative predictive value (NPV) were also calculated. For SII (≥547), the PPV was 31.7% and the NPV was 95.5%. For SIRI (≥1.42), the PPV was 32.7% and the NPV was 93.2%, providing critical thresholds for clinical risk stratification.

The superior performance of the composite SII and SIRI indicators underscores the limitation of relying on a single cellular component for assessment. The results support the use of SII as the predictive indicator, with its AUC of 0.769 meeting clinically practical standards.

3. Association of SII and SIRI with Long-Term Outcomes

The impact of baseline systemic inflammation indices on long-term survival was further evaluated (Table 3). Multivariable Cox regression analysis, adjusted for age, gender, BMI, smoking, alcohol consumption, hypertension, and diabetes, revealed that patients with high SII levels (> 700) had a trend towards increased risk of 3-year mortality compared to the low SII group (< 404), with a hazard ratio (HR) of 1.82 (95% CI 0.65–5.08, P = 0.253). Similarly, a high SIRI level (> 1.89) was associated with an HR of 2.41 (95% CI 0.82–7.08, P = 0.11) for 3-year mortality compared to the low SIRI group (< 0.83), although these associations did not reach statistical significance.

Table 3. Multivariable Cox and logistic regression analysis between SII, SIRI, and TRG and 3-year mortality and tumor recurrence.

Variables	3-year mortality		3-year tumor recurrence	
	OR (95% CI)	***P-value***	**OR (95% CI)**	***P-value***
SII				
Low (< 404)	Ref		Ref	
Medium (404–700)	1.44 (0.54–4.05)	0.486	1.18 (0.96–1.45)	0.112
High (> 700)	1.82 (0.65–5.08)	0.253	1.27 (1.03–1.56)	**0.029**
SIRI				
Low (< 0.83)	Ref		Ref	
Medium (0.83–1.89)	1.65 (0.59–4.64)	0.340	1.05 (0.85–1.29)	0.661
High (> 1.89)	2.41 (0.82–7.08)	0.110	1.17 (0.94–1.46)	0.153
TRG				
0	Ref		Ref	
1	2.73 (0.56–13.45)	0.216	1.21 (0.97–1.50)	0.101
2	4.89 (1.02–23.39)	**0.047**	1.48 (1.18–1.85)	**0.001**
3	7.72 (1.52–39.33)	**0.014**	1.85 (1.45–2.37)	**< 0.001**

All models were adjusted for age, gender, BMI, smoking, alcohol, hypertension, and diabetes.

In contrast, the association between SII levels and 3-year tumor recurrence was more pronounced. Patients with high SII exhibited a significantly increased risk of tumor recurrence, with an odds ratio (OR) of 1.27 (95% CI 1.03–1.56, P = 0.029) compared to the low SII group. For SIRI, the high level group showed an OR of 1.17 (95% CI 0.94–1.46, P = 0.153) for recurrence, which was not statistically significant. Notably, the tumor regression grade (TRG) demonstrated a strong and graded association with both 3-year mortality and recurrence risk. Compared to TRG 0, patients with TRG 2 had an HR of 4.89 (95% CI 1.02–23.39, P = 0.047) for mortality and an OR of 1.48 (95% CI 1.18–1.85, P = 0.001) for recurrence. Patients with TRG 3 had the highest risk, with an HR of 7.72 (95% CI 1.52–39.33, P = 0.014) for mortality and an OR of 1.85 (95% CI 1.45–2.37, P < 0.001) for recurrence.

Although the direct associations of SII and SIRI with long-term mortality were not statistically significant, their consistent and significant correlation with TRG, which itself is a powerful predictor of survival outcomes, suggests an indirect link. The observed trends for SII and SIRI with mortality align directionally with the strong prognostic impact of TRG.

Discussion

SII and SIRI comprehensively reflect the balance between systemic inflammatory status and immune function by integrating counts of neutrophils, lymphocytes, monocytes, and platelets. Neutrophils can promote tumor angiogenesis and matrix degradation through the release of inflammatory cytokines [20–23]; monocytes differentiate into M2-type macrophages, which mediate immunosuppression [24, 25]; lymphocytopenia directly impairs antitumor immune response [26, 27]; and platelets protect circulating tumor cells from immune attack by facilitating microthrombus formation [28]. The abnormal alterations in these cellular subsets collectively drive tumor progression and therapeutic resistance, which explains why the multi-parameter indices SII and SIRI demonstrate superior predictive performance compared to single inflammatory markers such as neutrophil or lymphocyte counts. Our study investigated the predictive value of baseline SII and SIRI for the efficacy of neoadjuvant chemoimmunotherapy in patients with locally advanced ESCC. The results demonstrated that both SII and SIRI showed a significant positive correlation with TRG. Consistent predictive performance was also observed in radiological response assessment and evaluation of RTP. Notably, SII achieved an AUC of 0.769, indicating that these peripheral blood-derived composite inflammatory indices may serve as clinically practical tools for predicting treatment response.

Previous studies have confirmed that SII and SIRI possess predictive value for the prognosis of multiple solid tumors. SII is an independent predictor of OS after radical surgery in patients with ESCC [29]. Additionally, SII is considered a good predictor of systemic immune inflammatory status in lung cancer, and a study has confirmed that SII can effectively predict survival rates after resection of lung invasive mucinous adenocarcinoma [30]. In hepatocellular carcinoma, SII has also been shown to predict recurrence and survival after curative resection [13]. Beyond predicting tumor patient outcomes, SII also holds value in predicting cancer risk. Analysis of the UK Biobank further revealed that elevated SII levels are positively correlated with the risk of developing various cancers, with the strongest associations observed for colorectal and lung cancer, suggesting its potential value in primary cancer prevention [31]. SIRI was initially used to predict survival outcomes in advanced pancreatic cancer patients undergoing chemotherapy and effectively reflected systemic inflammatory status [11]. Due to its accessibility, the prognostic value of SIRI has been studied in various cancers, including urological [32], respiratory [12, 33], and gastrointestinal malignancies [34, 35] as well as head and neck cancer [36], all of which confirmed that high SIRI is associated with lower OS and higher metastasis risk. Additionally, the combined use of SII and SIRI in tumors such as gastric cancer [8], colorectal cancer [9, 37], renal cancer [10], prostate cancer [38], and thyroid cancer [39] has demonstrated superior prognostic accuracy compared to single indicators and can effectively identify high-risk populations requiring enhanced postoperative follow-up. In summary, SII and SIRI, as low-cost, easily accessible systemic inflammation-immunity composite indicators, have established an evidence-based foundation for predicting invasive behavior, postoperative survival, and metastasis risk across tumor types. In the future, combining these indices with molecular biomarkers could further enhance the precision of individualized treatment decisions.

Our findings suggest that baseline SII and SIRI may serve as predictors of the efficacy of neoadjuvant therapy in patients with locally advanced ESCC. However, this study has several limitations. Its single-center, retrospective design with a limited sample size (n = 126) and lack of external validation may constrain the generalizability of the results. Patients with disease progression, poor treatment tolerance, or poor general condition who did not undergo surgery could not be fully captured due to technical and staffing constraints and considerable loss to follow-up. Accordingly, the results may not be fully generalizable to all patients who initiated neoadjuvant therapy, and potential selection bias should be considered when interpreting the findings. Furthermore, the exclusion of other inflammatory biomarkers (e.g., C-reactive protein, IL-6) precludes an assessment of their combined predictive utility with SII/SIRI. The study also did not serially monitor SII/SIRI during treatment, leaving their dynamic predictive value unexplored. Finally, as patients receiving radiotherapy were excluded, the findings may not extend to those undergoing contemporary triple-modality neoadjuvant therapy (chemoradiotherapy plus immunotherapy and radiotherapy), which is increasingly used in locally advanced ESCC. Future multicenter prospective studies with larger cohorts are needed to validate these indices across diverse treatment regimens and ESCC subtypes. Research should also evaluate the prognostic relevance of on-treatment SII/SIRI dynamics and explore integrating them with molecular profiling to build more robust, composite predictive models for personalized therapy.

Abbreviations

SII: systemic immune-inflammation index

SIRI: systemic inflammation response index

ESCC: esophageal squamous cell carcinoma

TRG: tumor regression grade

DFS: disease-free survival

OS: overall survival

ROC: receiver operating characteristic

EC: esophageal cancer

ECOG: Eastern Cooperative Oncology Group

BMI: body-mass index

CT: computed tomography

PET: positron emission tomography

RECIST: Response Evaluation Criteria in Solid Tumors

CR: complete response

PR: partial response

SD: stable disease

PD: disease progression

IQR: interquartile range

Scr: serum creatinine

RTP: residual tumor proportion

PPV: positive predictive value

NPV: negative predictive value

HR: hazard ratio

OR: odds ratio

Declarations

Clinical trial number

Not applicable.

Ethics approval and consent to participate

The Ethics Committee of the First Clinical Medical College of Nanjing Medical University (2024-SR-615) approved this retrospective study and waived the requirement for informed consent because the research used anonymized data and posed minimal risk to participants.

Patient consent for publication

Not applicable. The need for obtaining consent for publication was waived by the Ethics Committee of the First Clinical Medical College of Nanjing Medical University (2024-SR-615) as the study used retrospectively collected and fully anonymized data.

Availability of Data and Materials

The data and analysis results of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Authors' Contributions

Zhonghua Zhang: Conceptualization, Data curation, Writing-original draft.
Lijun Zhu: Writing-original draft.
Xiaodong You: Formal analysis, Data curation.
Wen Jiang: Writing-original draft.
Chengan Zhang: Writing-original draft.
Ting Wang: Writing-review & editing, Supervision, Project administration.
Yanhong Gu: Writing-review & editing, Supervision, Resources.

All authors made a significant contribution to the work reported; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Figures

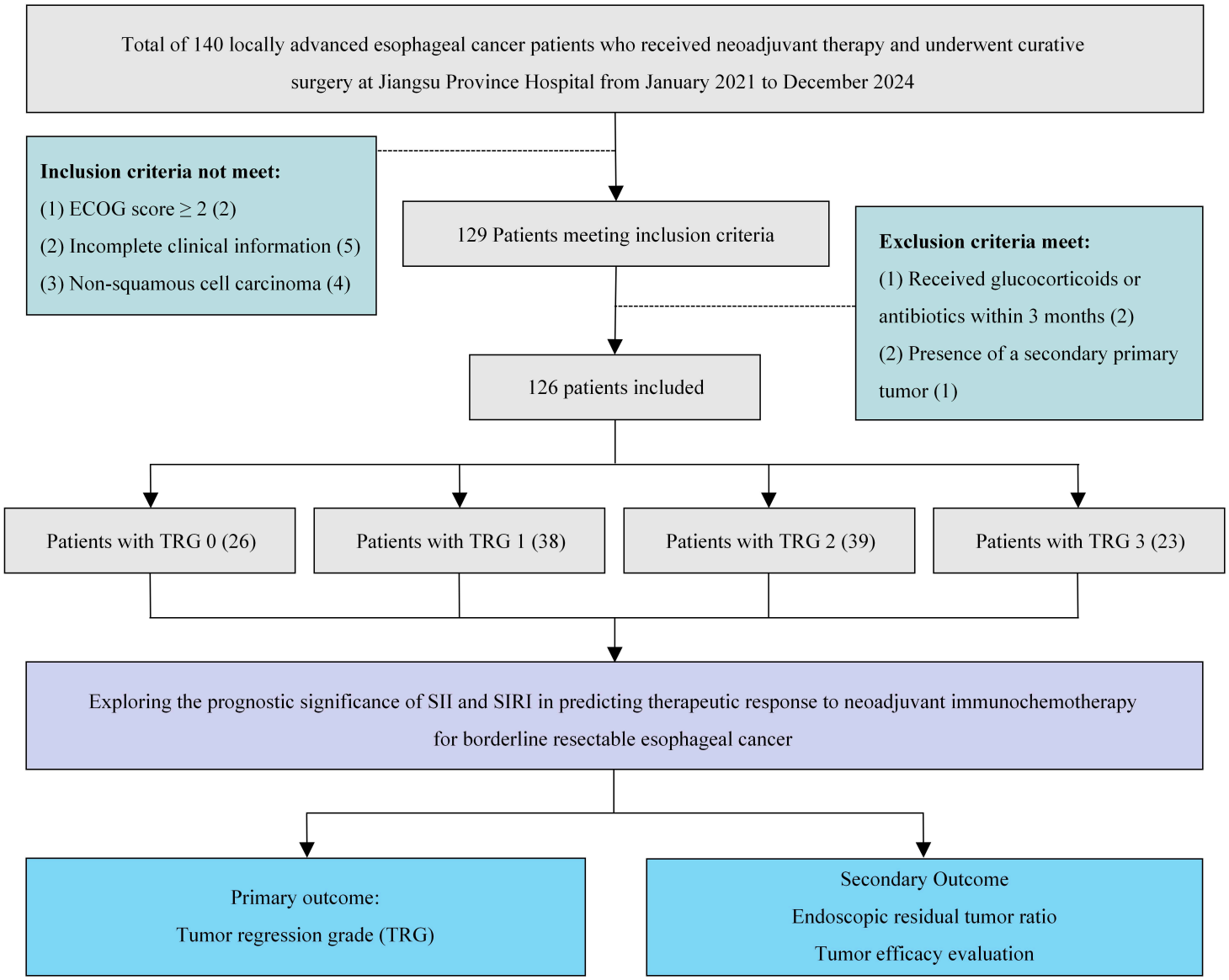


Figure 1

Flowchart of the study population.

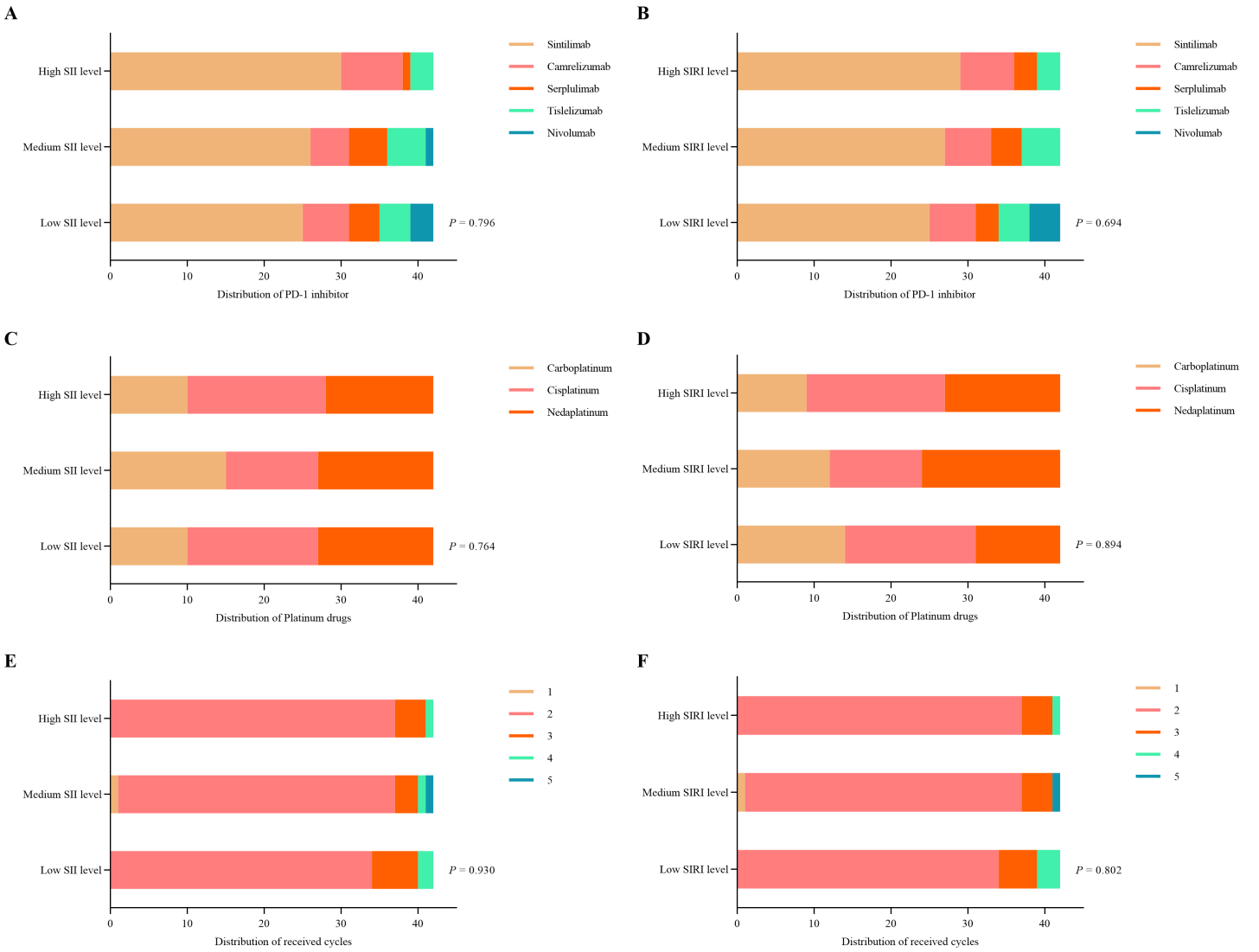


Figure 2

Distribution of treatment regimens across SII and SIRI tertile groups. (A–B) Distribution of PD-1 inhibitor types. (C–D) Distribution of platinum-based drug types. (E–F) Distribution of the number of treatment cycles received.

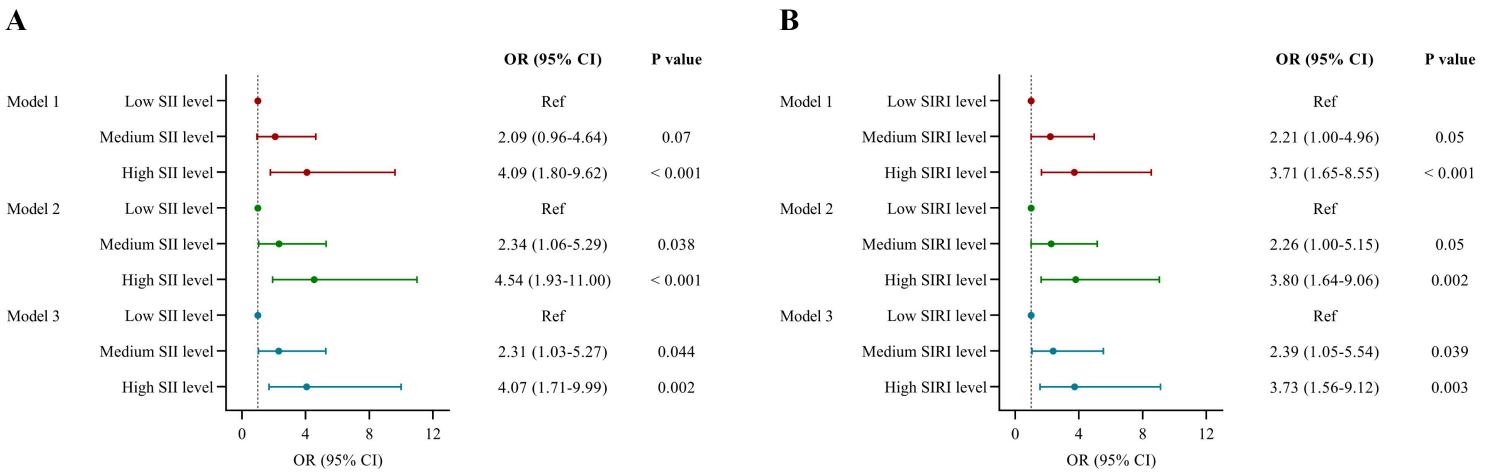


Figure 3

Univariable and multivariable ordinal logistic regression analysis for tumor response assessment. (A) SII relative analysis. (B) SIRI relative analysis.

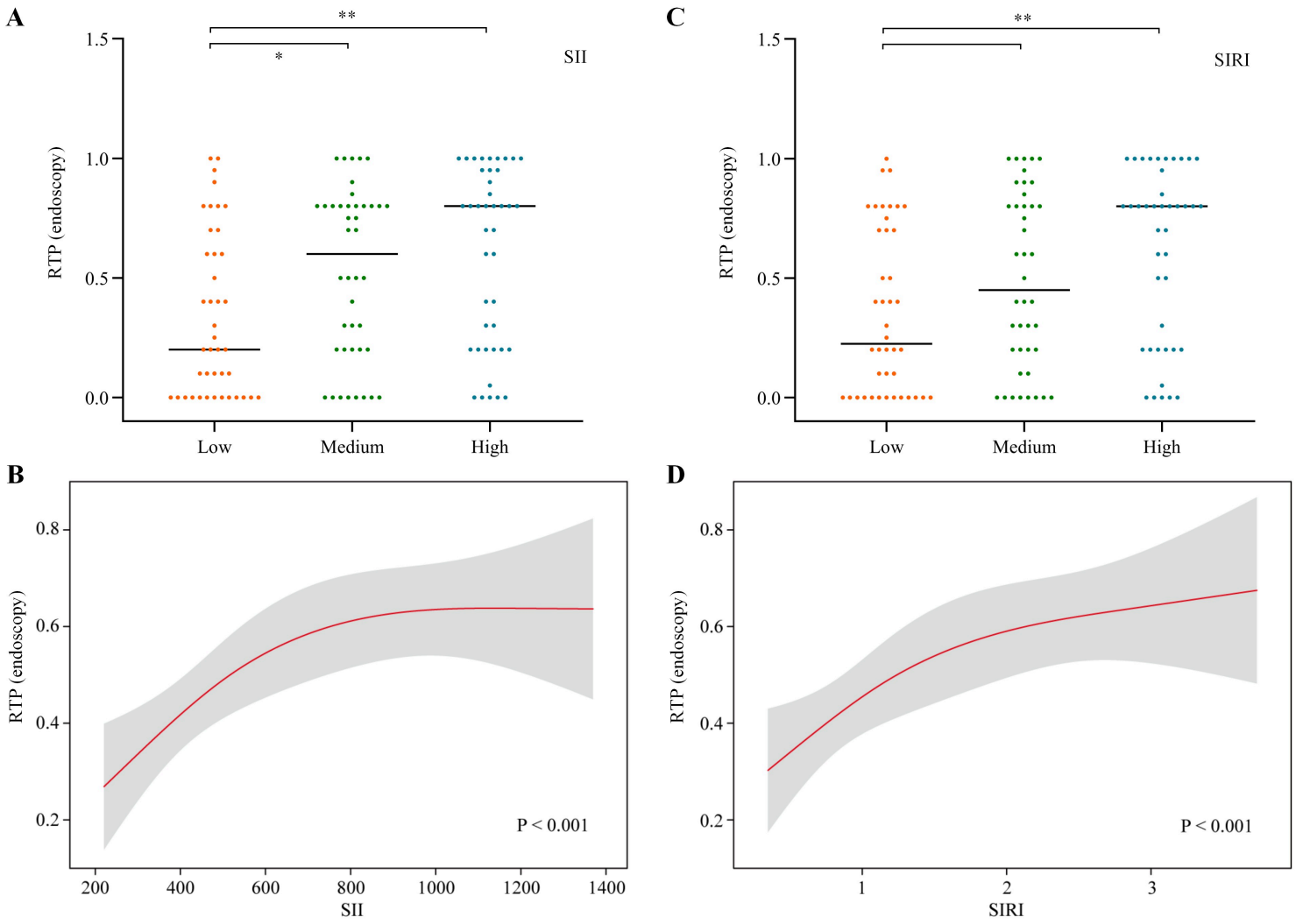


Figure 4

Correlation analysis between RTP and SII/SIRI. (A) Intergroup RTP comparison of SII-based tertile groups. (B) Nonlinear correlation between SII and RTP. (C) Intergroup RTP comparison of SIRI-based tertile groups. (D) Nonlinear correlation between SIRI and RTP.

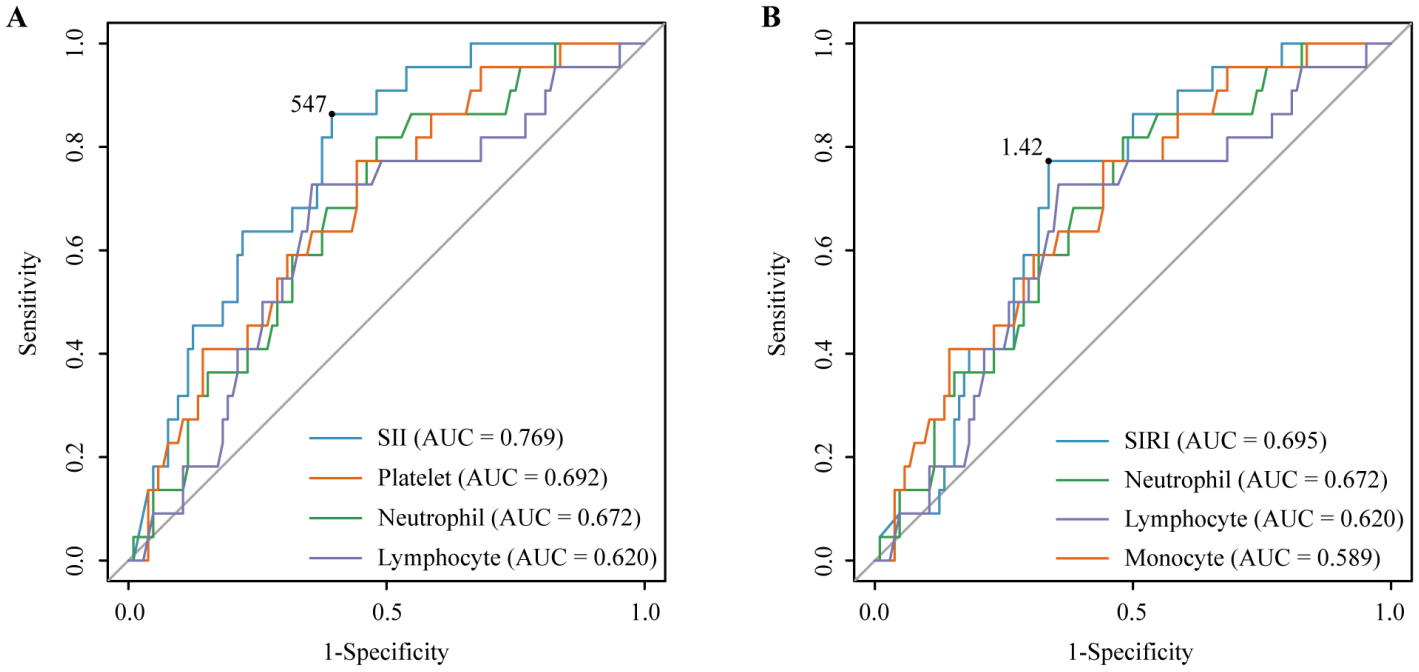


Figure 5

ROC curves for SII, SIRI and relative indices. (A) ROC curves for SII, platelet, neutrophil and lymphocyte. (B) ROC curves for SIRI, monocyte, neutrophil and lymphocyte.

Supplementary Files

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