The prognostic value of preoperative inflammation-based prognostic scores and nutritional status for overall survival in resected patients with nonmetastatic Siewert type II/III adenocarcinoma of esophagogastric junction

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Abstract

Background: Immune and nutritional status of patients have been reported to predict postoperative complications, recurrence, and prognosis of patients with cancer. Therefore, this retrospective study aimed to explore the prognostic value of preoperative inflammation-based prognostic scores [neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR)] and nutritional status [prognostic nutritional index (PNI), body mass index (BMI), hemoglobin, albumin, and prealbumin] for overall survival (OS) in adenocarcinoma of esophagogastric junction (AEG) patients.

Methods: A total of 355 patients diagnosed with Siewert type II/III AEG and underwent surgery between October 2010 and December 2011 were followed up until October 2016. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff values of NLR, PLR, and PNI. Kaplan–Meier curves and Cox regression analyses were used to calculate the OS characteristics.

Results: The ideal cutoff values for predicting OS were 3.5 for NLR, 171 for PLR, and 51.3 for PNI according to the ROC curve. The patients with hemoglobin <120 g/L ($P=.001$), prealbumin <180 mg/L ($P=.000$), PNI <51.3 ($P=.010$), NLR >3.5 ($P=.000$), PLR >171 ($P=.006$), and low BMI group ($P=.000$) had shorter OS. And multivariate survival analysis using the Cox proportional hazards model showed that the tumor-node-metastasis stage, BMI, NLR, and prealbumin levels were independent risk factors for the OS.

Conclusion: Our study demonstrated that preoperative prealbumin, BMI, and NLR were independent prognostic factors of AEG patients.

Abbreviations: AEG = adenocarcinoma of esophagogastric junction, AUC = area under the curve, BMI = body mass index, CT = computed tomography, EGJ = esophagogastric junction, GC = gastric cancer, NLR = neutrophil-lymphocyte ratio, OS = overall survival, PLR = platelet-lymphocyte ratio, PNI = prognostic nutritional index.

Keywords: adenocarcinoma of esophagogastric junction, neutrophil-lymphocyte ratio, overall survival, platelet-lymphocyte ratio, prognostic nutritional index

1. Introduction

Gastric cancer (GC) is the second most prevalent malignant tumors worldwide and has a high mortality.[1] The adenocarcinoma of the esophagogastric junction (AEG), as one of special clinical disease with unique clinicopathological characteristic and biological behavior, was initially proposed in 1999 by Siewert.[2] According to the location of tumor epicenter, Siewert classified AEG into 3 subgroups, type I is esophageal cancer located 1 to 5 cm above the esophagogastric junction (EGJ), which is correlative with the occurrence of gastroesophageal reflux and Barrett esophagus; types II and III AEG are more common than type I and they are mostly treated as GC.[3,4] During recent decades, the incidence and prevalence of AEG were arising globally.[5–7] The reason was still unclear. Despite the improvements in multiple treatment strategies, the prognosis of AEG remains poor.[8]

In the clinic, electronic gastroscope, computed tomography (CT), and endoscopic ultrasonography are important methods to diagnose GC and judge the disease progression, but the value of these techniques are limited by its cost, risk, and inconvenience. Therefore the development of noninvasive and sensitive index that can accurately evaluate the prognosis of GC would be beneficial, among them, immune and nutritional status of patients have been reported to predict postoperative complications, recurrence, and prognosis.[9–12] Related studies have shown that the presence of malnutrition and systematic inflammatory response can cause shorter survival and higher possible complications in patients with malignancy.[13,14] The

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indexes of systemic inflammatory and nutritional scores include neutrophil-lymphocyte ratio (NLR),[15,16] platelet-lymphocyte ratio (PLR),[17,18] prognostic nutritional index (PNI),[19,20] body mass index (BMI),[21] hemoglobin,[22] albumin,[23–25] and prealbumin,[26,27] and they can get easily and conveniently before surgery. However, the value of these indexes for prediction of overall survival (OS) in AEG patients is still unclear. To our best knowledge, there are few studies that had republished to access the prediction of these indexes for OS in AEG patients.

Therefore, this retrospective study aimed to explore the prognostic value of preoperative inflammation-based prognostic scores (NLR, PLR) and nutritional status (PNI, BMI, hemoglobin, albumin, and prealbumin) for OS in AEG patients.

2. Materials and methods

2.1. Patients

Clinicopathological data of 355 patients, who were diagnosed as Siewert type II/III AEG based on postoperative pathology in the First Affiliated Hospital of Anhui Medical University between October 2010 and December 2011, were analyzed retrospectively in this study; all patients received the preoperative peripheral blood tests, including neutrophil, lymphocyte, platelet, hemoglobin, albumin, and prealbumin. In addition, complete clinicopathological characteristics including age, sex, height, weight, tumor location, differentiation grade, tumor size, invasion depth, lymph node metastasis, the surgery time, and tumor-node-metastasis (TNM) stage were also recorded in our study.

2.2. Inclusion and exclusion criteria

Before surgery, endoscopy and barium swallows were performed to help diagnose Siewert type, CT, and magnetic resonance imaging examinations were used to determine the clinical stage. The eligibility criteria included the following: the clinical information of AEG patients was complete; they had no heart disease or other important organ dysfunction; the need of surgery was definite.

Exclusion criteria from the study included the following conditions: the patient had previous malignant tumors or multiple primary cancers; the patient had received radiotherapy or chemotherapy before the operation; the patients had some disease, which can affect the counting of peripheral blood cells, such as liver cirrhosis, infection, and so on; the patient died within 30 days after surgery in the process of follow-up.

2.3. Treatment and follow-up

The resected specimens were examined by the same group of gastrointestinal pathologists in our hospital. All AEG patients were classified based on the AEG criteria recommended by Siewert (1998), the disease progression was classified using the guidelines outlined in the seventh edition of the American Joint Committee on Cancer (AJCC) about TNM staging.[28]

All Siewert type II/III of AEG patients underwent radical surgery with celiac and mediastinal lymphadenectomy. They accepted 4 to 6 cycles of first-line adjuvant combination chemotherapy after surgery with oxaliplatin plus 5-fluorouracil/leucovorin or a prodrug of 5-fluorouracil (capecitabine; CapeOX), and they were prospectively followed up until October 2016, follow-up results were obtained through reviews of the hospital records and outpatient visit. Follow-up was performed

Table 1

The new scores model.

The factors of the new scores model	Scores
BMI ≥25	2
BMI within 18.5–24.9	1
BMI <18.5	0
NLR <3.5	1
NLR ≥3.5	0
Prealbumin ≥180	1
Prealbumin <180	0

BMI = body mass index, NLR = neutrophil-lymphocyte ratio.

in regular intervals (every 3 months for the first 2 years after treatment, every 6 months in years 3–5, and every 12 months after 5 years). The OS was calculated from the day of surgery to AEG-related death or the end of follow-up.

2.4. Definition of prognostic factors

Peripheral blood tests were obtained within 1 week before surgery, we determine the following indexes (NLR, PLR, BMI, hemoglobin, albumin, prealbumin, and PNI). NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, PLR was calculated by dividing the absolute palate count by the absolute lymphocyte count, PNI was calculated using the following formula: serum albumin (g/L) + $5 \times$ total lymphocyte count ($\times 10^9$/L).[29] The recommended cutoff values for preoperative NLR, PLR, and PNI were determined using receiver operating characteristic (ROC) curve analysis based on the Youden index [maximum (sensitivity + specificity − 1)].[30] The BMI was calculated from preoperative height and weight, BMI was divided into 3 groups: <18.5 (low group), 18.5 to 24.9 (normal group), and ≥25 (high group). According to clinical standard, the cut-off values of albumin and prealbumin were set at 40 g/L and 180 mg/L, respectively. The surgery time was divided into 2 groups according to the median value.

The new scores model (including BMI, prealbumin, and NLR) was calculated as follows (Table 1).

2.5. Statistical analysis

All statistical analyses were conducted using SPSS software (version 16.0). For analysis of survival data, Kaplan–Meier curves were constructed, and statistical analysis was carried out using the log-rank test. Both univariate and multivariate survival analyses were performed using the Cox proportional hazard model. For all 2-sided tests, a P value of <.05 was considered to be statistically significant.

2.6. Ethics statement

This study was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University. Written informed consent was obtained from each patient.

3. Results

3.1. Patients' characteristics

A total of 467 patients were initially enrolled, and 355 cases were included in the final analysis based on the eligibility criteria.
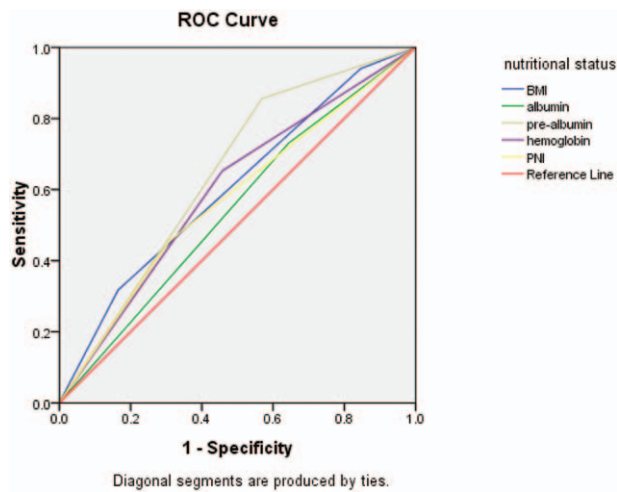
Figure 1. The ROC curve of nutritional status (BMI, albumin, prealbumin, hemoglobin, and PNI). BMI = body mass index, PNI = prognostic nutritional index, ROC = Receiver operating characteristic.

Based on the cut-off values of NLR, PLR, and PNI, the patients were divided into low- and high-level groups for further analysis. Overall, 281 (79.2%) patients were men and 74 (20.8%) patients were women. The median age of patients was 64 years (range, 34–82). The median follow-up month was 52 (range, 1–81).

3.2. The cutoff values of prognostic factors

The predictive ability of prognostic factors for OS was compared by ROC curves (Figs. 1 and 2). Using the ROC curve, we determined the recommended cutoff value of NLR, PLR, and PNI was 3.5 [area under the curve (AUC), 0.585; $P=.006$], 171 (AUC, 0.565; $P=.034$), and 51.3 (AUC, 0.573; $P=.017$), respectively.

3.3. The Kaplan–Meier survival curves of patients

The Kaplan–Meier survival curves for patients in high BMI group, normal BMI group, and low BMI group (Fig. 3); high
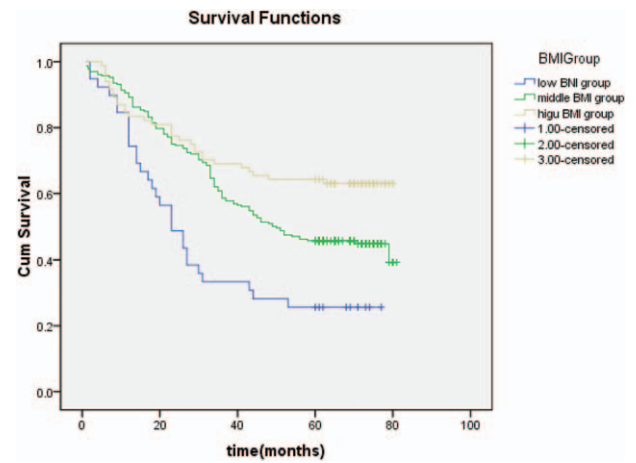

Figure 3. The Kaplan–Meier survival curves of BMI. BMI = body mass index.

NLR group and low NLR group (Fig. 4); high PLR group and low PLR group (Fig. 5); high PNI group and low PNI group (Fig. 6); high albumin group and low albumin group (Fig. 7); high prealbumin group and low prealbumin group (Fig. 8); and high hemoglobin group and low hemoglobin group (Fig. 9) are showed as follows. The patients with hemoglobin <120 g/L ($P=.001$), prealbumin <180 mg/L ($P=.000$), PNI <51.3 ($P=.010$), NLR >3.5 ($P=.000$), PLR >171 ($P=.006$), and low BMI group ($P=.000$) had shorter OS.

3.4. The risk factors for overall survival

As indicated by a univariate analysis, hemoglobin, BMI, prealbumin, PNI, NLR, PLR, TNM, tumor size, and differentiation grade significantly impacted the OS (Table 2). And multivariate survival analysis using the Cox proportional hazards model showed that the TNM stage, BMI, NLR, and prealbumin levels were independent risk factors for the OS (Table 3).
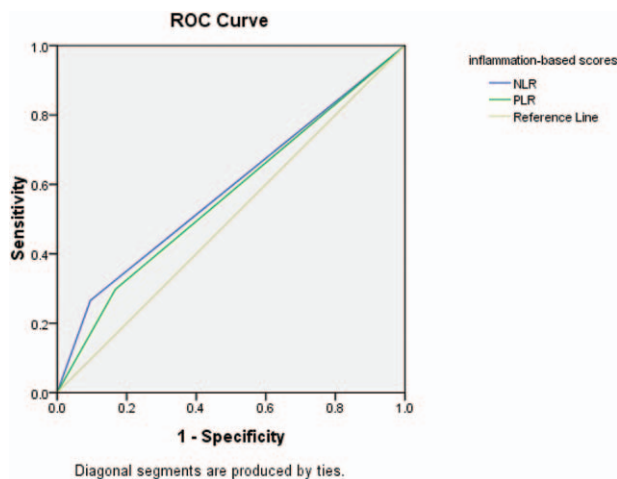

Figure 2. The ROC curve of inflammation-based scores (NLR and PLR). NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, ROC = Receiver operating characteristic.
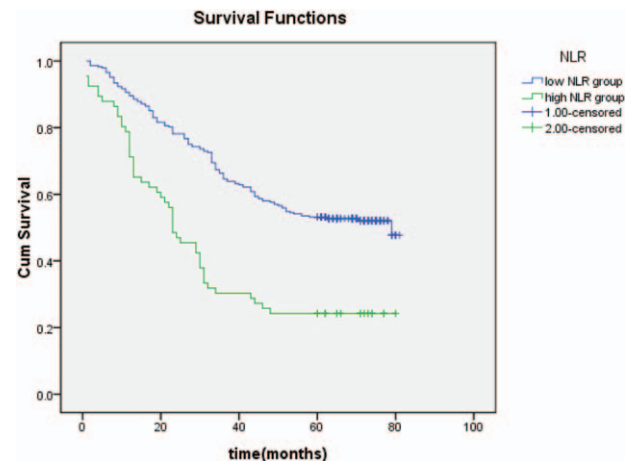

Figure 4. The Kaplan–Meier survival curves of NLR. NLR = neutrophil-lymphocyte ratio.
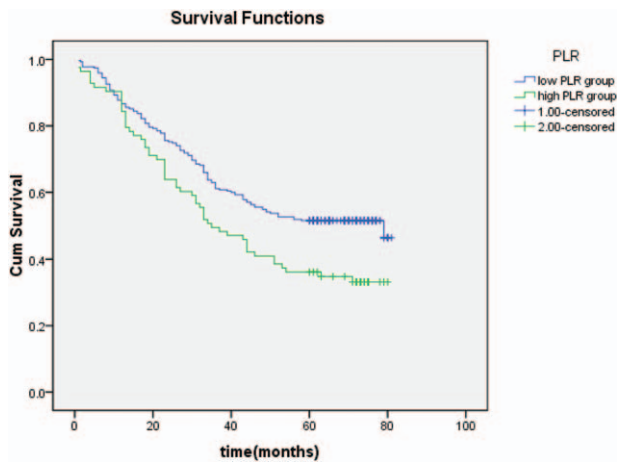
Figure 5. The Kaplan–Meier survival curves of PLR. PLR = platelet-lymphocyte ratio.
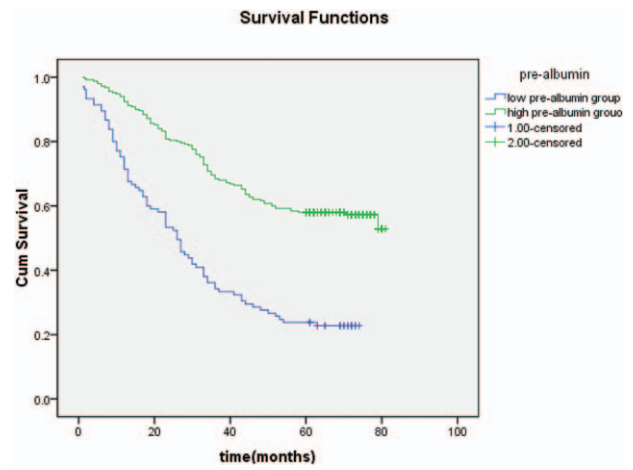

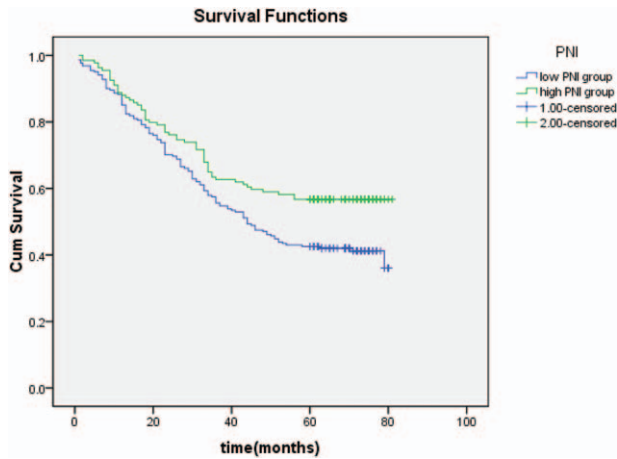**Figure 8.** The Kaplan–Meier survival curves of prealbumin.

4. Relationship of baseline NLR, prealbumin, and BMI levels with clinicopathologic characteristics

The association is shown in Table 4. The serum NLR was significantly correlated with tumor size ($P = .011$); the BMI was significantly with surgery time ($P < .05$); the associations between prealbumin and tumor size ($P < .001$), differentiation grade ($P < .05$), and TNM stage ($P < .05$) were significant.

5. Predictive value of the new scores model

To further evaluate the prognostic values of the prognostic scores, ROC analysis was performed (Figs. 10 and 11). The new scores model had a higher AUC value (0.712; $P = .000$) than BMI (AUC, 0.604; $P = .001$), prealbumin (AUC, 0.644; $P = .000$), NLR (AUC, 0.585; $P = .006$), and TNM (AUC, 0.673; $P = .000$).

Figure 6. The Kaplan–Meier survival curves of PNI. PNI = prognostic nutritional index.

6. Discussion

Adenocarcinoma of the esophagogastric junction (AEG), which located within 5 cm from EGJ, was classified into 3 subgroups. Type I AEG (adenocarcinoma of the distal esophagus) is the most prevalent type in Western countries, types II (adenocarcinoma of
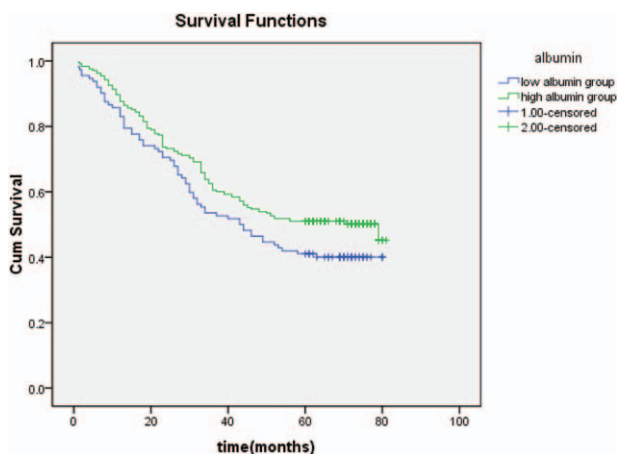
Figure 7. The Kaplan–Meier survival curves of albumin.
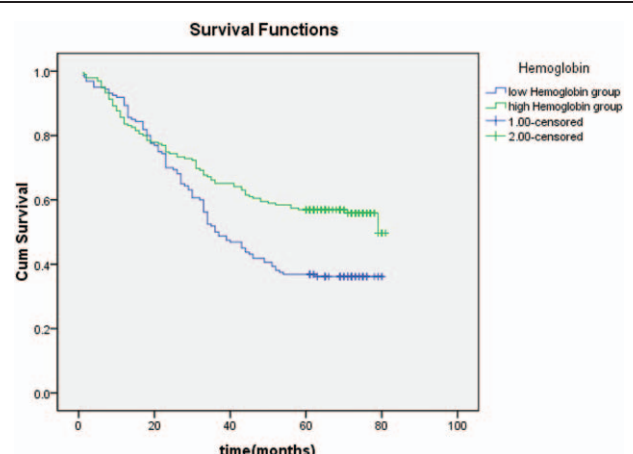
Figure 9. The Kaplan–Meier survival curves of hemoglobin.

Table 2

The univariate analyses of prognostic factors for OS in AEG patients.

Characteristics	No. of patients	Five-year survival (%)	χ^2 value	P
Sex			0.251	.992
Men	281	47.4		
Women	74	43.8		
Age, yr			4.460	.035
<60	89	49.4		
≥60	266	46.2		
Tumor size			23.821	.000
<5	164	61.6		
≥5 cm	191	34.4		
Differentiation grade			5.636	.018
Poor	226	42.9		
Well	129	54.3		
TNM stage			34.559	.000
I, II	154	66.9		
III, IV	201	31.8		
Tumor location			0.444	.505
Siewert II	202	48.5		
Siewert III	153	44.4		
BMI, kg/m^2			17.253	.000
<18.5	39	25.6		
≥18.5 and <25	232	44.8		
≥25	84	63.1		
Hemoglobin, g/L			10.614	.001
<120	160	36.2		
≥120	195	55.9		
Albumin, g/L			3.512	.061
<40	112	40.2		
≥40	243	50.2		
Prealbumin, g/L			48.110	.000
<180	105	22.9		
≥180	250	57.2		
PNI			6.537	.011
<51.3	221	41.2		
≥51.3	134	56.7		
NLR			28.786	.000
<3.5	289	52.2		
≥3.5	66	24.2		
PLR			7.421	.006
<171	270	51.1		
≥171	85	33.3		

BMI = body mass index, NLR = neutrophil lymphocyte ratio, PLR = platelet lymphocyte ratio, PNI = prognostic nutritional index, TNM = tumor-node-metastasis.

the cardiac) and III AEG (subcardial adenocarcinoma) are commoner than type I in Asia. In a few decades, there has been an alarming rise in the incidence of AEG, but the etiological factor is not clear. Radical resection with D2 lymph node cleaning remains the only potentially curative treatment option, the overall 5 years survival rates of locally advanced AEG was poor.[31,32] Immune and nutritional status had gradually become the focus in the field of predicting prognosis of patients with cancer nowadays.[33] The

Table 3

Multivariate analyses of prognostic factors for OS in AEG patients.

Characteristic	χ^2 value	HR (95% CI)	P
Age	1.684	1.018 (0.999, 1.038)	.063
Differentiation grade	3.444	1.242 (0.895, 1.724)	.194
BMI	6.480	0.724 (0.564, 0.928,)	.011
Prealbumin	26.348	0.428 (0.310, 0.592)	.000
Hemoglobin	0.119	0.943 (0.671, 1.318)	.730
NLR	21.393	2.303 (1.617, 3.280)	.000
PLR	0.420	1.124 (0.789, 1.062)	.517
PNI	0.892	1.192 (0.828, 1.715)	.345
Tumor size (<5/≥5 cm)	0.867	1.178 (0.836, 1.661)	.352
TNM stage (I, II/III, IV)	25.292	2.476 (1.739, 3.525)	.000

CI = confidence interval, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, PNI = prognostic nutritional index, TNM = tumor-node-metastasis.

Table 4

Association of the patients' characteristics with NLR, BMI, and prealbumin.

Characteristic (number of patients)	NLR		BMI		Prealbumin	
	χ^2	P	χ^2	P	χ^2	P
Sex	0.042	.837	2.249	.325	4.746	.029
Male (281)						
Female (74)						
Age, yr	2.048	.152	7.156	.028	2.879	.090
<60 (89)						
≥60 (266)						
Tumor location	7.339	.025	0.805	.938	1.696	.428
Siewert II (202)						
Siewert III (153)						
TNM	0.010	.919	0.363	.834	4.024	.045
I, II (154)						
III, IV (201)						
Differentiation grade	1.276	.259	0.850	.654	3.888	.049
Poor (226)						
Well (129)						
Tumor size	6.414	.011	1.137	.566	13.574	.000
<5 cm (164)						
≥5 cm (191)						
Surgery time, min	0.239	.625	7.567	.023	0.335	.563
<177 (184)						
≥177 (171)						

BMI = body mass index, NLR = neutrophil lymphocyte ratio, TNM = tumor-node-metastasis.

aim of our retrospective study was to compare the prognostic value of inflammation-based prognostic scores (NLR, PLR) and nutritional status (BMI, hemoglobin, PNI, albumin, and prealbumin) for OS in AEG patients.

In recent years, the study about the relationship between the tumor and inflammation has been developed, the inflammation caused by tumors can lead to DNA damage, out control of cell cycle, and micrometastasis lesions.[34] Preoperative NLR and PLR detected in peripheral blood are simple inflammatory markers, which have been identified in various malignancies, including colon cancer, esophageal cancer, ovarian cancer, lung cancer, and breast cancer.[35–39] But few studies about the relationship between the value of NLR and PLR with prognosis

of AEG patients have been published. This large retrospective evidence showed that NLR was an independent prognostic factor in patients with nonmetastatic Siewert type II/III AEG, whereas PLR had limited significance. Considering the interactions of inflammation-based scores for survival outcomes, ROC curve was constructed to estimate their discrimination ability (Fig. 2). The AUC of NLR was 0.585 [95% confidence interval (CI) 0.526–0.644]; the AUC of PLR was 0.565 (95% CI 0.506–0.625); therefore, the performance abilities of NLR may be more significant than PLR for predicting OS of AEG patients. The high NLR and PLR group of AEG patients have a poor prognosis, and the NLR was significantly related with the tumor size ($P < .05$), so the inflammation indexes may have a connection
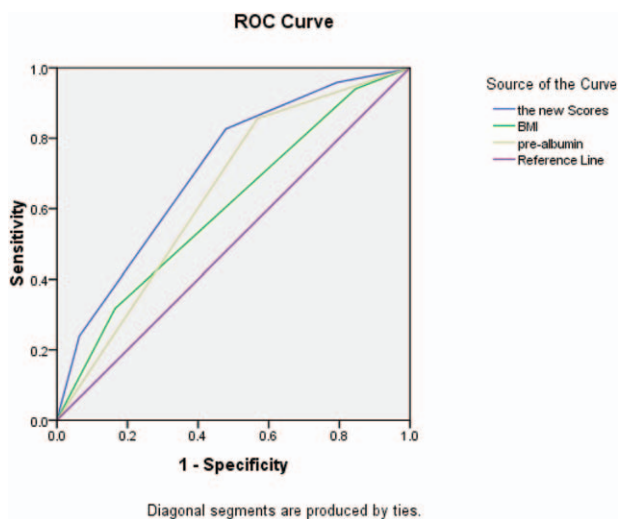

Figure 10. The ROC of new scores model and independent risk factors (BMI and prealbumin) of overall survival in adenocarcinoma of esophagogastric junction (AEG) patients. BMI = body mass index, ROC = receiver operating characteristic.
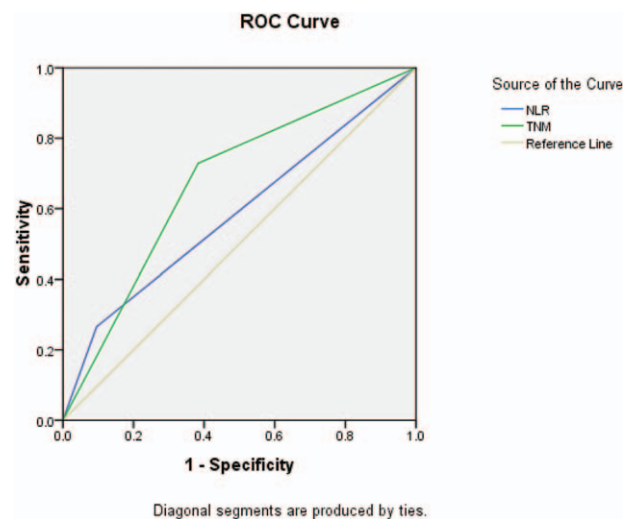

Figure 11. The ROC of independent risk factors (NLR and TNM) of overall survival in adenocarcinoma of esophagogastric junction (AEG) patients. NLR = neutrophil-lymphocyte ratio, ROC = Receiver operating characteristic, TNM = tumor-node-metastasis.

with pathological progression of tumors. Thus we may delay the tumors' progression through anti-inflammatory treatment, but the conclusion need more experiments to prove.

Another index for assessing nutritional status and systematic inflammatory response was BMI. Obesity is showing a rising trend in the worldwide with the improvement of living standards[40]; it had been reported that the BMI was associated with the surgical outcomes in colorectal cancer, pancreatic cancer, liver cancer, and so on.[41–45] This study suggested that BMI was not related with the pathological features of tumor; however, BMI had a significant value with surgery time ($P < .05$). Patients with a normal level of BMI had a longer OS than the low-level group in AEG patients, and BMI was also an independent factor for predicting OS. Related studies have shown that low BMI was associated with postoperative pulmonary infection and other complications.[46] Postoperative complications of surgery are still the most troublesome problems, which can lead to longer hospital stay and increased medical expenses; thus, if we can provide potential nutrition support before surgery, the low preoperative BMI concentrations of patients may be modified, which can reduce the risk of postoperative complications. Some studies showed that higher BMI of the patients (BMI ≥25) would bring longer operative time and fewer lymph nodes,[47] our study was consistent with this. The patients with obesity need proper exercise, which may have some help to their surgery outcome.[48] The patients with a higher level of BMI had a longer OS. Some experiments showed that low PNI combined with low BMI accurately predicted poorer outcome[49]; the main mechanism is that the higher BMI patients may have a higher nutritional level to withstand the occurrence of perioperative complications.

Studies have showed that serum albumin is related with the survival of patients[23,50,51]; however, prealbumin is a 54 kDa protein, which synthesized in the liver has a shorter half-life (nearly 2 days) than albumin (nearly 20 days), so prealbumin is affected earlier in acute protein change especially during the perioperative period. Currently, prealbumin became the research focus as a serum index for assessment of nutritional status. In this study, we explored the prognostic value of prealbumin in AEG patients, we concluded that prealbumin was an independent factor for predicting postoperative survival outcomes, and ROC curve was constructed to estimate its discrimination ability with albumin (Fig. 1). The AUC of prealbumin was 0.644 (95% CI 0.586–0.701) and the AUC of albumin was 0.543 (95% CI 0.484–0.603); therefore, prealbumin may have a more sensitive value for predicting OS of AEG patients than albumin. What's more, from the relationship of baseline prealbumin levels and clinicopathologic characteristics, we can know that the serum prealbumin was significantly correlated with tumor size ($P < .001$) and TNM stage ($P < .05$), so the prealbumin may have a significant value to determine the progression of AEG patients.

The Kaplan–Meier survival curves revealed that AEG patients with hemoglobin <120 g/L ($P = .001$), prealbumin <180 g/L ($P = .000$), low BMI group ($P = .000$), PNI < 51.3 ($P = .010$), NLR >3.5 ($P = .000$), PLR >171 ($P = .006$) had shorter OS; thus, we can make comprehensive assessment with patients before surgery, and then using different therapies. For example, we can take radio or chemotherapy or provide potential nutrition support before surgery to improve the prognosis of these patients to achieve better treatment effect, and these patients also need more attention to care and follow-up after surgery.

Our study has determined the value of NLR, BMI, and prealbumin to be comparable to TNM stage, were independent prognostic factors of AEG patients, so these indexes should be included in the routine assessment of AEG patients. These markers in combination may effectively provide individualized prognostic support for AEG patients.

In addition, we constructed a new score model to better evaluate the prognosis of AEG patients. Multivariate survival analysis showed that the TNM stage, BMI, NLR, and prealbumin levels were independent risk factors for the overall survival. Considering that the pTNM stage can only be evaluated in specimens after surgery, so the TNM stage was excluded from this score model. We can see the new scores model had a higher AUC value (0.712; $P = .000$) than BMI, NLR, TNM, and prealbumin, showing a reliable discrimination ability to act as a prognostic index of AEG patients. This index is also simple and inexpensive to get before surgery; it may benefit a lot to our patients.

There are some potential limitations of this study. Firstly, other potential confounding factors including specific tumor markers and inflammatory markers that are not included in this study, besides, there might be other reasonable cut-off levels for each ratio.

To our knowledge, this is the first study about the prognostic value of preoperative inflammation-based prognostic scores (NLR, PLR) and nutritional status (PNI, BMI, hemoglobin, albumin, and prealbumin) for OS in AEG patients and we found that the patients with a high level of albumin, pre-albumin, hemoglobin, PNI, BMI, and low NLR, PLR level had longer OS. Moreover, our study further demonstrated that preoperative prealbumin, BMI, and NLR were independent prognostic factors of AEG patients and the new scores model may serve as a reliable index to evaluate the prognosis of GC patients.

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