Systemic immune-inflammation index in predicting non-curative resection of endoscopic submucosal dissection in patients with early gastric cancer

Yun-he Tang, Lin-lin Ren, Ya-Nan Yu, Shao-hua Zhang, Zi-Bin Tian and Tao Mao

Background and purpose Although endoscopic submucosal dissection (ESD) is considered standard treatment for early gastric cancer (EGC), patients with non-curative resection (NCR) of ESD may still require gastrectomy. The systemic immune-inflammation index (SII) showed great potential in predicting the prognosis of gastric cancer patients. This study aims to investigate the predictive validity of SII of NCR in EGC patients.

Methods We reviewed data from EGC patients who underwent ESD in the past. The relationship between SII and clinicopathologic features was investigated. We used Receiver operating characteristic curves to compare the predictive values of NCR between SII and other inflammation indices. Binary logistic analysis was used to identify independent risk factors for NCR. These factors were then used to construct a predictive nomogram.

Results SII was associated with larger tumor size, male gender, older age, submucosal invasion, and a greater risk of NCR. SII showed better predictivity of NCR than platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR). SII [odds ratio (OR) = 1.003, $P = 0.001$], NLR (OR = 1.520, $P = 0.029$), PLR (OR = 1.009, $P = 0.010$), upper stomach tumors (OR = 16.393, $P < 0.001$), poorly differentiated type (OR = 29.754, $P < 0.001$), ulceration (OR = 4.814, $P = 0.001$), and submucosal invasion (OR = 48.91, $P < 0.001$) were independent risk factors for NCR. The nomogram model based on these factors exhibited superior concordance and accuracy.

Conclusion SII could be considered a simple and effective predictor of NCR of ESD in EGC patients. Eur J Gastroenterol Hepatol 35: 376–383

Introduction

Early gastric cancer (EGC) is defined as gastric cancer confined to the mucosa or submucosa, regardless of the presence or absence of lymph node metastasis. With improvements in endoscopic technology in recent years, endoscopic submucosal dissection (ESD) has become the standard treatment for EGC because it preserves gastric function, causes less trauma, and shortens hospital stays [1]. The 5-year overall survival (OS) rate for EGC patients who underwent curative resection was over 90% [2]. However, ESD can only be as effective as surgery under the condition that a curative resection is performed. According to previous studies, there are still 24.6–39.5% of patients with non-curative resection (NCR) [3–5] who face the risk of local recurrence and lymph node metastasis and may require additional gastrectomy. Previous studies have identified tumor size, depth of infiltration, gender, presence of ulceration, certain endoscopic findings, and postoperative pathologic results as independent risk factors for NCR [6,7]. However, the features listed above were either lacking in specificity or could only be obtained after the ESD procedure. A simple and objective indicator to help endoscopists assess the risk of NCR before ESD and choose the most suitable treatment for patients individually has yet to be discovered.

Studies have shown that inflammation plays a significant role in carcinogenesis, tumor invasion, and migration [8,9]. Some inflammation indices, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been shown to have great prognostic value in various cancer patients [10,11]. The systemic immune-inflammation index (SII), an inflammation index based on platelet, neutrophil, and lymphocyte, has been shown to be more accurate than other inflammation indices in predicting the prognosis of gastric cancer patients [12]. However, the majority of studies on SII focused on patients with advanced gastric cancer who underwent gastrectomy, whereas the efficacy of SII in predicting the prognosis and NCR risk of EGC patients remains to be determined [13]. Therefore, we conducted a retrospective analysis of the predictive value of SII for NCR of EGC patients.

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Keywords: early gastric cancer, endoscopic submucosal dissection, non-curative resection, systemic immune-inflammation index

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Materials and methods

Patients

We reviewed data from patients who underwent ESD at the Department of Gastroenterology, Affiliated Hospital of Qingdao University between October 2013 and March 2021. Inclusion criteria included gastric adenocarcinoma confirmed by postoperative histopathology; availability of all clinical and pathologic data; and no prior chemotherapy, radiotherapy, or immunosuppressive treatment.

Patients were excluded if any of the following conditions were met: history of other malignant tumors; history of gastrectomy due to gastric carcinoma; and clinical evidence of infection, cardiovascular disease, or systemic inflammatory disease. The study design is shown in Fig. 1.

Data collection

The following data were collected from our hospital's medical record database: age, sex, expense and length of hospitalization, endoscopic features (tumor location, tumor size, and gross type), pathologic features (depth of invasion, lymphatic invasion, vascular invasion, horizontal margin, vertical margin, histological type, and tumor differentiation), preoperative serum carcinoembryonic antigen (CEA), neutrophil count, lymphocyte count, and platelet count. Preoperative blood samples (neutrophil, lymphocyte, mono, and platelet) were collected within 7 days prior to ESD. SII was calculated using the formula platelet × neutrophil/lymphocyte (10^9/L). PLR and NLR were calculated using the formulas platelet/lymphocyte and neutrophil/lymphocyte, respectively. Cutoff values for age, tumor size, and CEA were set according to previously published studies.

Written consent was obtained from all patients prior to ESD. This study was approved by the ethics committee of the Affiliated Hospital of Qingdao University.

Endoscopic submucosal dissection

The ESD procedure involves marking the surrounding area of the lesion, submucosal injection of saline solution to lift the lesion, circumferential incision around the marking sites, and submucosal dissection. All ESD procedures were performed by a senior endoscopist with experience in over 100 gastric ESDs or by a junior endoscopist under the supervision and guidance of an experienced senior endoscopist. The main device used for ESD was the FLUSH knife (Olympus, Tokyo, Japan).

Gross and pathologic evaluation

According to the Japanese Gastric Cancer Association Classification, lesions were categorized into three types (elevated, depressed, and flat) [14]. Endoscopically tumor size and location were also observed and reported. Before a general histological assessment, each specimen was fixed in 10% formalin and serially sectioned at 2 mm intervals. Before general assessment, all slides were stained with hematoxylin-eosin, which included the depth of invasion, lesion size, lymphatic and vascular invasion, and tumor involvement on lateral and vertical margins. Well-differentiated adenocarcinoma (tub1) or moderately differentiated adenocarcinoma (tub2) was defined as the differentiated type, whereas poorly differentiated adenocarcinoma (por) or signet ring carcinoma (sig) was defined as the undifferentiated type [1]. EGC with a mixture of differentiated and undifferentiated type components was classified based on the histological predominance.

Evaluation of resection efficacy

En-bloc resection is defined as the removal of a lesion in a single piece without any fragments (complete resection is achieved when histopathological examination confirms that a tumor is free of horizontal and vertical margin invasion after an en-bloc resection). According to the guidelines published by the Japanese Gastric Cancer Association (JGCA), curative resection is defined as en bloc resection without evidence of margin invasion or lymphatic/vascular involvement. The criteria are as follows: predominantly differentiated type, regardless of size, pT1a, without ulceration; predominantly differentiated type, ≤3 cm, pT1a, with ulceration; predominantly undifferentiated type, pT1a, ≤2 cm, without ulceration;

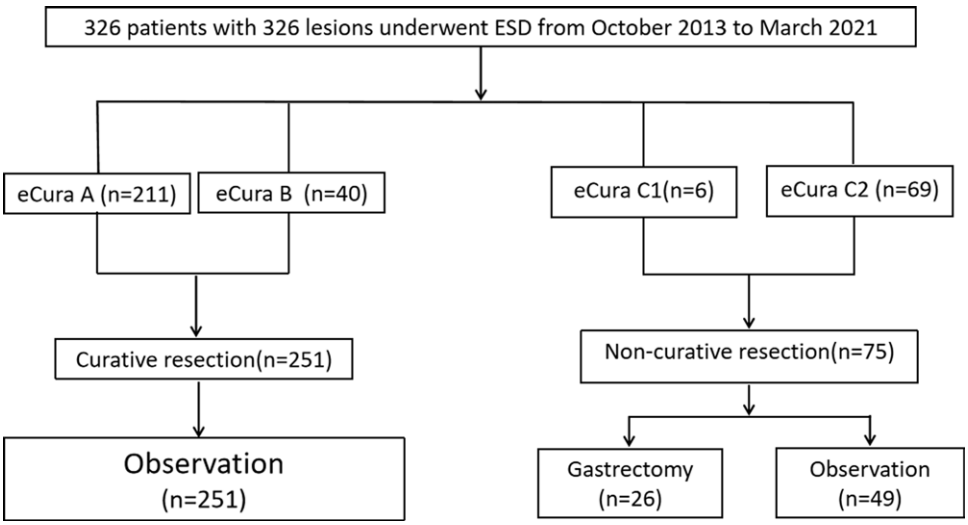

Fig. 1. Study design. A total of 326 patients, including both the curative and non-curative resection groups, were reviewed retrospectively.

and predominantly differentiated type, tumor size ≤3 cm, pT1b (SM1, <500 µm from the muscularis mucosa). NCR is defined as the failure of resection to meet any of the above criteria [1]. The endoscopic curability of patients was also divided into endoscopic curability A (eCura A), endoscopic curability B (eCura B), and endoscopic curability C (eCura C) according to the guideline of JGCA to help decide whether additional gastrectomy should be performed after NCR. All patients that were rated as eCura C were advised to receive surgical treatment.

Statistical analysis

Continuous variables are presented as the mean ± SD. Categorical variables are represented as numbers with percentages. The area under the receiver operating characteristic (ROC) curve (AUC) was used to investigate the prognostic value of SII, PLR, and NLR. The Youden Index was used to determine the optimal cutoff values for SII, PLR, and NLR. A χ^2 test was used to categorize the factors associated with the NCR of ESD in a univariate analysis. Variables with $P < 0.05$ were further included in the multivariate analysis using a binary logistic analysis to identify independent risk factors for NCR. Following that, a nomogram was constructed based on the logistic regression influence factors. Validation of this nomogram included evaluation of discrimination and calibration. We applied the concordance index and the AUC to assess the discriminative ability of the nomogram. The AUC was calculated by running the predictive model through a ROC curve. The AUC or concordance index of 0.5 indicates that the model has no predictive effect, while the AUC or concordance index of 1.0 indicates that there is perfect concordance between the actual results and those predicted by the model. Calibration was carried out using the bootstrap method, which consisted of 1000 bootstrap sample corrections. Variables with $P < 0.05$ were considered statistically significant. All the calculations were carried out using the latest version of SPSS software, version 26.0 (SPSS, Chicago, Illinois, USA). The nomogram was constructed and validated using R Software 4.0.4 (www.r-project.org).

Results

Baseline characteristics and follow-up data

A total of 326 patients who underwent ESD were enrolled, with 232 being male and 94 female. The average age was 63 years (ranging from 39 to 91 years). The number of curative resections was 251 (76.99%). Among the 75 patients (23.01%) who were unable to undergo curative resection, 3 were not resected en bloc. Twenty-six patients underwent additional gastrectomy within 3 months of ESD, the rest 49 patients refused to undergo additional treatment of any kind. Recurrence was detected in 1 patient 4 years after ESD, and no sign of local recurrence or tumor metastasis was observed in the rest 48 patients until March 2021.

Receiver operating characteristic analysis

The ROC analysis was conducted to determine the optimal cutoff value for each inflammation index, with non-curative resection serving as the endpoint. The optimal cutoff value for each index with the highest sensitivity and specificity was 1.21, 140, and 414.8 for NLR, PLR, and SII, respectively: (sensitivity and specificity: 0.918 and 0.249, 0.425 and 0.775, and 0.562 and 0.648 for NLR, PLR, and SII, respectively). And patients were grouped based on the SII cutoff value for further investigation [SII ≤ 414.8 (low) and SII > 414.8 (high)]. Figure 2 shows the ROC curve for each index.

Comparison between inflammation indices

The AUC was used to compare the prognostic value of all inflammation indices for non-curative resection. The AUC for non-curative resection of SII, NLR, and PLR was 0.611, 0.602, and 0.593, respectively (sensitivity: 0.918, 0.425, and 0.562, and specificity: 0.249, 0.775, and 0.648 for NLR, PLR, and SII, respectively), indicating that the prognostic value of SII for NCR is superior to that of NLR and PLR.

Relationship between preoperative systemic immune-inflammation index and clinicopathological factors

As shown in Table 1, the high SII group was more prone to developing a non-curative resection than the low SII group. ($X^2 = 10.832$, $P = 0.001$). A higher SII was also correlated with larger tumors, male gender, older age, submucosal invasion, a higher eCura grade, and larger hospital expenses. The difference was statistically significant ($P < 0.05$). There was no between-group difference in tumor localization, ulceration, differentiation, or gross type, which is consistent with previous studies [12,15].

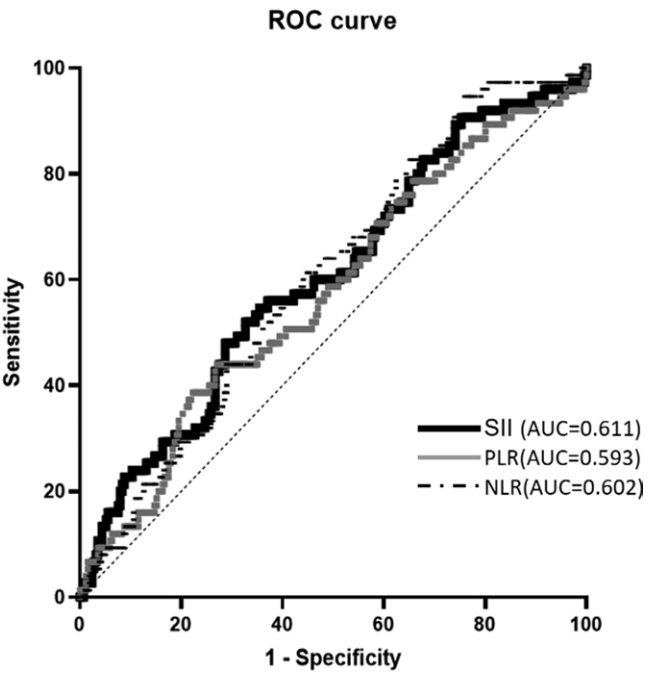

Fig. 2. ROC curves for SII, PLR, and NLR. AUC, area under the receiver operating characteristic (ROC) curve; PLR, platelet-to-lymphocyte ratio; NLR, lymphocyte ratio; SII, systemic immune-inflammation index.

Prognostic significance of preoperative systemic immune-inflammation index for non-curative resection

According to univariate analysis, patients with non-curative resection were more likely to have larger tumors, a poorly differentiated histological type, elevated CEA, PLR, SII, and NLR levels, and an increased risk of submucosal infiltration than patients with curative resection. Patients who underwent non-curative resection had a high tendency to develop upper stomach tumors [6,16]. As for the multivariate analysis, we found that higher SII [odds ratio (OR) = 1.003, $P = 0.001$], PLR (OR = 1.009, $P = 0.019$), NLR (OR = 1.043, $P = 0.029$), larger tumor size (OR = 2.055, $P < 0.001$), tumor on the upper third of the stomach (OR = 16.393, $P < 0.001$), poorly differentiated type (OR = 29.754, $P < 0.001$), ulceration (OR = 4.814, $P = 0.001$), and submucosal invasion (OR = 48.91, $P < 0.001$) were associated with NCR and could be considered as the independent risk factors (Table 2).

The nomogram for non-curative resection prediction

The nomogram was built using independent variables derived from the binary logistic regression (SII, tumor size, location, ulceration, pathology, and depth of invasion). Since the depth of invasion can only be identified through pathological examination after ESD while all other four

Table 1. The relationship between preoperative systemic immune-inflammation index and clinicopathological features

Parameters	Number (%)	Low SII < 414.87	High SII ≥ 414.87	χ^2	*P*
Cases (*n*)	326	*n* = 197	*n* = 129		
Age				0.356	0.551
>65	133 (40.8)	87	46		
<65	193 (59.2)	120	73		
Sex				4.457	0.035
Male	232 (71.2)	139	93		
Female	94 (28.8)	68	26		
Location				0.126	0.939
Upper 1/3	29 (8.9)	18	11		
Middle 1/3	129 (39.6)	79	50		
Lower 1/3	168 (51.5)	100	68		
Size				6.165	0.013
>3cm	43 (13.2)	20	23		
<3cm	280 (86.8)	187	96		
CEA (ng/mL)				4.883	0.057
>2.34	113 (34.7)	59	54		
<2.34	213 (65.3)	138	75		
Differentiation				0.671	0.715
Poorly differentiated	71 (21.8)	40	31		
Moderately differentiated	136 (41.7)	83	53		
Well differentiated	119 (36.5)	74	45		
Depth of invasion				5.069	0.024
Mucosa	267 (81.9)	169	98		
Submucosa	59 (18.1)	28	31		
Gross type				3.550	0.169
Elevated	164 (50.3)	101	63		
Flat	19 (5.8)	9	10		
Depressed	143 (43.9)	97	46		
BMI ($kg \cdot m^2$)				0.694	0.405
<25	196 (60.1)	128	68		
>25	130 (29.9)	79	51		
Sex				4.457	0.035
Male	232 (71.2)	139	93		
Female	94 (28.8)	68	26		
Ulceration				0.023	0.880
Yes	39 (12.0)	24	15		
No	287 (88.0)	173	114		
PLR					
<140.08	240 (73.6)	180	60	80.772	<0.001
>140.08	86 (26.4)	17	69		
NLR					
<1.21	69 (21.2)	68	1	53.192	<0.001
>1.21	257 (78.8)	129	128		
Hospital stay (days)				0.201	0.654
<7	197 (60.4)	133	64		
>7	129 (39.6)	84	45		
Hospital expense (CHY)				5.763	0.016
<28688	196 (60.1)	142	54		
>28688	130 (39.9)	78	52		
Curability of endoscopic resection (eCura)				9.815	0.007
A	211 (64.7)	144	67		
B	40 (12.3)	26	14		
C	75 (23.0)	36	39		
Non-curative resection				9.663	0.002
Yes	251 (76.9)	170	81		
No	75 (23.1)	36	39		

CNY, Chinese Yuan; NLR, lymphocyte ratio; SII, systemic immune-inflammation index.

Table 2. Comparative multivariate analysis of curative resection and non-curative resection

	Multivariate analysis			
Parameters	OR	95% CI		*P* value
Tumor size (cm)	2.055	1.563	2.701	<0.001
CEA	1.083	0.911	1.289	0.366
SII	1.003	1.001	1.004	0.001
PLR	1.009	1.001	1.016	0.019
NLR	1.520	1.043	2.215	0.029
Location				
Lower 1/3	1			
Middle 1/3	1.082	0.513	2.280	0.836
Upper 1/3	16.393	5.035	53.377	<0.001
Differentiation				
Well differentiated	1			
Moderately differentiated	1.627	0.649	4.080	0.300
Poorly differentiated	29.754	10.655	83.090	<0.001
Ulceration				
No	1			
Yes	4.814	1.846	12.566	<0.001
Infiltration depth				<0.001
Mucosa	1	17.383	149.728	
Submucosa	51.017			

CEA, carcinoembryonic antigen; CI, confidence interval; NLR, lymphocyte ratio; OR, odds ratio; SII, systemic immune-inflammation index.

variables could be obtained during the evaluation before ESD, it was excluded when constructing this nomogram. Each variable was assigned a score on a point scale ranging from 0 to 100, and a total score for the prediction of NCR was calculated by adding the scores that each variable corresponds to (Fig. 3). The total points subsequently could be used to predict the probability of NCR by applying a vertical line to the 'Risk of NCR' scale as shown in Fig. 3. We also created a scoring table that combines all five variables to simplify this scoring system (Table 3). A calibration curve generated using the bootstrap method for internal validation (repetition of sample correction = 1000) demonstrated a high degree of concordance between the deviation correction prediction and the ideal interface line (Fig. 4). The AUC (95% confidence interval) of the ROC curve (Fig. 5) for discrimination evaluation was 0.858, and the concordance index of this nomogram was 0.942.

Discussion

Inflammation, as one of the 10 hallmarks of cancer, has been linked to tumor growth, invasion, and metastasis [17]. Inflammatory cells such as neutrophils, platelets, and lymphocytes engage in this process through various pathways. As the most common kind of leukocyte in circulating blood, neutrophils were believed to be a protective factor against tumor invasion in most cases. However, recent studies have shown that a subset of neutrophils known as tumor-associated neutrophils can promote tumor growth and metastasis by secreting cytokines and chemokines such as matrix metalloproteinase-9, vascular endothelial growth factor, and hepatocyte growth factor [18–20]. They can also produce neutrophil extracellular traps to act as a carrier of circulating tumor cells, thereby facilitating tumor metastasis [19]. Platelets have also been shown to have pro-metastatic functions. Besides protecting tumor cells from natural killer cell attack, they can also promote epithelial to mesenchymal transition, which enhances the motility and aggressiveness of tumor cells and hence accelerates tumor metastasis [21,22]. Lymphocytes, as our primary weapon against tumor growth and invasion, may reflect our ability to combat cancer [23].

Numerous studies have shown that inflammation indices such as PLR and NLR are prognostic factors in a variety of cancers, including gastric cancer. SII, as a

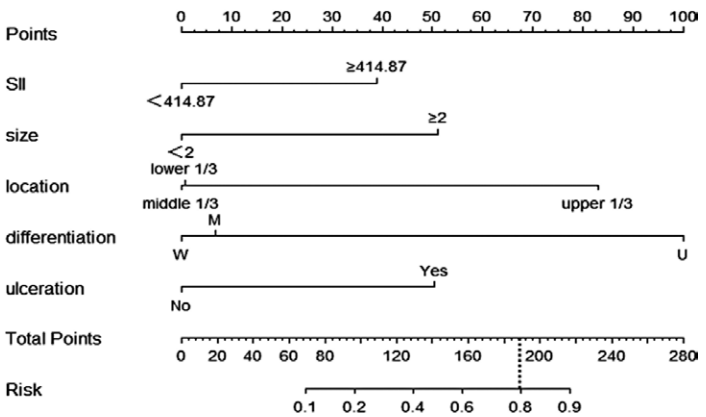

Fig. 3. Nomogram for predicting non-curative resection in EGC patients undergoing ESD. EGC, early gastric cancer; ESD, endoscopic submucosal dissection; M, moderately differentiated adenocarcinoma; P, poorly differentiated adenocarcinoma; SII, systemic immune-inflammation index; W, well-differentiated adenocarcinoma.

Table 3. The scoring table based on the nomogram, the total points could be utilized to estimate the chance of non-curative resection in the nomogram

SII				
	<414.87		>414.87	Points
	0		39	
Size	<2cm		>2cm	Points
	0		51	
ulceration	Yes		No	Points
	0		55	
location	Middle1/3	lower1/3	upper1/3	Points
	0	1	82.5	
Differentiation	Well differentiated	Moderately differentiated	Poorly differentiated	Points
	0	7.5	100	
Total points				

SII, systemic immune-inflammation index.

combination of these three inflammation cells, represents the overall balance of immune and inflammatory responses of cancer patients. An elevated SII may indicate a decline in the immune system's anti-tumor function or an increase in systemic inflammatory responses. Eventually, the balance between immune and inflammatory response is disrupted, leading to the promotion of carcinogenesis and tumor metastasis. Multiple studies have demonstrated that the prognostic value of SII in gastric cancer patients is superior to PLR and NLR [12]. A recent study found that, when compared to PLR and NLR, SII was a better predictor of OS in patients with stage I–II gastric cancer, especially stage II patients undergoing gastrectomy [24]. Such findings confirmed that even in the early stages of cancer, patients with a higher systemic inflammatory response, as manifested by an elevated SII, were more likely to have a more aggressive clinical course and less-conducive prognosis. Therefore, it became reasonable to hypothesize that a higher SII in EGC patients could indicate a higher risk of NCR. To validate our hypothesis, we conducted a retrospective study to establish a correlation between SII and NCR in EGC patients.

We found that higher SII was associated with larger tumors, male gender, and submucosal infiltration, which was consistent with previous studies [13,25]. Although the presence of ulcers was found to be one of the independent factors for NCR, SII did not correlate with them. Furthermore, no significant difference was found in the length of stays, gross type, or differentiation between high and low SII groups, but higher SII did correlate with higher health expenses. We also discovered that patients with higher SII were more likely to receive NCR, suggesting that SII could act as a potential prognostic factor for NCR in EGC patients.

We used ROC analysis to compare the prognostic value of various inflammation indices for NCR. The AUC of SII was 0.611, which was higher than that of PLR (0.593) and NLR (0.602), suggesting that SII was a superior indicator of NCR among them. However, the difference in AUC between these parameters was not as distinct as in the former study, implying that this result may still need to be validated by further investigation.

Our multivariate analysis demonstrated that upper stomach tumors, poorly differentiated types, and the presence of ulceration were associated with NCR, which is consistent with previous studies [6,7]. However, in this study, we did not identify old age and females as independent NCR risk factors. Whether or not these features are effective at predicting NCR is still debatable, as they may be influenced by sample size and selection bias. CEA, a traditional tumor marker that often shows no sign of increase in the early stages of cancer, was found to be incapable of predicting NCR. What's interesting is that we identified SII, PLR, and NLR as being associated with NCR. To our knowledge, this is the first time an inflammation index has been identified as an independent risk factor for NCR in EGC patients. Unlike traditional tumor markers such as CEA, which are typically elevated only in the advanced stages of cancer, our study found that an increase in SII could be detected in the early stages of cancer, exposing patients to a state of growing proliferation

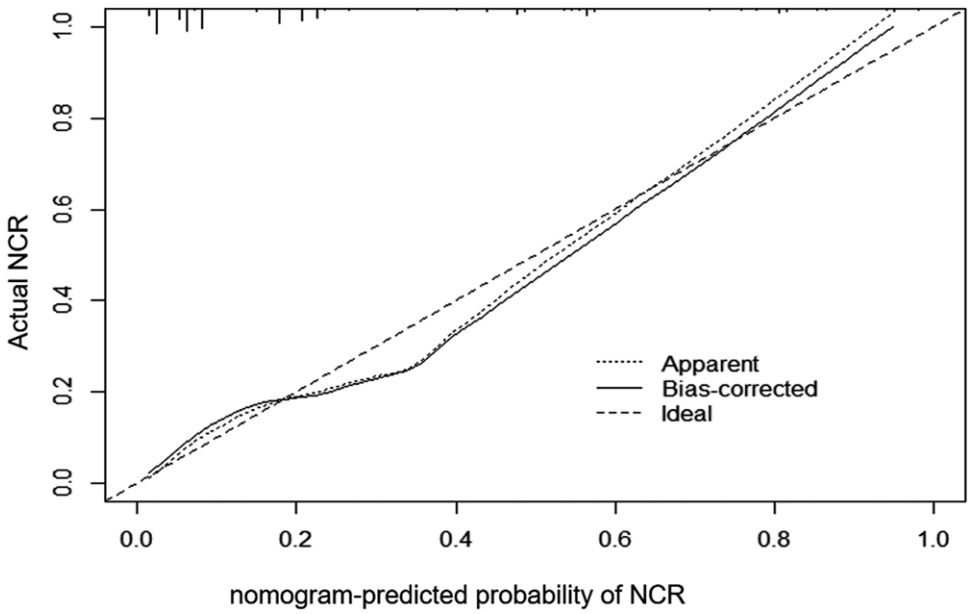

Fig. 4. Calibration curve of the nomogram. NCR, non-curative resection.

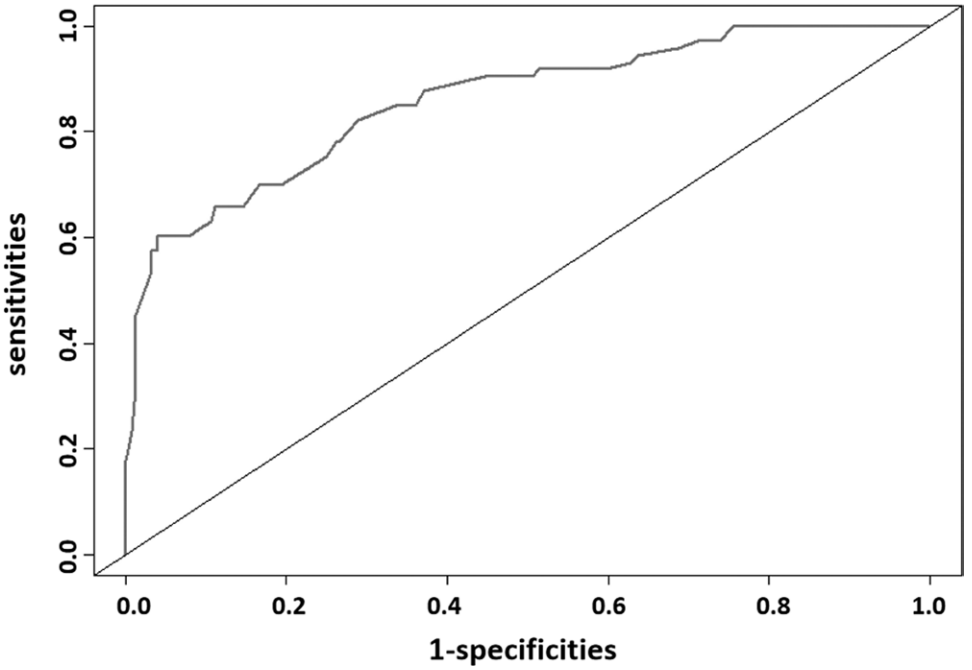

Fig. 5. ROC curve for the nomogram. Area under the ROC curve (AUC) = 0.8578. ROC, receiver operating curve.

and metastasis. Therefore, it could be used as a predictor of NCR in EGC patients.

In recent years, the nomogram has gradually evolved into an effective and promising tool for predicting the prognosis of gastric cancer patients [26–28]. Additionally, nomograms involving inflammation indices were not uncommon. Shi *et al.* established a nomogram based on SII that demonstrated better accuracy in predicting the OS of gastric cancer patients undergoing gastrectomy than the American Joint Committee on Cancer staging system [29]. Ma *et al.* constructed a nomogram that demonstrated superior discriminative ability when predicting NCR for patients undergoing ESD/EMR compared to traditional risk score models [6]. In this study, we constructed a predictive nomogram model that incorporated SII and found it to have satisfactory concordance and accuracy after validation. Compared to Ma *et al.*, our model had better discriminative ability (area under the ROC, 0.931; $P < 0.05$), suggesting that our model could help endoscopists make decisions for EGC patients. It is worth mentioning that all information required to build this nomogram can be obtained before the ESD procedure, which enables endoscopists to choose whether to perform ESD or surgery based on the probability of NCR that was calculated using the nomogram. When the total score of the patients exceeds 234, the probability of NCR if ESD is performed rises to nearly 90%. In this case, it would probably be safer for these patients to receive surgical treatment instead of ESD according to the JGCA guideline, especially when the lesion is undifferentiated.

This study has limitations as well. First, because this is a retrospective, single-center study, selection bias might have influenced our results. The prognostic value of SII needs to be verified by multi-center prospective studies. Second, due to the lack of data, we did not include the surrounding mucosa of EGC before ESD in our study, though certain endoscopic findings such as fusion of fold, nodularity, and spontaneous bleeding were found to be predictors of NCR. Third, although SII was an independent predictor of NCR and outperformed NLR and PLR, its sensitivity and specificity were not very high, and prospective studies are still needed to determine a proper SII cutoff value. Fourth, due to a lack of data, we only performed internal validation for our nomogram model; external validation involving a larger number of patients from multiple medical centers is still pending.

Conclusion

We identified preoperative SII, which was superior to inflammation indices such as NLR and PLR, as an independent predictor of NCR of EGC patients who underwent ESD. The nomogram containing SII could serve as a reliable and effective prediction model for non-curative resection following ESD.

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Conflicts of interest

There are no conflicts of interest.

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