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Original Article

Clinical value and application of a novel nomogram containing inflammatory, nutritional and clinical markers in predicting overall survival of stage II/III gastric cancer patients after radical resection: a bi-centered retrospective study of 2,443 patients

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Abstract: Objectives: We aimed to identify nutritional, inflammatory and clinical indicators associated with stage II/III gastric cancer in patients, and construct a nomogram model for accurate prediction of prognosis of patients. Methods: We retrospectively recruited stage II/III gastric cancer (GC) patients who underwent radical gastrectomy at Fudan University Shanghai Cancer Center, from 2012 to 2019. The patients were randomly divided into training and internal validation sets, and then the Maximum log-rank statistic method was used to determine the optimal cut-off value. Next, we performed univariate and multivariate Cox regression analyses to identify independent risk factors associated with overall survival (OS). These were subsequently used to develop a nomogram model. We validated this model in patients with stage II/III gastric cancer (from 2010 to 2019) at Guangxi Medical University Affiliated Tumor Hospital. Results: A total of 2,443 patients met our inclusion criteria and were therefore included in our study. Patients from Fudan University Shanghai Cancer Center were randomly divided into training (n=1725) and internal validation (n=430) sets, while those from Guangxi Medical University Affiliated Tumor Hospital were used as the external validation set (n=288). Results from univariate and multivariate Cox regression analyses revealed that age (adjusted HR, 1.23; 95% CI, 1.05-1.44; P=0.012), TNM stage (adjusted HR, 3.62; 95% CI, 2.79-4.68; P<0.001), CEA (adjusted HR, 1.40; 95% CI, 1.14-1.71; P<0.001), CA199 (adjusted HR, 1.47; 95% CI, 1.21-1.79; P<0.001), and Prognostic Nutritional Index (PNI, adjusted HR, 0.81; 95% CI, 0.67-0.98; P=0.026) were independent prognostic factors for OS in the training set. The established nomogram model, with a C-index of 0.67, had 3- and 5-year Area under Curve (AUC) values of 0.719 and 0.714, respectively. Notably, the model effectively distinguished patients' OS in both the internal (P<0.001) and external (P<0.001) datasets. Conclusions: PNI is an independent prognostic factor for stage II/III GC patients after radical resection. The established novel nomogram model, based on nutritional, inflammatory and clinical indicators, can accurately and efficiently predict prognosis of stage II/III GC patients.

Keywords: Gastric cancer, nomogram, prognosis, prognostic nutritional index

Introduction

Gastric cancer (GC), which severely affects quality of life, is a neoplastic disease ranked fifth and third with regards to highest global diagnosis and mortality rates, respectively [1]. Gastric cancer has a wide regional distribution differences worldwide, with East Asia, Eastern Europe and South America accounting for the hardest hit areas [2]. At present, radical surgical resection remains the primary treatment modality for patients with locoregional gastric cancer (from stage I to stage III). Notably, the postoperative treatment strategies and prog-

nosis of stage II/III gastric cancer patients are significantly different compared to those with stage I gastric cancer. Currently, however, effective indicators for predicting prognosis of patients with stage II/III patients remain dearth [3].

Previous studies have showed that a patient's nutritional status and system inflammation play a key role in occurrence, development and metastasis of tumors [4, 5]. Clinical indicators used to evaluate the nutritional status of patients before surgery, such as body mass index (BMI), hemoglobin, and albumin, among others, have been associated with survival and prognosis of patients with various cancers to some extent [6-9]. In recent years, some studies have demonstrated that some composite indicators that reflect the immune and nutritional status of patients, such as the Prognostic Nutritional Index (PNI), neutrophil lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and systemic immune-inflammation index (SII), are independent prognostic predictors for a variety of cancers [10]. Furthermore, tumor markers, such as carcinoembryonic antigen (CEA), carbohydrate antigen 199(CA 199), have important reference value in routine screening, diagnosis and treatment of GC. Results from large-scale trials in GC cohorts have revealed the prognostic value of tumor markers [11]. Therefore, we hypothesized that combining the aforementioned indicators with basic clinical characteristics of GC patients could reveal more comprehensive and sensitive indicators than individual markers.

In the present study, we recruited a big bi-centered retrospective GC cohort at Fudan University Shanghai Cancer Center and Guangxi Medical University Affiliated Tumor Hospital and evaluated the aforementioned indices. Next, we built a scoring system based on basic clinical information, nutritional and system inflammation status of postoperative patients, for effective prediction of outcomes for pathological stage II/III GC patients after surgery.

Methods

Study cohort

We retrospectively recruited patients who underwent radical gastrectomy at Fudan University Shanghai Cancer Center from 2012 to 2019 and Guangxi Medical University Affiliated Tumor Hospital from 2010 to 2019. Patients were included in the trial if they met the following criteria: 1) had pathologically confirmed stage II/III GC; 2) received adjuvant chemotherapy; 3) underwent neither neoadjuvant chemotherapy nor radiotherapy; 4) had D2 lymph node dissection; 5) had detailed clinical and biochemical information, including data on their age, sex, family history, CEA, CA199, NLR, SII and PNI, two weeks before surgery. Conversely, cases who met the following criteria were excluded: 1) exhibited metastases during surgery; 2) had no clinical or follow-up information. Pathological analysis was performed according to criteria by the American joint committee on cancer, 8th edition.

Follow-up and clinical end point

Patients at Fudan University Shanghai Cancer Center were followed up every 3 months in the first 3 years, and every 6 months thereafter. The latest follow-up date was December 2021. Patients at Guangxi Medical University Affiliated Tumor Hospital were followed up every three months until 5 years, with the latest follow-up date at December 2021. Information collected during follow-up included: the patient's survival status; whether there was ongoing tumor-related treatment; and the latest examination results. Follow-up was carried out by querying the patient's examination records and through telephone interviews. The endpoint of this clinical study was patient's OS, which was defined as postoperative patient death from any cause.

Definition of indexes

BMI, NLR, PLR, LMR, SII and PNI were calculated using the following equations: BMI = weight (kg)/height (m)^2; NLR = absolute neutrophil count (μl)/absolute lymphocyte count (μl); PLR = absolute platelet count (μl)/absolute lymphocyte count (μl); LMR = the absolute lymphocyte count (μl)/the absolute monocyte count (μl); SII = absolute platelet count (μl) * the absolute neutrophil count (μl)/absolute lymphocyte count (μl); and PNI = albumin (g/l) + 0.005× total lymphocyte count (μl).

Statistical analysis

Data were statistically analyzed using SPSS statistical software (SPSS statistic 20.0), and packages implemented in R software (version

4.0.2). Differences between training and validation sets were determined using the Chi-square test. We employed Maximally Selected Log-rank Statistic method to determine the best cut-off point, and then we used Kaplan-Meier survivorship to generate survival curves in order to test the optimal cut-off point and construct a nomogram model in both the internal and external validation group. Next, we employed the Multivariate Cox proportional hazards regression model to calculate independent prognostic factors. Significant factors in the univariate analysis were obtained at a p value less than 0.05. The significant independent factors were subsequently incorporated into multivariate analysis for model building using the rms package (Version 6.2-0) in R. Bootstrap cross-validation with 1,000 replicates of one quarter of the total sample size was used to test model accuracy, while its performance was tested by generating Receiver operating characteristic (ROC) curves were generated using the "timeROC" package (Version 0.4) and decision curve analysis (DCA) using the ggDCA package (Version 1.2).

Results

Patient characteristics

A total of 2,443 GC cases were included from Fudan University Shanghai Cancer Center and Guangxi Medical University Affiliated Tumor Hospital. In the Fudan cohort, 1,552 (72.0%) and 603 (28.0%) patients were men and women, respectively, with a mean age of 61 (range, 15-87) years. Their median follow-up time and OS were 1,154 and 1,030 days, respectively. Moreover, 729 (33.8%) and 1,426 (66.2%) patients were diagnosed with stage II and III GC, respectively. In the Guangxi cohort, 199 (69.1%) and 89 (30.9%) patients were men and women, respectively, with a mean age of 59 (range, 23-87) years. Their median follow-up and OS times were 1,355 and 1,167 days, respectively. Moreover, 72 (25.0%) and 216 (75.0%) patients were diagnosed with stage II and III GC, respectively. Patients in the Fudan cohort were randomly divided into training (n=1725) and validation (n=430) sets, at a ratio of 4:1 ratio by random number method, whereas those from Guangxi Cohort were used for external validation (n=288). Details on additional clinical information, including patients' sex, age, family history of cancer, Hemoglobin, Albumin, CEA, CA199, BMI and TNM stage, are outlined in **Table 1**.

Cut-off points and patient stratification based on indices

Firstly, we determined cut-off points for PNI, NLR, LMR, PLR and SII in the training set, and found that 49.6, 3.69, 2.75, 230.71 and 962.5 were the best cut-off points in our dataset (**Figures 1A**, S1A, S2A, S3A and S4A). Consequently, we used these cut-off points to stratify the patients into two groups, namely high and low groups. This significantly distinguished patients' overall survival (P<0.0001, **Figures 1B**, S1B, S2B, S3B and S4B).

Univariate analysis

Results from univariate analysis indicated that gender (male), old age, high score of CEA and CA199, poor TNM stage, abnormal ALB and HB value, low PNI score, high SII and high NLR score were significant prognostic factors for poor OS in GC patients. Multivariate analysis results showed that high CEA and CA199 scores, poor TNM stage and low PNI scores were significant independent prognostic factors of poor OS (**Table 2**).

Nomogram for predicting OS of GC patients

Old age, CEA, CA199, TNM stage and PNI score, which were significant independent prognostic factors for poor OS, were used to construct a nomogram for predicting clinical outcomes of GC patients. Each factor was calculated with a specific score through the nomogram model, such as PNI≤49.6 which corresponded to 23.1 points. The overall score was used to obtain an estimate of patient's OS (**Figure 2A**), with a higher score implying worse clinical prognosis. One interesting instance was where a patient had an age <61 (0 points), CEA>5.2 (26.3 points), CA199<27 (0 points), PNI>49.6 (0 points) and TNM stage corresponded to III (100 points). Thus, the total score was 126.3, while the patient's 3- and 5-year OS rates were 61.8 and 47.2%, respectively. Next, we performed 1,000 internal cross-validations of this model using the bootstrap method with a c-index value of 0.67 (**Figure 2B**). Results from decision curve analysis (DCA) revealed that the model had a favor-

Table 1. Clinicopathological characteristics of patients in the training group, internal validation group and external validation group

FACTOR	TRAINING (n=1725)	INTERNALVALIDATION (n=430)	EXTERNAL VALIDATION (n=288)
SEX			
male	1240 (71.9%)	312 (72.6%)	199 (69.1%)
female	485 (28.1%)	118 (27.4%)	89 (30.9%)
AGE (years)			
≤61	895 (51.9%)	227 (52.8%)	195 (67.7%)
>61	830 (48.1%)	203 (47.2%)	93 (32.3%)
Family History of cancer			
no	1414 (82.0%)	356 (82.8%)	259 (89.9%)
yes	311 (18.0%)	74 (17.2%)	29 (11.1%)
TNM stage			
II	587 (34.0%)	142 (33.0%)	72 (25.0%)
III	1138 (66.0%)	288 (67.0%)	216 (75.0%)
BMI			
Normal (18~24)	1064 (61.7%)	262 (60.9%)	194 (67.4%)
Abnormal (<18, >24)	661 (38.3%)	168 (39.1%)	94 (32.6%)
Hemoglobin (g/L)			
Normal (≥120)	1179 (68.3%)	301 (70.0%)	150 (52.1%)
Abnormal (<120)	548 (31.7%)	129 (30.0%)	138 (47.9%)
Albumin (g/L)			
normal (35~55)	1642 (95.2%)	399 (92.8%)	232 (80.6%)
Abnormal (<35, >55)	85 (4.8%)	31 (7.2%)	56 (19.4%)
CEA			
normal	1394 (80.8%)	355 (82.6%)	254 (88.2%)
abnormal	331 (19.2%)	75 (17.4%)	34 (11.8%)
CA199			
normal	1372 (79.5%)	331 (77.0%)	233 (80.9%)
abnormal	353 (20.5%)	99 (23.0%)	55 (19.1%)

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199.

able net benefit rate at three and five years after the operation (**Figure 2C**). We also used timeROC curve to evaluate efficacy of the nomogram model (**Figure 2D**). AUC of the summing score for predicting 3- and 5-year OS were 0.719 and 0.714 respectively.

The survival curve was used to evaluate efficiency of the nomogram model in the internal and external validation group. The OS of the two groups (high and low) divided by the median value of nomogram score (118.5) were significantly distinguished in internal validation (P<0.0001, **Figure 3A**) and external validation (P<0.0001, **Figure 3C**) sets. The 1,000 internal cross-validations of this model performed in internal and external sets using the bootstrap method with a c-index value of 0.70 and 0.65 respectively (**Figure 3B**, **3D**).

Discussion

Gastric cancer, with a malignancy characterized by high incidences and high mortality rates, has widely been reported in East Asia is [2]. Numerous studies have associated preoperative malnutrition and systemic inflammation with occurrence and development of malignant tumors as well as prognosis of patients after surgery [12, 13]. Radical gastric cancer surgery can reduce the food intake of patients after surgery. Studies have also shown that GC patients will generally lose 5-15% of their body weight one month after surgery. Therefore, ensuring a patient's nutritional status before gastric surgery is of paramount importance [14]. Patients suffering from malnutrition have also been found to be prone to systemic inflammation. For example, nutritional deficiency

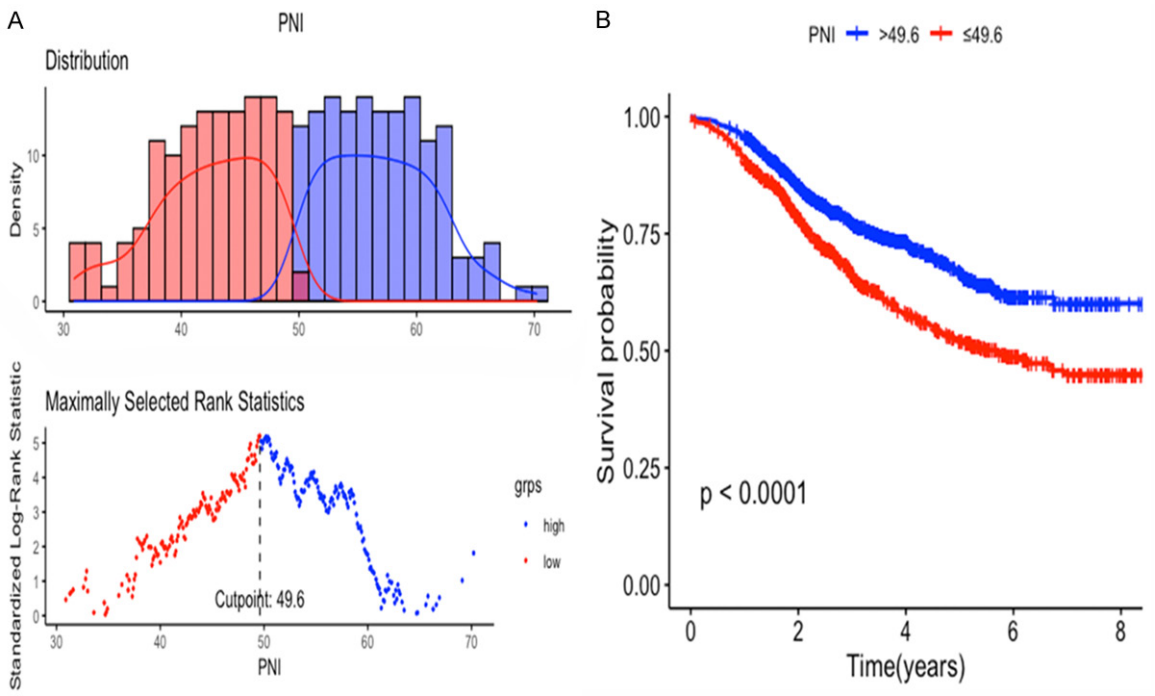

Figure 1. Optimal cut-off value of Prognostic Nutritional Index (PNI) for overall survival (OS) in training group (A) Surv_function revealed a cutoff value of PNI 49.6, which was significantly associated with OS; (B) OS was significantly different between groups PNI≤49.6 and PNI>49.6 (P<0.001).

Table 2. Univariate and multivariate analyses for OS in training group gastric cancer patient

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	0.99	0.82~1.2	0.936	-	-	-
Age	1.35	1.14-1.61	0.001	1.23	1.05~1.44	0.012
Family History of cancer	1.07	0.86-1.35	0.533	-	-	-
TNM	3.83	2.97-4.95	0	3.62	2.79~4.68	<0.001
CEA	1.6	1.31-1.95	0	1.40	1.14~1.71	<0.001
CA199	1.73	1.42-2.09	0	1.47	1.21~1.79	<0.001
BMI	0.88	0.74-1.06	0.172	-	-	-
Albumin	0.58	0.42-0.8	0.001	0.84	0.59~1.20	0.361
Hemoglobin	0.81	0.68-0.97	0.023	1.07	0.87~1.31	0.436
PNI	0.63	0.53-0.75	0	0.81	0.67~0.98	0.026
SII	1.64	1.34-2.02	0	1.19	0.87~1.62	0.239
NLR	1.65	1.34-2.03	0	1.14	0.86~1.50	0.688
PLR	1.53	1.22-1.92	0	1.02	0.76~1.38	0.917
LMR	0.6	0.48-0.74	0	0.93	0.69~1.26	0.565

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; PNI,Prognostic Nutritional Index; NLR, neutrophil lymphocyte ratio, LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index.

may affect the metabolism of T cells through cytoplasmic nutrient sensors, thereby causing immune dysfunction in patients. Inflammation is also one of the signs of malignant tumors, where immune cells representing the inflammatory state in the tumor microenvironment communicate with cancer cells dynamically and complicatedly. This phenomenon not only

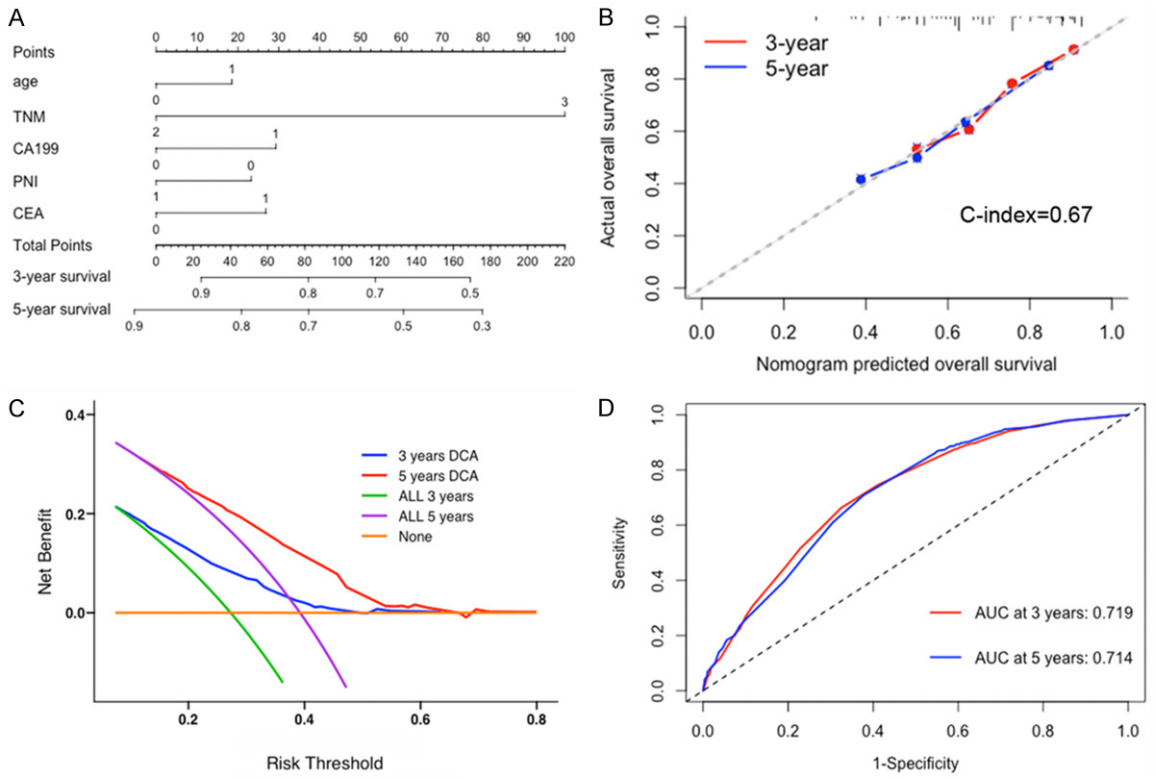

Figure 2. The novel nomogram for predicting prognostic of GC patients using a training set. A. Nomogram based on TNM stage, age, CA199, CEA and PNI; B. Calibration curves of the nomogram and reference model for predicting 3- and 5-year overall survival rates by 1000 bootstrap repetitions; C. Decision curve analysis (DCA) to show the net benefit of nomogram model of 3- and 5-year overall survival; D. Time-dependent AUC values of the established nomogram for predicting 3- and 5-year overall survival rates.

promotes both occurrence and development of cancer, but also significantly affects patient prognosis [15].

In the present study, we included Hemoglobin, Albumin, and BMI (representing the nutritional status of the patient); NLR, PLR, LMR and SII (representing the patient's systemic inflammatory status); PNI, a composite indicator of inflammation; the patient's nutritional status, their basic clinical information, including their sex, age, family history of cancer and TNM stage; s well as recognized tumor markers, such as CEA and CA199, to predict prognosis of the postoperatively recruited GC patients.

Among these nutritional and system inflammation indicators, we previously demonstrated that PNI is an independent risk factor for patient's OS [16]. It has also been shown to be an independent prognostic factor in multiple types of cancer, including cervical, colorectal, esophageal and gastric cancers [17-20]. Notably, PNI is calculated from serum albumin and peripheral blood lymphocytes, of which serum albumin represents a common indicator of a patient's nutritional status in clinical practice, while peripheral blood lymphocytes are an important part of the human immune system during the fight against cancer [21]. Several studies have revealed that both serum albumin and peripheral blood lymphocytes are associated with survival rates of patients with various cancers [22-24]. This validates our selection of PNI in this study.

However, the optimal cut-off point for PNI has always been a controversial issue, owing to limited heterogeneity and number of participants across research cohorts. In the present study, 49.6 was the best cut-off based on a training set of 1,725 participants, which represents a large training set on the prognosis of PNI in GC. Consequently, we used the optimal cut-off point to stratify patients into two groups, namely PNI-high and PNI-low. Results indicated that

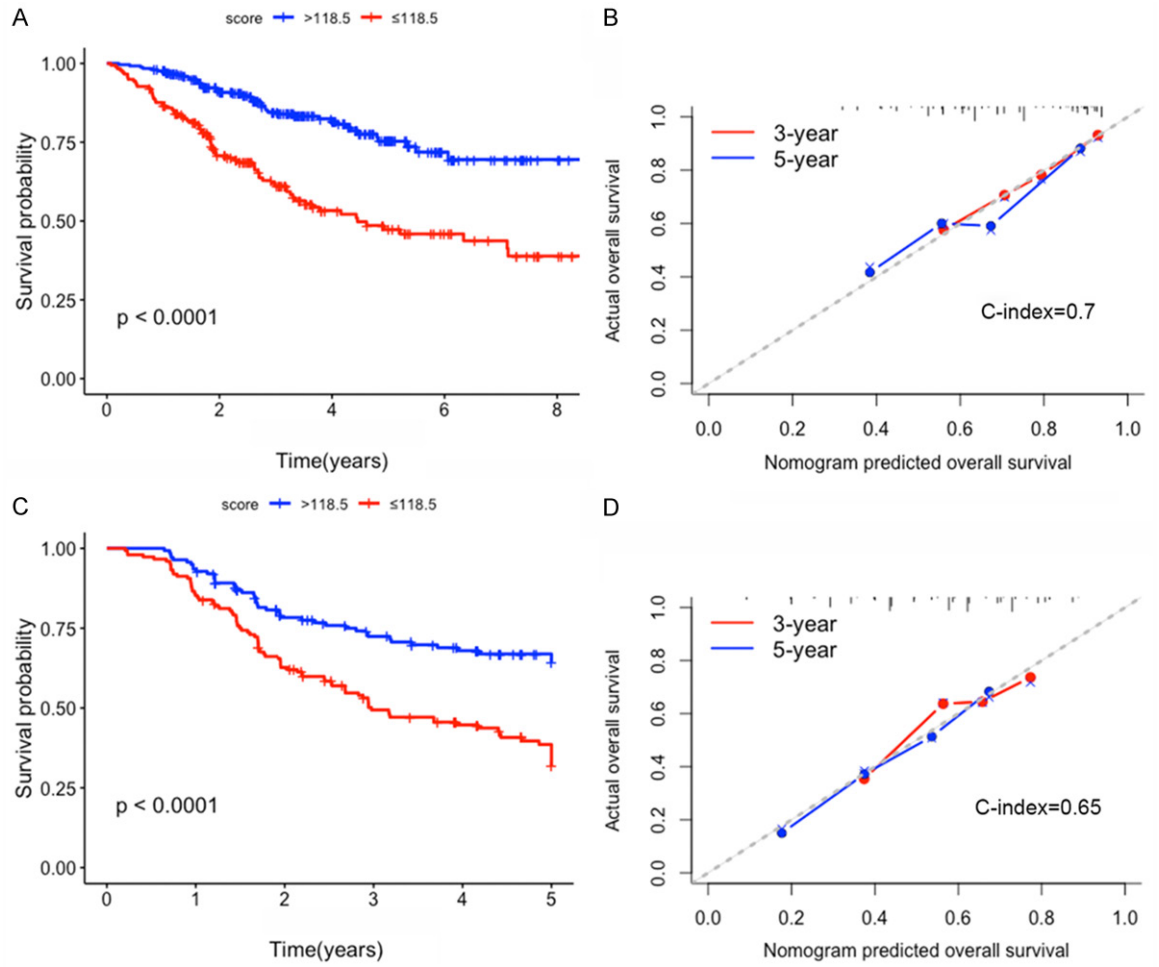

Figure 3. Model validation using internal and external cohorts. A. Kaplan-Meier survival curves for predicting overall survival rates of patients based on internal validation set for patients with nomogram score ≤118.5 and nomogram score >118.5; B. Calibration curves of the nomogram and reference model for predicting 3- and 5-year overall survival rates by 1,000 bootstrap repetitions on internal validation set; C. Kaplan-Meier survival curves for predicting overall survival rates of patients based on external validation set for patients with nomogram score ≤118.5 and nomogram score >118.5; D. Calibration curves of the nomogram and reference model for predicting 3- and 5-year overall survival rates by 1,000 bootstrap repetitions on external validation set.

patients in PNI-high group had significantly better OS rates than those in the PNI-low group, indicating that high PNI score was a protective factor for GC patient after surgery. However, it is difficult to fully reflect the patient's preoperative state simply through the indicators of nutrition and inflammation. Therefore, we attempted to combine PNI with other indicators to predict prognosis of patients after surgery, in accordance with previous studies [25, 26].

We used indicators reflecting the patients' basic clinical information, namely age, sex, BMI, family history of tumor, Hemoglobin and Albumin, tumor markers, such as CEA, and CA199, as well as PNI, to build an easy-to-use and accurate model that can predict prognosis of GC patients. Results from univariate analysis revealed that male (gender), old age, high TNM stage, abnormal level of Albumin, CEA and CA199, as well as low PNI scores, were risk factors for poor prognosis of GC patients. Results of multivariate analyses suggested that high TNM stage, abnormal CEA and CA199 level and low PNI scores were independent risk factor for dismal prognosis of GC patients. Univariate analysis (adjusted HR=0.63, P<0.001) and multivariate analysis (adjusted HR=0.81, P=0.033) of PNI and especially the multivariate analysis with TNM, CEA and CA199, which were demonstrated to be strongly correlated with the prognosis of GC patients [27, 28],

which showed PNI's key effect for GC patient's overall survival.

We selected 5 significant independent risk factors and used them to build a nomogram model for predicting GC patients' OS using the training set. The 1,000 repetition bootstrap revealed good model accuracy, as evidenced by a C-index value of 0.67. The DCA curve demonstrated the potential of this model in predicting patient survival from a net clinical benefit perspective, while the resulting AUC values for 3- and 5-year OS indicated that the model had high diagnosis efficacy in predicting OS of GC patient. To validate this model, we used the median value of the nomogram model to stratify patients in the internal and external validation cohorts into high and low groups, and found that this risk-based stratification significantly distinguished patient's OS across both datasets. Moreover, Bootstrap validation also proved that our model had excellent efficiency across both internal and external validation sets.

The present study had several limitations. Firstly, although we designed a bi-centered retrospective study comprising 2,443 patients, it did not meet multicenter criteria. Secondly, the retrospective design of this study may have resulted in bias. Thirdly, we did not evaluate postoperative radiotherapy and immunotherapy as well as other factors affecting patient survival, mainly due to the small number of patients receiving this type of treatment.

Conclusion

In summary, results of this study provide new evidence on the effect of PNI on postoperative survival of gastric cancer patients. The established prediction model, which combined nutrition, inflammation and basic clinical indicators, may help surgeons to design more effective perioperative management and follow-up strategies for stage II/III gastric cancer patients.

Disclosure of conflict of interest

None.

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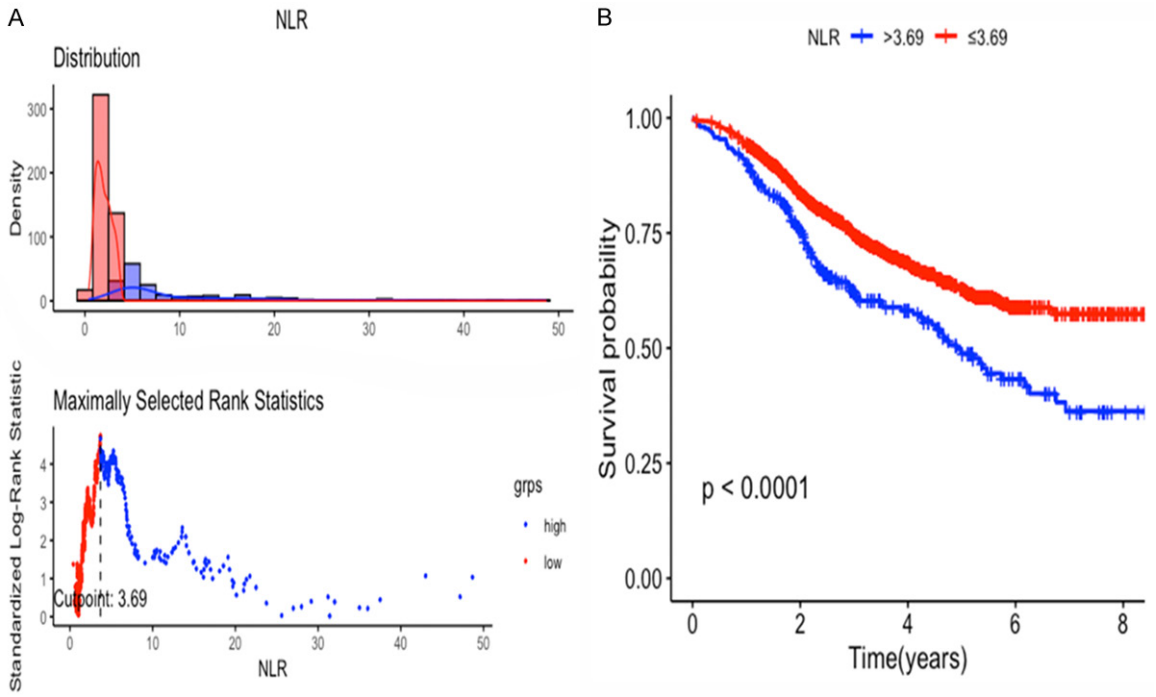

Figure S1. Optimal cut-off value of neutrophil lymphocyte ratio (NLR) for overall survival (OS) in training group (A) Surv_function provided a cutoff value of NLR 3.69 that corresponded to the most significant relation with OS; (B) The OS was significantly different between groups NLR≤3.69 and NLR>3.69 (P<0.001).

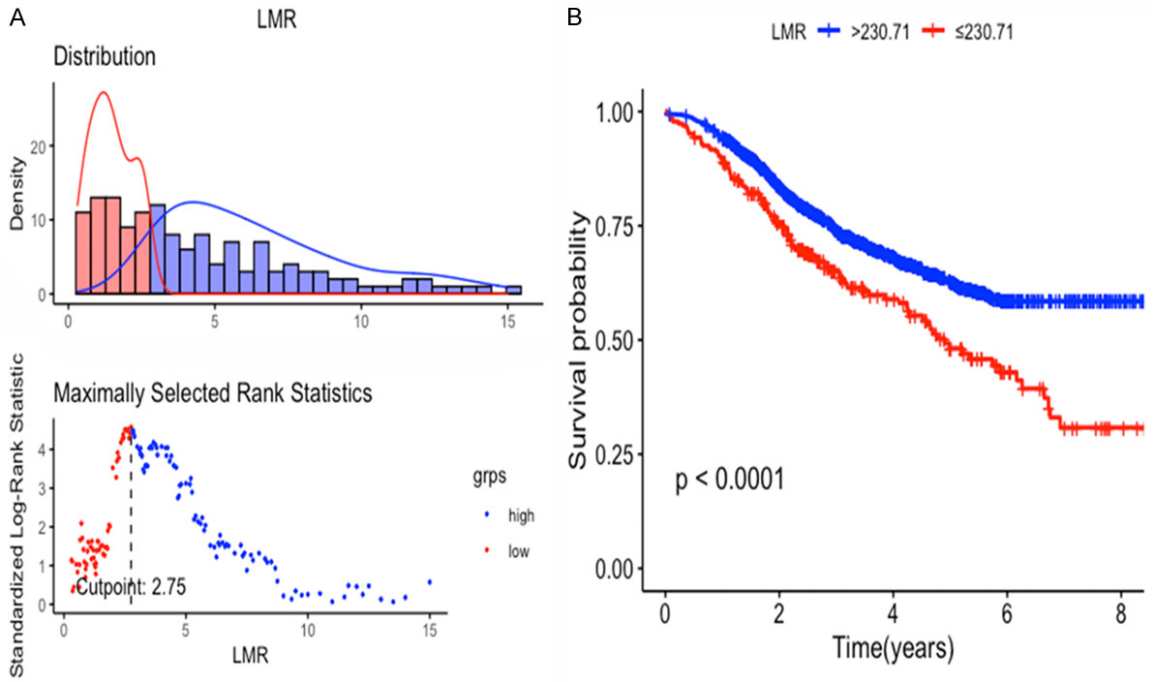

Figure S2. Optimal cut-off value of neutrophil lymphocyte ratio (LMR) for overall survival (OS) in training group (A) Surv_function provided a cutoff value of LMR 2.75 that corresponded to the most significant relation with OS; (B) The OS was significantly different between groups LMR≤2.75 and LMR>2.75 (P<0.001).

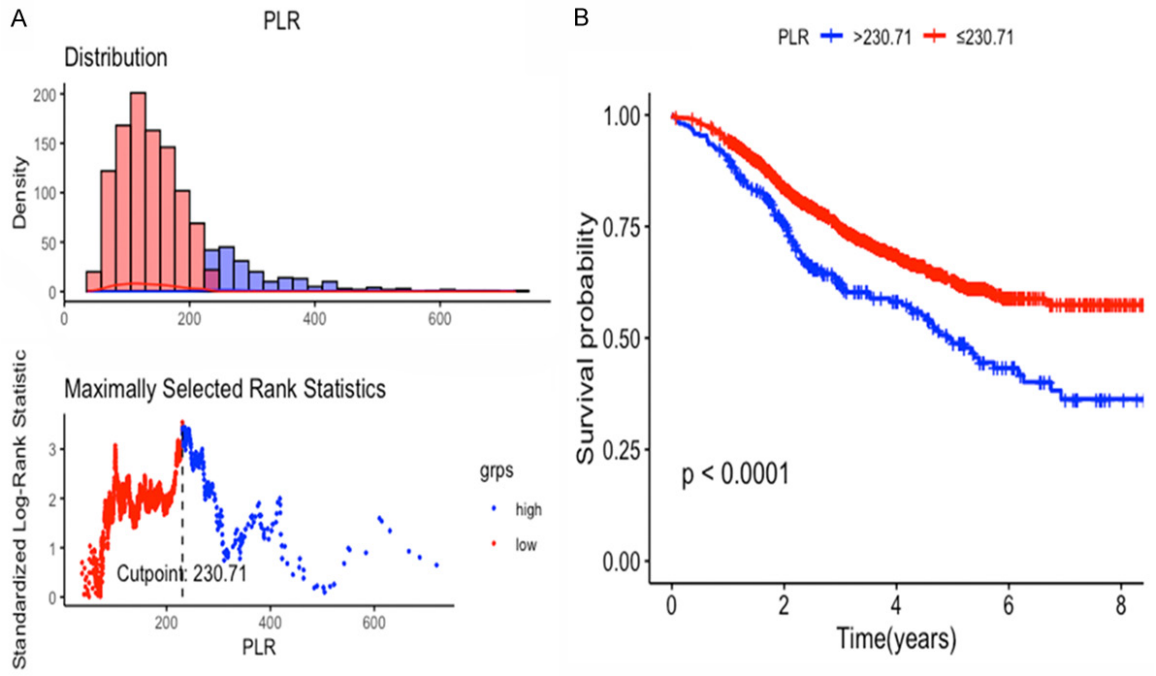

Figure S3. Optimal cut-off value of neutrophil lymphocyte ratio (PLR) for overall survival (OS) in training group (A) Surv_function provided a cutoff value of PLR 230.71 that corresponded to the most significant relation with OS; (B) The OS was significantly different between groups PLR≤230.71 and PLR>230.71 (P<0.001).

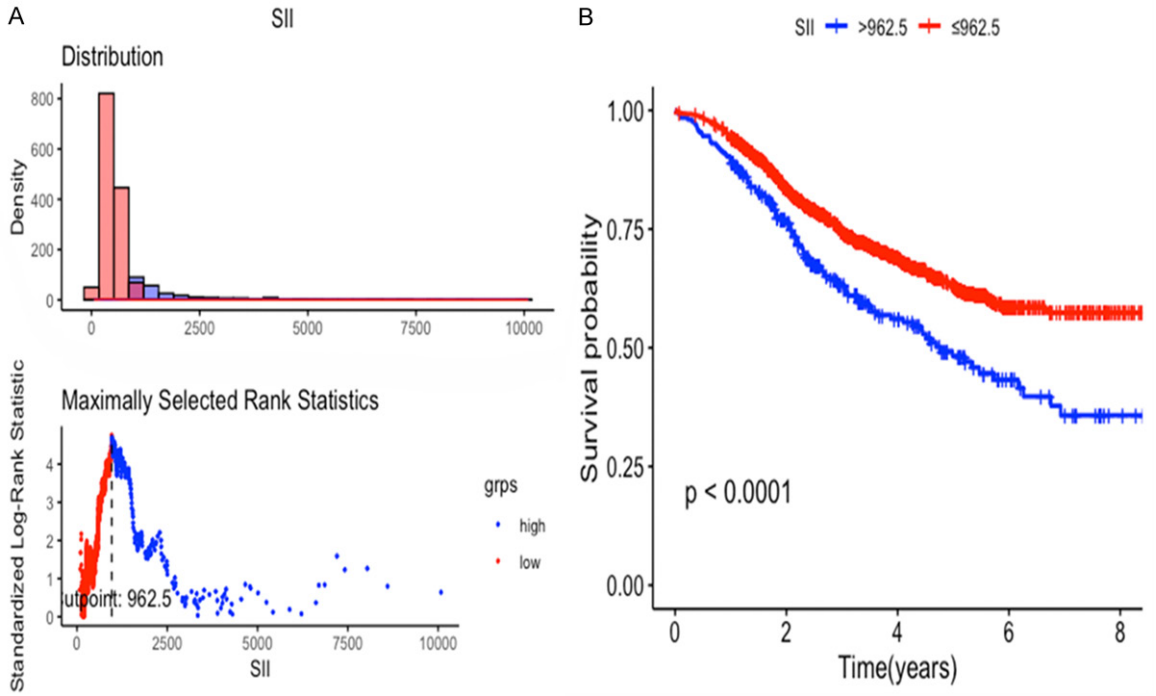

Figure S4. Optimal cut-off value of neutrophil lymphocyte ratio (PLR) for overall survival (OS) in training group (A) Surv_function provided a cutoff value of PLR 962.5 that corresponded to the most significant relation with OS; (B) The OS was significantly different between groups PLR≤962.5 and PLR>962.5 (P<0.001).