Clinical Significance of Systemic Inflammation Response Index and Platelet–lymphocyte Ratio in Patients with Adenocarcinoma of The Esophagogastric Junction and Upper Gastric Cancer

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Abstract

Background: Tumor immunity plays an important role in assessing the tumor progression. The purpose of this study was to investigate the prognostic value of combined systemic inflammation response index (SIRI) and platelet–lymphocyte ratio (PLR) for treatment of gastroesophageal junction cancer (AEG) and upper gastric cancer (UGC).

Methods: In this study, patients from 2003 to 2014 were divided into training and validation sets. The prognostic accuracy of each variable was compared using time-independent ROC analysis. The scoring system was calculated by cut-off values of SIRI and PLR in 5-year. Kaplan-Meier and Log-rank tests were used to analyze overall survival (OS). Chi-square test was used to analyze the association between clinical characteristics and the scoring system. Univariate and multivariate analyses based on the competitive risk regression model were used to analyze independent predictors of death due to AGC and UGC. R software was used to construct the Nomogram model of risk assessment.

Results: Patients with SIRI–PLR=2 had worse survival time than those with 0 and 1 (P<0.001) and more suitable for postoperative adjuvant chemotherapy (P=0.002). High PLR patients were more suitable for proximal gastrectomy (P=0.049). SIRI and PLR were independent predictors in training set (P=0.036, P=0.045), which could be combined with age and pTNM to construct Nomogram for predicting OS.

Conclusions: Preoperative SIRI–PLR score was an independent predictor for patients with AEG and UGC. The Nomogram model constructed by age, SIRI, PLR and pTNM can correctly predict the prognosis of patients.

Introduction

Gastric cancer (GC) is still the third leading cause of cancer mortality worldwide [1]. With the increasing awareness of malignant tumor prevention in countries with high incidence, such as Japan, Korea and China, GC has been decreasing. However, the incidence of gastroesophageal junction cancer (AEG) and upper gastric cancer (UGC) has increased annually, especially in Japan, where it has increased from 2.3% to 10% in the past 40 years [2]. For AEG, according to Siewert type, 93% of type I patients are mainly treated by esophageal and surrounding lymph node dissection, and >66% of Siewert type II and 90% of Siewert type III patients are mainly treated by radical gastrectomy [3-6]. AEG and UGC have the clinical features of strong invasion, poor prognosis, advanced clinical stage and high rate of postoperative recurrence [7,8]. Regarding the surgical method, there is debate about total gastrectomy (TG) and proximal gastrectomy (PG). Golematis et al. [9] found that TG can ensure a sufficient distal margin and extended lymph node dissection, which can brings survival benefit. However, Harrison et al. found that patients who underwent TG and PG had no difference in overall survival (OS) rate, although PG led to better postoperative nutritional status [10]. Therefore, in addition to tumor location, size and clinical stage, it is important to find suitable clinical prognostic factors to help surgeons choose a suitable method of gastrectomy as well as evaluate prognosis after surgery.

Researchers have proposed use of the American Joint Committee on Cancer (AJCC) eighth edition for treatment guidelines for AEG. It is recommended that the distance from the tumor center to the gastroesophageal junction should be >2 cm and the gastric cardia should not be injured, as in GC treatment. However, these recommendations do not entirely meet the clinical requirements [11]. We found that the current clinical guidelines are only based on assessment of the tumor's general progression and do not consider the immune response

caused by tumor cells. In 2014, Galon et al. [12] first proposed pTNM-I, which combines the immune response in the tumor microenvironment and pTNM stage. In 2018 [13], pTNM-I staging was used to guide postoperative chemotherapy in patients with colon cancer. We consider that tumor immunity is also important in assessing tumor progression. However, the high degree of heterogeneity makes it difficult for pathologists to assess the immune status of patients individually and the randomness of field selection of paraffin sections also limits the study of pTNM-I in GC. Reichert et al. [14] found that changes in the peripheral immune microenvironment of the tumor can be reflected by circulating immune-related cells such as neutrophils (N), platelets (P), monocytes (M) and lymphocytes (L). Systemic immune inflammation score (SII) [15-17], neutrophil–lymphocyte ratio (NLR) [18,19], platelet–lymphocyte ratio (PLR) [20], lymphocyte–monocyte ratio (LMR) [21], and scoring systems that combine with inflammation index, such as C-reactive protein (CRP)–NLR [22], NLR–PLR [23], Fibrinogen (F)–NLR [24] and SIRI–PLR [25] have been confirmed to evaluate accurately the prognosis of GC and other malignant tumors. Therefore, as a new comprehensive inflammatory index scoring system combining lymphocytes, neutrophils, monocytes and platelets, the systemic inflammatory response index (SIRI) and platelet-lymphocyte ratio (PLR) are expected to predict the prognosis of GC more accurately, and even help clinicians choose appropriate operation methods for AEG and UGC.

In this study, 371 patients with AEG and UGC who underwent radical surgery at the Cancer Hospital of Harbin Medical University were randomly selected consecutively. The relationship between SIRI–PLR and pathological factors was investigated by cohort study to explore the clinical significance of SIRI–PLR scoring.

Materials And Methods

Patients

Tumors that were mainly located in the upper third of the stomach were designated UGC. Tumors that were mainly located at 2–5 cm from the gastroesophageal junction were designated Siewert type Ⅱ GC [26], as well as AEG. A total of 371 patients who underwent radical surgery at the Harbin Medical University Cancer Hospital from 2003 to 2014 were randomly selected consecutively. Inclusion criteria were: (a) patients diagnosed with gastric adenocarcinoma by experienced pathologists, (b) tumors mainly located in the upper third of stomach or 2–5 cm from the gastroesophageal junction, (c) patients without neoadjuvant chemotherapy, (d) complete follow-up records and (e) compete clinical and pathological data. Exclusion criteria were: (a) history of blood transfusion in the last 2 months, (b) thyroid diseases, (c) intravascular coagulation, (d) history of heparin treatment in the last 1 month, (e) connective tissue diseases and (f) active bleeding.

Total patients were divided into two independent cohorts according to admission time, 194 patients from 2003 to 2010 were the training set, and 177 patients from 2011 to 2014 were the validation set. Over the all known died patients, 186 patients died due to GC and 21 patients (11 patients in the training set, 10 patients in the validation set) died from other causes (7 deaths because of heart disease, 4 patients died naturally, 2 patients died from accidents and 8 deaths from unknown causes).

Operation methods and postoperative chemotherapy standards are based on The Japanese gastric cancer treatment guidelines [27]. The range of gastrectomy is determined according to the patient's clinical stage and tumor location. TG is for clinically node-positive (cN+) or T2-T4a. PG is for the patients with acceptable proximal resection margin (>5cm or frozen section examination of the resection line is desirable). The invasion of the pancreas by tumors requiring pancreaticosplenectomy must also be performed by TG, regardless of the location

of the tumor and distance of the surgical margin. TG includes all gastric tissues, including pylorus and cardia, combined with D2 lymph node dissection range (No. 1–7 and No. 8a, 9, 10, 11p, 11d, 12a). Digestive tract reconstruction methods are Roux-en-Y esophagojejunostomy, Jejunal interposition and Double tract. PG involves proximal 2/3 of the gastric tissues, with gastroesophageal junction and pylorus retained, in combination with the D1+ lymph node dissection area (No. 1, 2, 3a, 4sa, 4sb, 7 and No. 8a, 9, 11p, and No.110 dependent on the need for surgery), and the methods of digestive tract reconstruction include Esophagogastrostomy, Jejunal interposition and Double tract method. There were 38 patients with T4b, of which 7 patients had intragastric resection of adjacent organs (2 patients with partial liver resection, 1 with transverse colon, 2 with spleen, and 2 with pancreatic tail). In addition, oxaliplatin+capecitabine (XELOX) or oxaliplatin+S-1 (SOX) are the main treatment options for patients with postoperative pathological stages II-III, which were 336 patients in the study. In order to ensure the accuracy of this study, we included all patients in our institution with a total of 117 patients. The remaining 219 patients were not included in the postoperative chemotherapy patient group. This is because these patients did not complete all postoperative chemotherapy regimens in our institution. Most of the patients returned to the local hospital for treatment after surgery and did not have complete chemotherapy records.

Patients' clinicopathological data were saved in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (*Copyright No. 2013SR087424, http:www.sgihmu.com*). All patients were re-examined by checking tumor markers or radiological examination [computed tomography (CT), ultrasound and gastroscopy] every 3-6 months, and positron emission tomography-CT were performed as needed.

Inflammation index

Blood samples were collected from patients in fasting condition 1 week before surgery. Neutrophil, lymphocyte, monocyte and platelet counts were obtained by hematological examination. For inflammation index, systemic immune inflammation score (SII) = N×P/L, neutrophil–lymphocyte ratio (NLR) = N/L, platelet–lymphocyte ratio (PLR) = P/L and systemic inflammation response index (SIRI) = N×M/L (N=Neutrophil count, L=Lymphocyte count, M=Monocyte count and P=Platelets).

Statistical analysis

Overall survival (OS) was calculated as the time from surgery to death from any cause. If patients were alive at the last follow-up, they were censored. Patients survival time in each group were shown as median±standard deviation. We used R software version 3.6.1 and the 'survivalROC' package to investigate the prognostic or predictive accuracy of each variable by time-dependent receiver operating characteristic (ROC) analysis. An optimal cutoff value was defined to classify the patients into two groups (high vs low) for each variable with use of the receiver operating characteristic curve for survival in 5-year, and the maximum value of sensitivity - (1-specificity) in 'Youden index' is the best cutoff value. Delong nonparametric method was used to estimate the AUC confidence interval. Kaplan–Meier method and Log–rank test were used to analysis survival curves. Median follow up was calculated by the reverse Kaplan–Meier analysis. The chi-square test was used to analyze the association between SIRI–PLR and patients characteristics. Univariate and multivariate analyses based on the competitive risk regression model were used to analyze independent predictors for high risk of death due to AGC and UGC. The R software was used to construct the Nomogram model of risk assessment by 'SvyNom' and 'rms' packages. Standardized Hazard Ratio and 95% CIs were estimated for each factor. SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used for analysis and two-tailed *P* values <0.05 were considered statistically significant.

Results

SIRI–PLR

The time-dependent ROC curve shows that these variables were continuously keep satisfactory significance (Fig.1 a). For the SIRI and PLR, 0.82 and 134.62 were the cutoff value. The area under the curve (AUC) was 0.677 [95% confidence interval (CI): 0.602–0.752] and 0.678 (95% CI: 0.602–0.754). Similarly, the optimal cutoff values of SII and NLR were 464.23 and 2.46 by ROC curve analysis (Fig.1 b–d). And patients with SIRI ≤0.82 and PLR ≤134.62 were in the score 0 group, patients with SIRI ≤0.82 and PLR >134.62 and SIRI >0.82 and PLR ≤134.62 were in the score 1 group, and patients with SIRI >0.82 and PLR >134.62 were in the score 2 group.

ROC curve of inflammation index

In the training set patients, we compared the SIRI–PLR, NLR and SII by ROC. The AUC of the SIRI–PLR was 0.729 [95% confidence interval (CI): 0.658–0.800], the sensitivity was 47.5% and specificity was 86.3%. The AUC of NLR was 0.658 [95% confidence interval (CI): 0.581–0.735], the sensitivity was 50.5% and specificity was 81.1%. The AUC of SII was 0.669 [95% confidence interval (CI): 0.593–0.746], the sensitivity was 70.7% and specificity was 63.2%. (Fig.2 e) (Table 1).

Patient characteristics

Patient characteristics including sex, age, tumor size, tumor location, pTNM stage, blood cell count, histological type, vascular infiltration and adjuvant chemotherapy are shown in Table 2. The training set comprised 194 patients [166 (85.57%) male and 28 (14.43%) female]. The 5-year survival rate was 39.7%. The validation set comprised 177 patients [144 (81.36%) male and 33 (18.64%)]. The 5-year survival rate was 46.3%.

The relationship between SIRI–PLR score and clinical and pathological factors is shown in Table 3. In the training set, SIRI–PLR score had a significant association with tumor size, surgical procedure, NLR, SII and pTNM stage (P=0.004, P=0.014, P=0.002, P<0.001 and P=0.037). In the validation set, SIRI–PLR had a significant association with tumor size, NLR and SII (P=0.003, P<0.001 and P<0.001).

SIRI–PLR and patient survival

In the training and validation sets, patients with SIRI–PLR score 2 had worse survival than patients with score 0 and 1 (All P<0.001) (Fig.2 a–c). In the training set, patients with SIRI–PLR score 0, 1, and 2 had the survival times of 60.00±17.67, 52.04±21.76 and 18.52±20.16 months, respectively, and 5-year survival rates of 55.9%, 41.6% and 15.2%, respectively. In the validation set, the survival times were 60.00±20.53, 60.00±20.28 and 19.37±19.69 months, respectively, and 5-year survival rates were 56.0%, 44.0%, and 20.0%, respectively. In the total patients, the survival times were 60.00±20.15, 60.00±20.62 and 23.00±20.46 months, respectively, and 5-year survival rates were 52.8%, 57.1% and 21.3%, respectively.

SIRI–PLR and pTNM

In all training set patients. Patients in stage Ⅰ/Ⅱ and Ⅲ with SIRI–PLR score 2 had a worse survival rate than score 0 and 1. Patients in stage Ⅰ/Ⅱ with SIRI–PLR score 0, 1, and 2 had the survival times were 60.00±11.55, 60.00±18.05 and 26.07±22.07 months, respectively. The 5-year survival rates were 76.2%, 66.7% and 27.3%, respectively (P=0.002) (Fig.3 a). Patients in stage Ⅲ with SIRI–PLR score 0, 1, and 2 had the survival times were 56.07±19.74,

28.63±22.04 and 17.30±19.67 months, respectively. The 5-year survival rates were 41.4%, 33.3% and 18.4%, respectively (P<0.001) (Fig.3 b).

SIRI–PLR and postoperative chemotherapy and surgical method

In all patients. There was no significant difference between patients with and without postoperative chemotherapy in the score 0 and 1 groups (P=0.958), and patients without postoperative chemotherapy had shorter survival than patients with postoperative chemotherapy in the score 2 group (P=0.002) (Fig.4 a and b). In the score 0 and 1 groups, patients with and without postoperative chemotherapy had the survival times of 60.00±18.62 and 60.00±21.23 months, respectively, and 5-year survival rates were 53.6% and 51.1%, respectively. In the score 2 group, the survival times were 37.57±18.80 and 16.02±19.23 months, respectively, and 5-year survival rates were 33.3% and 14.9%, respectively.

There was also no significant difference between patients with PG and TG in the low PLR, low SIRI and high SIRI patients (P=0.271, P=0.271 and P=0.260), and patients with TG had shorter survival than patients with PG in the high PLR group (P=0.049) (Fig.4 c–f). In the high PLR group, patients with PG and TG had the survival times of 33.52±21.07 and 18.40±21.43 months, respectively, and 5-year survival rates were 36.4% and 25.0%, respectively.

Univariate and multivariate regression analyses

To identify the independent predictors for OS of patients with AGC and UGC, univariate and multivariate analyses based on competitive risk regression model in the training set. According to univariate analysis, age (P=0.001), NLR (P<0.001), SIRI (P<0.001), PLR (P<0.001) and pTNM stage (P=0.048) were significant. According to multivariate analyses, age (P=0.010), SIRI (P=0.036), PLR (P=0.045) and pTNM stage (P=0.001) were independent predictors for high risk of death due to AGC and UGC (Table 4).

Prognostic Nomogram for OS

Because age, SIRI, PLR and pTNM stage are independent predictors for patients with AGC and UGC in the training set, we first combined these clinical features in the training set and constructed a Nomogram model of continuous variable data to predict the 3-year and 5-year prognosis (Fig.5 a). Concordance was 0.710 and standard error was 0.017. Calibration curves for predicting survival at 3 and 5-year are shown in Fig.5 b and c. At the same time, all patients were scored and ROC analysis was performed. The AUC were 0.767 [95% confidence interval (CI): 0.699–0.835] (Fig.5 d) and 0.754 [95% confidence interval (CI): 0.687–0.822], respectively (Fig.5 f). The sensitivity were 88.8% and 84.8%, respectively, and the specificity were 57.9% and 60.0%, respectively.

We validate the Nomogram model in the validation set. The AUC related to 3-year prognosis was 0.750 [95% confidence interval (CI): 0.674–0.825], the sensitivity was 69.8%, and the specificity was 73.7% (Fig. 5 e). The AUC related to 5-year prognosis was 0.770 [95% confidence interval (CI): 0.701–0.838], the sensitivity was 64.4%, and the specificity was 80.0% (Fig. 5 g).

Discussion

AEG and UGC have shown an increasing ratio in all GC patients annually, and >70% of them are diagnosed with advanced GC [28], which has the characteristics of high rate of lymph node metastasis, poor prognosis and worse survival time. Although the 8th edition of the AJCC has classified the tumors in detail based on tumor location,

there is debate in gastrectomy, and suitable clinical prognostic factors that can help surgeons choose the appropriate treatment for individual patients are still needed. With recognition of the role of systemic inflammation in promoting tumor growth, progression and metastasis of malignant tumors, cytokines, inflammatory proteins and immune cells in the systemic inflammatory response are also considered as potential clinical markers to guide treatment decisions [29,30]. Hu et al. [31] found that high-sensitivity C-reactive protein in non-obese radiotherapy patients with malignant tumors could predict grade 4 skin toxicity, and advise doctors to change treatment options. Recently, the prognostic importance of SIRI for patients with renal, pancreatic and nasopharyngeal cancers has been confirmed [25,32-36]. The higher the SIRI score is, the shorter the disease-free survival and OS. SIRI score can also guide appropriate treatment. For patients undergoing thoracoscopy for lung cancer, SIRI >0.99 has the greatest survival benefit, and for those receiving mFOLFIRINOX chemotherapy in pancreatic cancer, SIRI ≥2.3 has the greatest survival benefit. Studies of upper tract urothelial carcinoma also have shown that combination of SIRI and PLR scoring evaluates prognosis more effectively, hence, evaluation of SIRI–PLR for other malignant tumors has developed.

In this study, the AUC of SIRI and PLR curve are 0.677 and 0.678, respectively, and the cut-off values are 0.82 and 134.62, respectively, which is similar to the research by Zheng et al. [25]. But we found the AUC of PLR in our study is higher than that reported by Zhang et al. [37]. According to chi-square analysis between SIRI–PLR with clinical and pathological features it could be firstly found that it was correlated with tumor size, NLR and SII. Many previous studies confirmed that NLR and SII could be used as inflammatory indexes for evaluating prognosis of GC patients, which means that SIRI–PLR is expected to become a more significant clinical biomarker. In our study, ROC analysis of SIRI–PLR, NLR and SII showed that the AUC of SIRI–PLR was not only larger than that of NLR and SII, but also had better specificity. We can conclude that the combination of SIRI and PLR is better to other inflammatory indexes in predicting the prognosis, which was consistent with the study by Li et al. [38] and Huang et al. [39], the larger the tumor diameter, the later the TNM stage, tumor lesion would metastasize from the original place to the distant place. However, Fridman et al. [40] showed that immune cells in microenvironment played an important role in the generation of such metastasis, proportion changes of the number of immune cells in microenvironment promoted distant metastasis of tumor cells. SIRI–PLR scoring system could not only effectively evaluate patients prognosis, but also conduct further subgroup patients with pTNM I–II and pTNM III.

The tumor immune microenvironment of GC patients can be reflected by postoperative pathological tissue sections or immune indexes. Postoperative pathological tissue sections can be used to analyze the condition of the tumor immune microenvironment, which can be individually evaluated precisely by immunohistochemistry. In this way, it had high specificity. However, the randomness of tissue site selection and development of preoperative adjuvant therapy reduce the accuracy of the tests. On the other hand, the immune indexes constructed by circulating immune cells were calculated based on preoperative hematological tests, whose clinical application is convenient and can reflect the inflammatory condition of the body. The immune indexes were obtained by retrospective analysis of clinical data from a large number of patients, although the specificity was low and couldn't reflect the immune environment of individual patients. However, immune index accuracy was high, because it was in line with the inflammatory condition in most patients. During treatment, hematological examination also was routine texts for GC patients before surgery, and the samples would be sent to hematology laboratory immediately after be collected. Soon, doctors would get reports. The immune index could be calculated by the corresponding mathematical model easily based on these reports. So, it is easy for clinical application [41,42].

The SIRI–PLR scoring system included circulatory neutrophils, platelets, monocytes and lymphocytes, which comprehensively covered the circulating immune cells for calculation of the inflammatory index. This enabled SIRI–PLR to evaluate more comprehensively the physical inflammatory status of patients than NLR and SII did. The study of tumor-related circulating immune cells and inflammation as important parts of the tumor microenvironment plays an important role in measuring tumor progression. GC cells can induce enrichment of neutrophils in tumors, especially GC positive for programmed death ligand 1 and correlative with Epstein–Barr virus [43-45]. Formation of neutrophils and secretion of interferon-γ and tumor necrosis factor-α can inhibit proliferation of lymphocytes and biological activity of CD4+ and CD8+ T cells, lead to immune escape of cancer cells and distant micro-metastasis of tumor cells. Nie et al. [46] showed that expression of a large number of monocytes can inhibit the immune response of T cells near the tumor and promote immune escape of cancer cells by increasing cyclo-oxygenase-2 expression. Senescence-associated secretory phenotype interaction between platelets also plays an important role in metastasis and invasion of cancer cells [47]. Tumor occurrence, development and metastasis lead to changes in immune cells and inflammation in the tumor microenvironment, which would affect the circulating immune cells with disease progression. Changes in immune cells can be indirectly detected by rapid hematological methods, and SIRI–PLR can be calculated to evaluate immune status and prognosis of patients.

As we all know, choosing appropriate individualized treatment for each patient can greatly improve the quality of life even survival time. Surgery is still generally the first choice intervention in patients with GC [48]. At present, clinicians mainly choose TG and PG methods for gastrectomy according to tumor size, tumor location, clinical stage and surgical experience. However, there is still a part of GC which is consistent with both surgical indications of TG and PG. Moreover, the different surgical methods of gastrectomy affect the quality of life and survival time after operation. This has led to a controversy about how to choose the operation method for such patient. Postoperative body mass index, albumin and nutrition index of patients treated with PG are higher than in those treated with TG, but there is no difference in postoperative nutritional quality [49,50]. PG patients have a high risk of gastroesophageal reflux, which may be related to the high rate of tumor recurrence. Golematis et al. [9] found that TG can ensure a sufficient distal surgical margin, extended lymph node dissection and dissection of tissues of organs surrounding the stomach, which can reduce the risk of recurrence and prolong survival. However Pu et al. [51] found that there was no difference in survival time between patients with PG and TG. Therefore, this study suggests that in addition to the conventional surgical guidelines, surgeons can also use an additional inflammatory index to help choose the method of gastrectomy. We found that for patients with high PLR patients. By comparing the postoperative survival of patients who received TG and PG, patients who underwent PG had better prognosis than those who underwent TG. These two methods can effectively remove tumor lesions and reduce the tumor burden, but Rashid et al. [52] showed that effective preservation of lesion-peripheral CD4+ and CD8+ T cells could retain tumor immunity potential after surgery, prolong survival, and reduce postoperative recurrence rate. This might explain the difference in postoperative survival between TG and PG patients. In addition, researchers worldwide have developed abundant preoperative and postoperative treatments for GC, such as neoadjuvant chemotherapy, postoperative chemotherapy, postoperative radiotherapy and targeted therapy. However, it was difficult to assess the sensitivity of patients to different treatment methods. Yuka et al. found that preoperative PLR can evaluate the sensitivity of postoperative chemotherapy [53]. This study also found that patients with SIRI–PLR score 2 had better prognosis than those who did not receive postoperative chemotherapy. Although patients with high SIRI score are reported not to be suitable for chemotherapy [31], we focused on the scoring system that combined SIRI with PLR, and on GC patients who also had AGC and UGC, which might lead to different results.

Previous studies using serum immune index alone to predict the prognosis of patients or guide therapy have unsatisfactory sensitivity and specificity, which is difficult to individualize evaluation. With the development of Real World Study and Big Data for Cancer Research, the mode combining clinicopathological features and serum immunity markers to predicting the prognosis of GC is widely used in clinical. Fanotto found that the patients with higher ECOG score and lower lactate dehydrogenase (LDH)NLR had better prognosis after chemotherapy [54] Huang et al. found that CA125, CA19-9, CA72-4 and Fibrinogen-to-Lymphocyte are risk factors for peritoneal dissemination among patients with GC, and used these indicators to constructe the Nomogram model [55]. We analyzed the clinical significance of the SIRI–PLR score through the The Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital database. According to multivariate analysis, it was found that age, SIRI, PLR, and pTNM were independent predictors for high risk of death due to AGC and UGC in the training set. Then, a Nomogram model was constructed in the training set to predict the prognosis for 3 and 5-year. Through ROC analysis, it was found that AUC was 0.767 and 0.754, sensitivity was 88.8% and 84.8%, and specificity was 57.9% and 60.0%. And the constructed Nomogram model also can be used well in the verification set. Although this result may be limited by the small number of patients and the cohort grouped by time of admission, it can still indicate that for the patients with AEG and UGC, the prediction model established by age, SIRI, PLR and pTNM is worth further clinical verification and application.

Limitatons

This retrospective study still had some limitations. First, it focused on AGC and UGC in an Asian population, therefore, prevalence of AGC and UGC in non-Asian populations needs further exploration. Second, it was difficult to determine whether preoperative gastritis and *Helicobacter pylori* infection affected circulatory immune cells in patients with GC, and this also needs further exploration. Because there are only 35 patients in stage I, it is not enough to analyze separately. Therefore, we combined 117 patients with stage II and stage I patients into this study. Therefore, whether the constructed Nomogram model has the same clinical significance for patients with stage I and stage II should be further studied.

Conclusion

SIRI–PLR score is an independent predictor of survival in patients who undergo curative surgery for AEG and UGC. It can further subgroup patients with stage /and to supplement the eighth edition of the AJCC guidelines. Patients with SIRI–PLR score 2 with postoperative chemotherapy have better survival than patients with SIRI–PLR score 0 or 1. Patients with high PLR with PG have better survival than patients with TG. SIRI–PLR may help clinicians to decide upon individualized treatment for patients with AEG or UGC. The Nomogram with combination of SIRI, PLR, age and pTNM can predict postoperative survival.

Declarations

Ethics approval

Approved by Harbin Medical University Cancer Hospital Ethics Committee of (Approval Number: SHGC-1029).

Consent to participate

Because this study is a retrospective analysis, the informed consent form has been signed when collecting patients' general information and clinicopathological data. This study has protected patient privacy under the guidance of the ethics committee.

Availability of data

Patients' data were saved in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, *http:www.sgihmu.com*).

Conflict of Interest

The authors declare that they have no conflict of interest.

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Consent for publication

Not applicable.

Authors' contributions

XY and TF developed the original idea and wrote the manuscript together. They contributed equally to this work. XY, TF and XL analyzed the data of this article. YX revised the manuscript for important intellectual content. XC, YW, CL and YM made the data collection.

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Tables

Table 1 Relevant results of inflammation index

Inflammation index	AUC	SE	*P* value	95% CI	Sensitivity (%)	Specificity (%)
SIRI–PLR	0.729	0.036	**0.001**	(0.658-0.800)	47.5	86.3
NLR	0.658	0.039	**0.001**	(0.581-0.735)	50.5	81.1
SII	0.669	0.039	**0.001**	(0.593-0.746)	70.7	63.2

AUC the area under the curve, *SE* Standard Error, *CI* confidence interval.

Table 2 General characteristics of patients with AEG and UGC in the two sets

Characteristics	Training set		Validation set	
	Number	Percentage (%)	Number	Percentage (%)
Sex				
Female	28	14.43	33	18.64
Male	166	85.57	144	81.36
Age (years)				
≤60	94	48.45	91	51.41
60	100	51.55	86	48.59
Tumor size (mm)				
≤50	114	58.76	83	46.89
50	80	41.23	94	53.11
Tumor location				
UE	33	17.01	32	18.08
U	124	63.92	106	59.89
UM/EUM/UML	37	19.07	39	22.03
Surgical procedure				
Proximal gastrectomy	123	63.40	79	44.63
Total gastrectomy	71	36.60	98	55.37
NLR				
≤ 2.46	126	64.95	134	75.71
2.46	68	35.05	43	24.29
PLR				
≤ 134.54	89	45.88	97	54.80
134.54	105	54.12	80	45.20
SII				
≤ 619.41	123	63.40	131	74.01
619.41	71	36.60	46	25.99
SIRI+PLR				
0	59	30.41	65	36.72
1	89	45.88	77	43.50
2	46	23.71	35	19.77

T stage				
T1	7	3.61	11	6.21
T2	10	5.15	21	11.86
T3	12	6.19	61	34.46
T4a	134	69.07	77	43.50
T4b	31	15.98	7	3.95
N stage				
N0	56	28.87	70	39.55
N1	46	23.71	38	21.47
N2	52	26.80	36	20.34
N3a	32	16.49	23	12.99
N3b	8	4.12	10	5.65
pTNM stage				
	12	6.19	23	12.99
	47	24.22	70	39.55
	135	69.59	84	47.46
Histological type				
Well-differentiated and Moderately differentiated adenocarcinoma	80	41.24	77	43.50
Poorly differentiated adenocarcinoma	95	48.97	79	44.63
Others	19	9.80	21	11.86
Vascular infiltration				
Yes	2	1.03	145	81.92
No	192	98.97	32	18.08
Adjuvant chemotherapy				
Yes	59	30.41	58	32.77
No	135	69.59	119	67.23

SII Systemic immune inflammation score, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *SIRI* systemic inflammation response index, *UE* esophagus and upper stomach, *U* upper, *UM* upper and middle, *EUM* esophagus and upper middle of stomach, *UML* total stomach.

Histological type, T stage, N stage and pTNM stage are according to the eighth edition of the AJCC Cancer Staging Manual. Tumor location and vascular infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P<0.05$).

Table 3 Connection between SIRI–PLR score and clinicopathologic factors of AEG and UGC patients in training, validation set.

clinicopathologic factors	Training set					Validation set				
	Score 0	Score 1	Score 2	χ^2	*P* value	Score 0	Score 1	Score 2	χ^2	*P* value
Sex				5.959	0.051				0.374	0.829
Male	46	66	54			43	64	37		
Female	4	18	6			10	13	10		
Age (years)				3.545	0.170				1.122	0.571
≤60	29	41	24			26	43	22		
60	21	43	36			27	34	25		
Tumor size (mm)				10.900	**0.004**				11.725	**0.003**
≤50	35	54	25			29	42	12		
50	15	30	35			24	35	35		
Tumor location				4.538	0.360				3.301	0.509
UE	12	14	7			13	12	7		
U	31	55	38			29	50	27		
UM/EUM/UML	7	15	15			11	15	13		
Surgical procedure				8.501	**0.014**				2.072	0.355
Proximal gastrectomy	35	59	29			28	32	19		
Total gastrectomy	15	25	31			25	45	28		
NLR				12.479	**0.002**				43.526	**0.001**
≤2.46	50	63	13			52	62	20		
2.46	0	21	47			1	15	27		
SII				82.294	**0.001**				75.729	**0.001**
≤464.23	48	35	6			49	46	3		
464.23	2	49	54			4	31	44		
T stage				8.101	0.424				8.029	0.431
T1	2	3	2			6	4	1		
T2	4	3	3			6	11	4		
T3	4	7	1			18	29	14		
T4a	32	62	40			22	29	26		

T4b	8	9	14			1	4	2		
N stage				15.288	0.054				8.993	0.343
N0	20	23	13			25	32	13		
N1	17	18	11			9	18	11		
N2	7	26	19			11	16	9		
N3a	6	13	13			7	7	9		
N3b	0	4	4			1	4	5		
pTNM stage				10.194	**0.037**				6.033	0.197
□	5	3	4			9	11	3		
□	16	24	7			22	33	15		
□	29	57	49			22	33	29		
Histological type				5.958	0.202				6.225	0.183
Well-differentiated and Moderately differentiated adenocarcinoma	20	41	19			26	32	19		
Poorly differentiated adenocarcinoma	23	38	34			18	40	21		
Others	7	5	7			9	5	7		

SII Systemic immune inflammation score, *NLR* neutrophil–lymphocyte ratio, *SIRI* systemic inflammation response index, *UE* esophagus and upper stomach, *U* upper, *UM* upper and middle, *EUM* esophagus and upper middle of stomach, *UML* total stomach.

Histological type, T stage, N stage and pTNM stage are according to the eighth edition of the AJCC Cancer Staging Manual. Tumor location and vascular infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P<0.05$).

Table 4 Risk factors of patients with AEG and UGC by univariate and multivariate based on competitive risk regression model.

Characteristics	Univariate analysis			Multivariate analysis		
	SHR	SE	*P* value	SHR	95 % CI	*P* value
Sex				-	-	-
Male	1					
Female	0.611	0.330	0.140			
Age (years)	1.033	0.010	**0.001**	1.028	(1.007-1.050)	**0.010**
Tumor location				-	-	-
UE	1					
U	1.065	0.270	0.820			
UM/EUM/UML	1.351	0.343	0.380			
Surgical procedure				-	-	-
Proximal gastrectomy	1					
Total gastrectomy	1.300	0.210	0.210			
NLR	1.211	0.049	**0.001**	0.977	(0.820-1.164)	0.790
SIRI	1.500	0.071	**0.001**	1.497	(1.141-1.964)	**0.036**
PLR	1.004	0.001	**0.001**	1.003	(1.000-1.005)	**0.045**
pTNM stage				1.833	(1.794-1.872)	**0.001**
	1					
	1.632	0.615	0.430			
	3.156	0.582	**0.048**			
Histological type				-	-	-
Well-differentiated and Moderately differentiated adenocarcinoma	1					
Poorly differentiated adenocarcinoma	1.066	0.219	0.770			
Others	1.523	0.278	0.130			

NLR neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *SIRI* systemic inflammation response index, *SHR* subdistribution hazard ratio, *SE* Standard Error, *CI* confidence interval, *UE* esophagus and upper stomach, *U* upper, *UM* upper and middle, *EUM* esophagus and upper middle of stomach, *UML* total stomach.

Histological type, T stage, N stage and pTNM stage are according to the eighth edition of the AJCC Cancer Staging Manual. Tumor location and vascular infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P<0.05$).

Figures

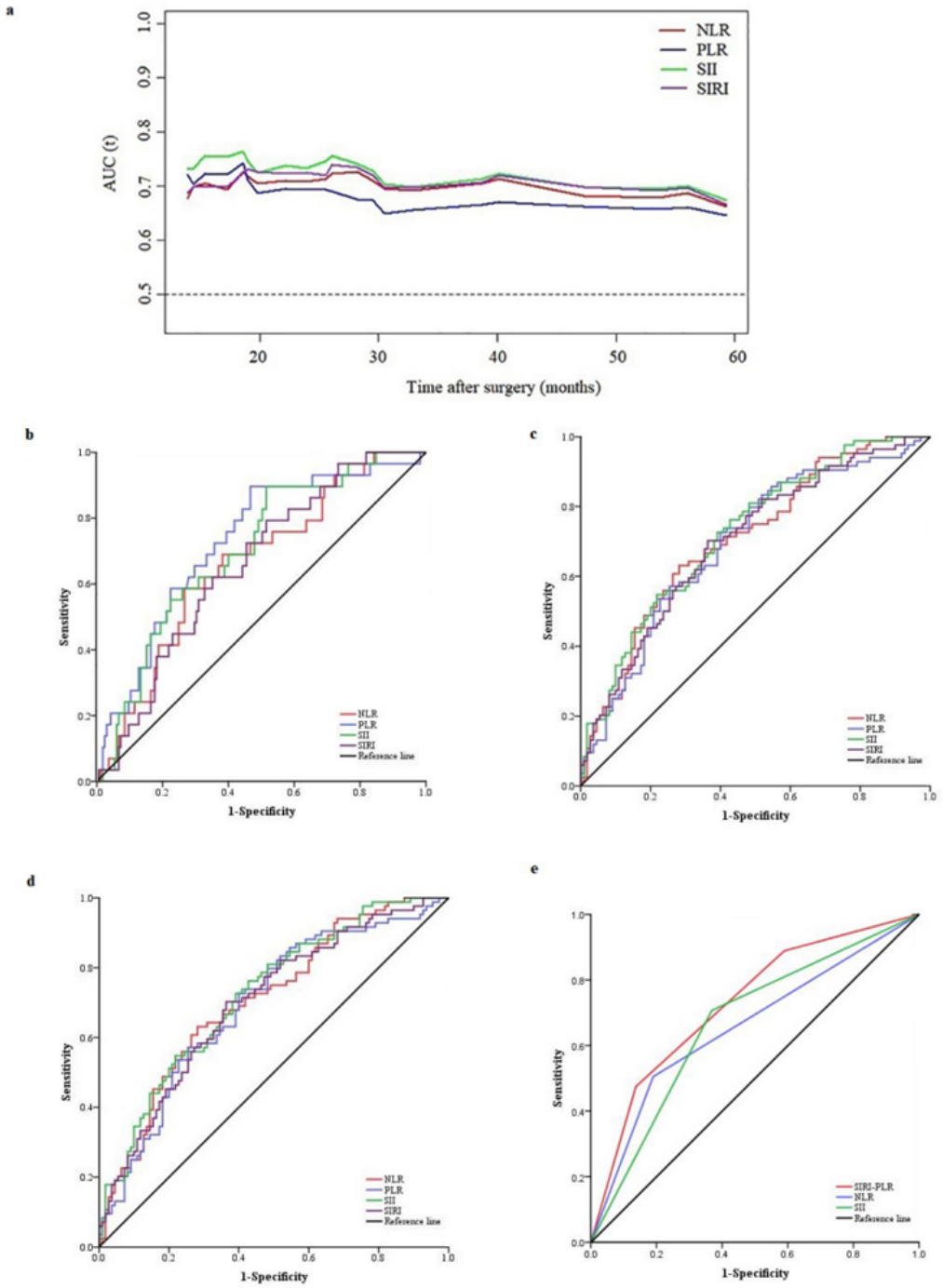

Figure 1

a: Time dependent ROC curve of SIRI, PLR, SII and NLR. b–d: Receiver operating characteristic curve of SIRI, PLR, SII and NLR in 1, 3 and 5-year. e: Receiver operating characteristic curve of inflammation index.

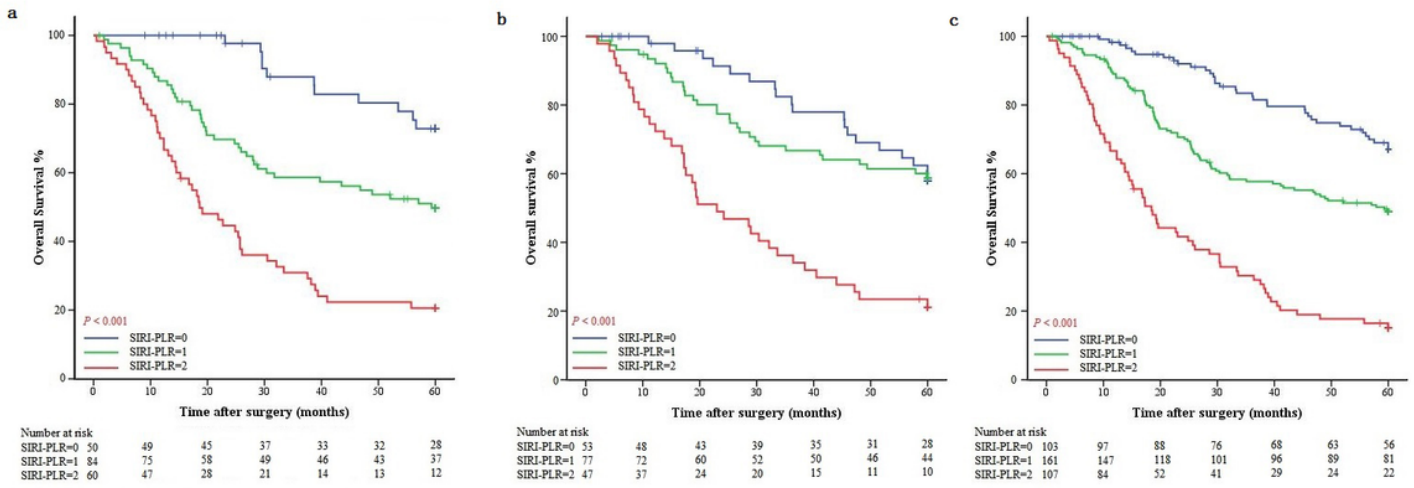

Figure 2

Survival curves of patients with AEG and UGC according to SIRI–PLR score. a: OS of patients with SIRI– PLR score 0, 1, and 2 in training set (n = 194, P<0.001), b–c: validation set (n = 177, P<0.001) and all patients (n = 371, P<0.001).

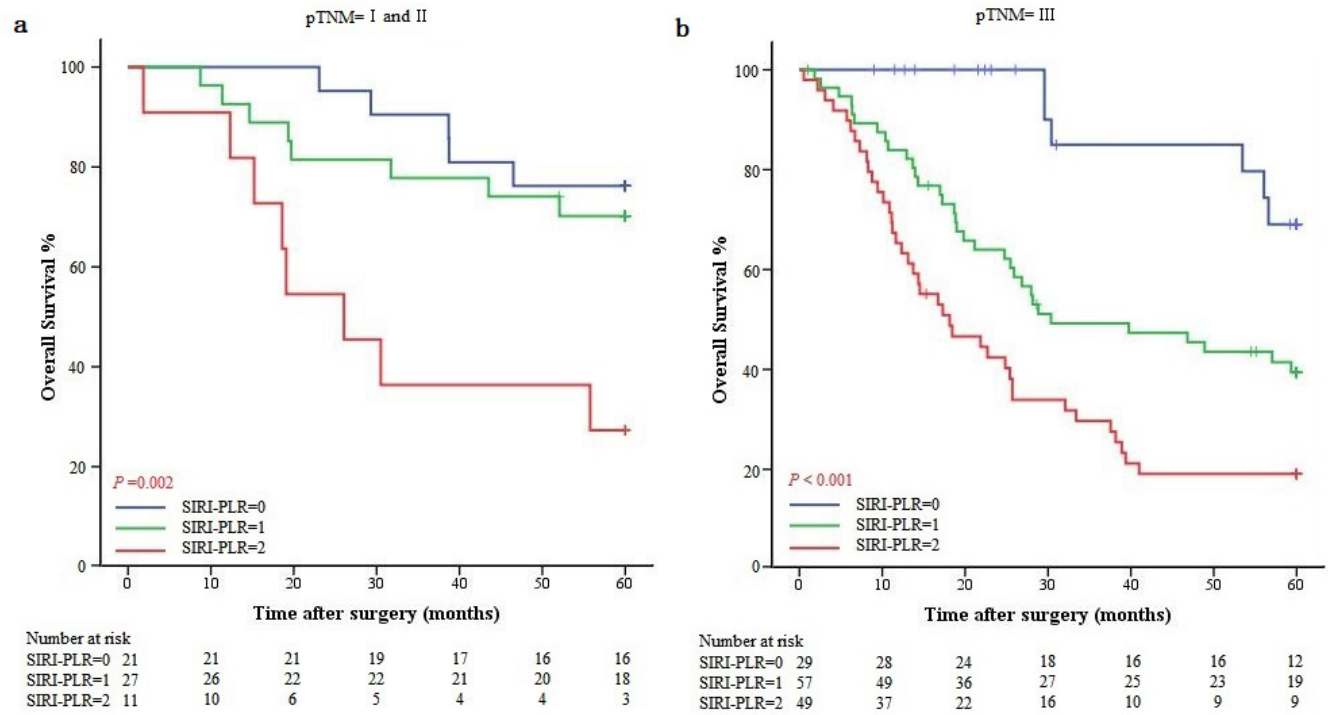

Figure 3

Survival curves based on SIRI–PLR of AEG and UGC patients (TNM stage I–III). a: Survival curves of patients with TNM stage I/II with SIRI–PLR score 0, 1 and 2 (P<0.001). b: Survival curves of patients with TNM stage III with SIRI–PLR score 0, 1 and 2 (P<0.001).

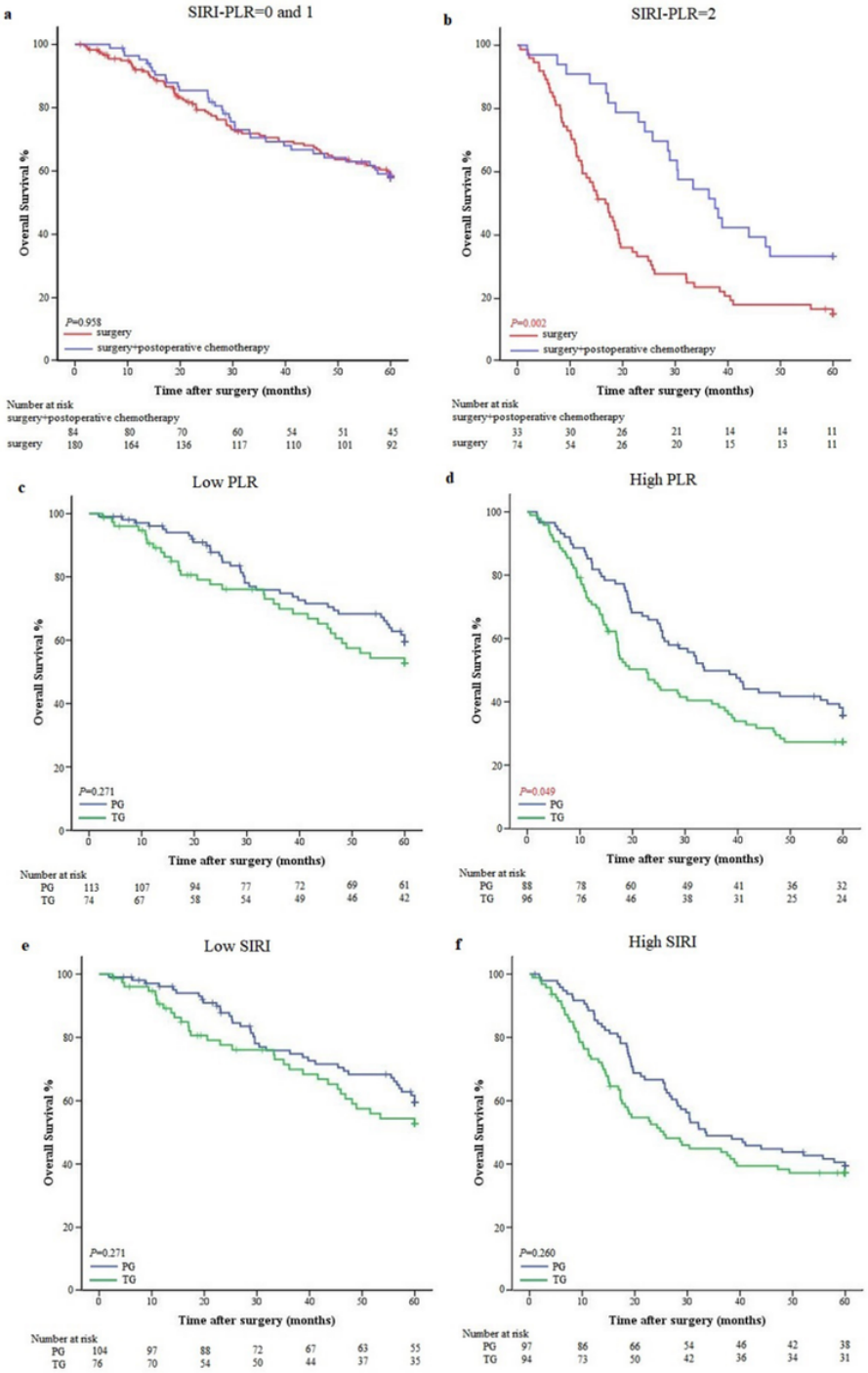

Figure 4

Relationship between SIRI–PLR score and benefit from postoperative chemotherapy in total patents with SIRI–PLR score 0,1 (a) and 2 (b). Relationship between SIRI, PLR and benefit from surgical method in patents with low PLR (c), high PLR (d), low SIRI (e) and high SIRI (f).

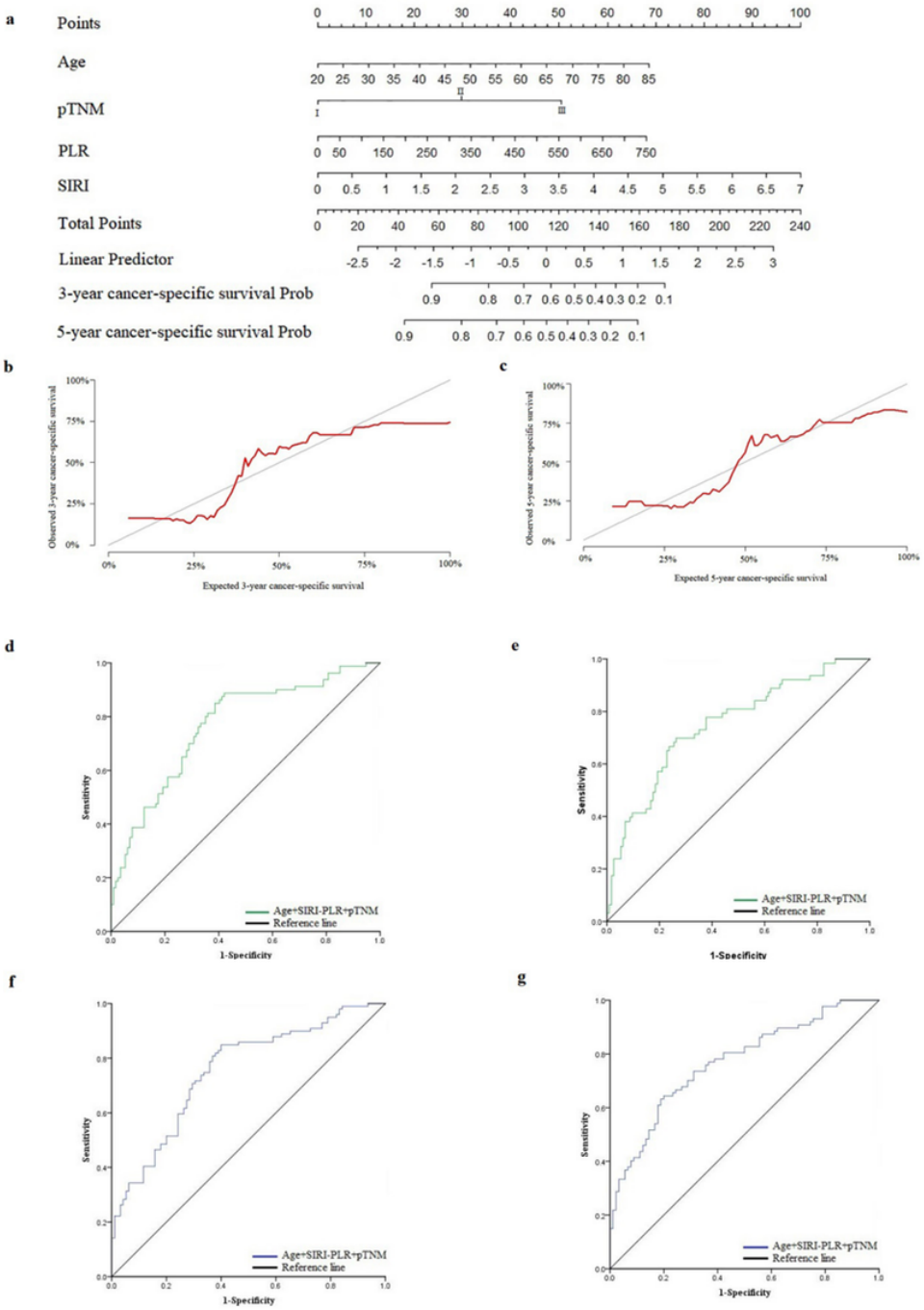

Figure 5

a: Nomogram model predicting 3-year and 5-year prognosis of patients in the training set. b–c: The calibration curve for predicting patient survival in 3-year and 5-year in the training set. d: ROC curve of Nomogram model predicting 3-year prognosis of patients in the training set. e: ROC curve of Nomogram model predicting 3-year prognosis of patients in the validation set. f: ROC curve of Nomogram model predicting 5-year prognosis of patients in the training set. g: ROC curve of Nomogram model predicting 5-year prognosis of patients in the validation set.