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ORIGINAL RESEARCH

Pathologic Complete Response Prediction to Neoadjuvant Immunotherapy Combined with Chemotherapy in Resectable Locally Advanced Esophageal Squamous Cell Carcinoma: Real-World Evidence from Integrative Inflammatory and Nutritional Scores

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Purpose: Neoadjuvant immunotherapy and chemotherapy (nICT) is an emerging hotspot that has been shown to be safe and feasible for locally advanced esophageal squamous cell carcinoma (LA-ESCC). This real-world study aimed to develop and validate a novel predictive model [integrative inflammatory and nutritional score (IINS)] in LA-ESCC patients receiving nICT to predict the pathologic complete response (pCR).

Patients and Methods: Patients with LA-ESCC who received nICT followed by surgery from Jun 2019 to Dec 2021 were enrolled and randomly divided into two sets (7:3). Using least absolute shrinkage and selection operator (LASSO) logistic regression analysis, the IINS was constructed in LA-ESCC patients received nICT to predict pCR. A nomogram based on IINS for pCR prediction was generated in the training cohort and verified in the validation cohort.

Results: Of the 285 enrolled LA-ESCC patients received nICT followed by radical resection, 84 (29.5%) patients achieved pCR. A predictive index of IINS based on 8 inflammatory and nutritional indicators was constructed using the LASSO model. According to the cutoff finder, patients were then stratified into two groups (high and low). The pCR rates were significantly higher in high-IINS group than in low-IINS group in both the training cohort (44.7% vs 17.4%, $P < 0.001$) and validation cohort (50.0% vs 13.3%, $P < 0.001$). The IINS [odds ratio (OR) = 0.237, 95% confidence interval (CI) = 0.117–0.480, $P < 0.001$] was an independent significant predictor for pCR in multivariate logistic analyses. The IINS-based nomogram showed an excellent discrimination for pCR prediction (C-indexes = 0.759 and 0.812 for training and validation cohorts, respectively).

Conclusion: Pretreatment IINS is an independent predictor for pCR in LA-ESCC patients who are treated with nICT. To our knowledge, the IINS-based nomogram is the first model for pCR prediction and may serve as a simple and potential risk stratification model in LA-ESCC who are treated with nICT.

Keywords: neoadjuvant therapy, pathologic complete response, esophageal squamous cell carcinoma, inflammatory and nutritional score, immunotherapy, chemotherapy

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Introduction

Globally, esophageal cancer (EC), mainly including adenocarcinoma (AC) and squamous cell carcinoma (SCC), is one of the most common cancers worldwide. Based on the global cancer statistics 2020 of EC, there were 604,100 new cases diagnosed and 544,076 cases died.[1] Although substantial treatment has improved in recent years, surgical resection remains the main treatment. However, the outcomes for patients with ESCC remain unsatisfactory.[2] In order to improve the survival of locally advanced ESCC (LA-ESCC), neoadjuvant therapy was proposed by the Chinese Society of Clinical Oncology (CSCO) and National Comprehensive Cancer Network (NCCN) guidelines.[3]

Recently, immune checkpoint inhibitor (ICI) plus chemotherapy has achieved remarkable results and has become one of the important regimens in advanced malignancies, including ESCC.[4,5] Following encouraging results in advanced ESCC, ICIs have already been used for LA-ESCC. Recent studies have revealed that neoadjuvant immunotherapy and chemotherapy (nICT), although small in sample size, is safe and feasible for patients with LA-ESCC.[6–10] It has been proposed that pathological complete response (pCR) after neoadjuvant therapy could be considered a good surrogate marker of postoperative survival.[11] However, there is a lack of studies regarding risk factors of pCR prediction in LA-ESCC patients who received nICT. Furthermore, there are no affordable and reliable indexes can predict pCR prior to treatment in patients with LA-ESCC who are treated with nICT. Therefore, it is of great significance to find more economical, effective and accurate indicators and establish more practical predictive models for personalized pCR prediction for patients with LA-ESCC who are treated with nICT.

Studies have indicated that inflammatory and nutritional status was associated with cancer prognosis.[12] In our previous study, Naples prognostic score (NPS) served as a new prognostic score in ESCC.[13] Recently, various inflammation and nutrition-based indices, such as platelet (PLT)-to-LY ratio (PLR), neutrophil (NEUT) to lymphocyte (LY) ratio (NLR), c-reactive protein (CRP) to albumin (ALB) ratio and LY to monocyte (MONO) ratio (LMR), have been used to predict pCR for neoadjuvant chemoradiotherapy (nCRT) in several cancers.[14–16] At the same time, researchers were not satisfied with the single indicator. Therefore, more and more integrative hematological indicators, including systemic inflammation response index (SIRI), systemic immune-inflammation index (SII) and prognostic nutritional index (PNI), were also applied for pCR prediction after nCRT in several cancers.[17,18]

However, nICT is an emerging hotspot and the predictive significance of these indexes for pCR prediction after nICT in LA-ESCC remains unclear. As far as we know, only one study including 64 LA-ESCC patients analyzed the associations between several inflammatory and nutritional indicators and pCR.[19] However, the mentioned above published study focused on the changes of several indexes between baseline and post treatment in small sample. We hypothesized that an integrative indicator might be more valuable than a single index, reducing the potential bias and providing more accurate information for pCR prediction. Moreover, there were no models for pCR prediction after nICT in LA-ESCC patients. Therefore, this study aimed to use various pretreatment indicators to predict pCR after nICT in LA-ESCC patients. In addition, we initially established a novel integrative inflammatory and nutritional score (IINS) based nomogram model and verified the validity of the model for pCR prediction after nICT in LA-ESCC.

Materials and Methods

Study Population

The present study was carried out based on the Declaration of Helsinki. The ethics committee of Zhejiang Cancer Hospital approved this study (IRB-2020-183). Each patient was assigned the informed consent. Patients with resectable LA-ESCC who received nICT followed by surgery from Jun 2019 to Dec 2021 were identified in the database of our department. The patients were divided into two groups (training set and validation set) according to the ratio of 7:3 by using the random number and sorting function of Excel software. First, a random number was generated for each patient and then the random numbers were arranged in ascending order. Finally, the patients were divided into two groups (the first 70% cases in ascending order were the training set and the remaining 30% cases were the validation set) (Figure 1). The inclusion criteria were (1) ESCC histologically confirmed with clinical stage II–IVA; (2) completed nICT followed by surgery; (3) underwent radical resection

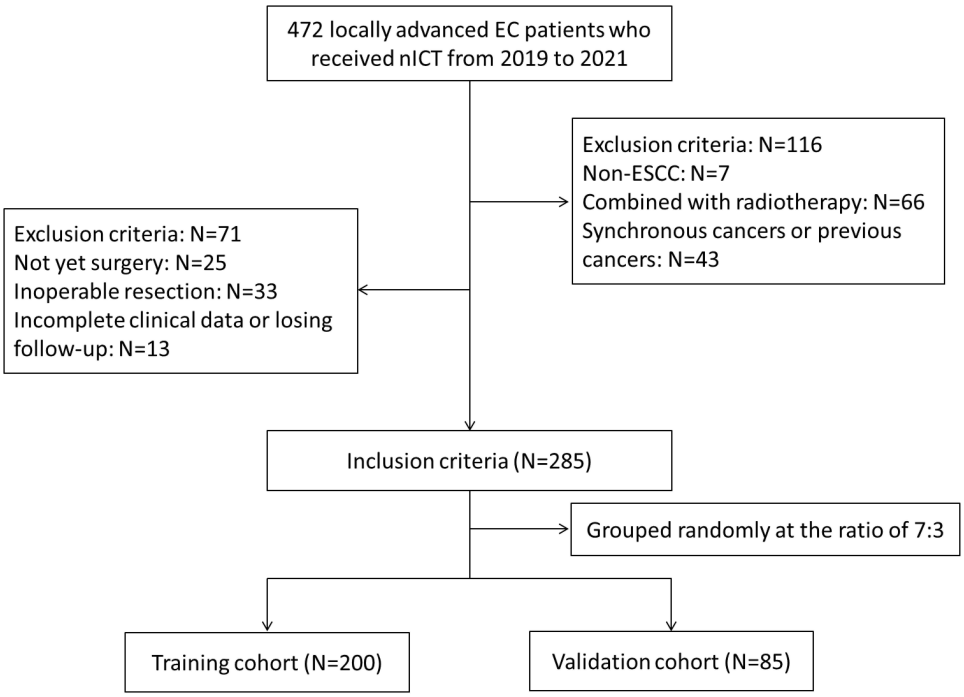

Figure 1 The flow diagram of selection of eligible LA-ESCC patients who received nICT followed by radical resection. Based on the inclusion and exclusion criteria, a total of 285 patients were randomly divided into two groups (training set, n=200 and validation set, n=85).

(R0 resection); (4) without any infection, autoimmune disease or hematologic disease; (5) without other synchronous or previous malignancy; and (6) completeness of full medical records and follow-up.

Treatment and Follow-Up

Patients received 2 cycles of neoadjuvant chemotherapy [albumin paclitaxel 100mg/m^2 on days 1 and 8 and carboplatin targeted at an area under the curve (AUC) of 5 mg/mL per minute on day 1] plus immunotherapy on day 1 (nivolumab 3mg/Kg, pembrolizumab 2mg/Kg, camrelizumab, tislelizumab or sintilimab 200 mg) every 3 weeks in this study. The Ivor Lewis procedure or McKeown procedure with two-field lymphadenectomy were the main surgical treatment.[20,21] To date, there are no relevant guidelines for adjuvant treatment following nICT in EC. Based on the evidences of KEYNOTE-181 and ATTRACTION-3 studies, patients with pembrolizumab or nivolumab had prolonged overall survival (OS) compared with those with chemotherapy in advanced EC.[4,5] Based on the CheckMate 577 study, EC patients who were treated with nCRT followed by surgery and disease-free survival (DFS) was significantly longer in nivolumab adjuvant group than in placebo group.[22] According to the EC expert consensus on perioperative immunotherapy, adjuvant immunotherapy was recommended to patients who did not achieve pCR.[22,23] Therefore, adjuvant therapy after nICT followed by surgery mostly depended on published studies and clinical experience of each institute. Two cycles of postoperative adjuvant ICT were performed after surgery. Then, mono-immunotherapy for 1–2 years, but not mandatory, was performed. Radiotherapy was also performed in patients with T3 or higher stage and/or positive node metastasis based on the pathological results after surgery.[24,25] The pCR was defined as the absence of residual tumor cells of the resected tumor specimen and regional lymph nodes.[26] The TNM staging system analyzed in the present study is based on 8th AJCC/UICC.[27] After treatment, patients were regularly checked, including physical examinations, tumor markers tests and contrast CT examinations. The last follow-up time was completed in Feb. 2022.

Inflammatory and Nutritional Scores Correction and Definition

The data from our medical records, including clinical characteristics, clinical staging and pretreatment hematological indexes, were retrospectively collected and arranged. The 18 pretreatment hematological indexes, such as NEUT, PLT, LY, MONO, ALB, CRP, hemoglobin (HB), lactate dehydrogenase (LDH), prealbumin (PALB) and body mass index (BMI), were obtained within one week before nICT. The CAR, NLR, PLR and LMR were defined as CRP divided by ALB, NEUTs divided by LYs, PLTs divided by LYs and LYs divided by MONOs, respectively. The hemoglobin albumin lymphocyte platelet (HALP) was defined according to previously published study: HALP = HB × ALB × LY/PLT.[28] The other variables (SII, SIRI and PNI) were calculated by the following formula: PNI = ALB (g/L) +5 × LY (10^9/L), SII = PLT × NEUT/LY and SIRI = MONO × NEUT/LY.[17,18]

Statistical Analysis

R software (version 4.1.2) and IBM SPSS 20.0 were carried out to conduct all statistical analyses. Continuous variables were performed by *t*-tests and categorical variables were analyzed by Chi-square or Fisher's exact tests. According to the least absolute shrinkage and selection operator (LASSO) logistic regression model, the IINS was calculated out of all the 18 indicators. The cutoff finder[29] was used to calculate the optimal cut-off value of IINS. The area under the curve (AUC) was compared by receiver operating characteristic (ROC) curves. Logistic regression in univariate and multivariate analyses were used to identify the predictors of pCR. The odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. Then, independent predictive factors of pCR prediction in multivariate logistic regression analyses were selected to establish and validate a nomogram. The C-index, calibration curve, ROC curve and decision curve analyses (DCA) were used to assess the discriminative ability of pCR prediction. A two-side P-value <0.05 was considered to be statistically significant.

Results

Patient Characteristics

A total of 285 (training set = 200 and validation set = 85) patients with LA-ESCC treated with nICT followed by radical resection were included in the current study. There were 267 (93.7%) male patients and 18 (6.3%) female patients. The mean age was 63.5 ± 6.6 years in the training cohort and 63.2 ± 6.9 years in the validation cohort, respectively. There were 17 (6.0%), 38 (13.3%), 150 (52.6%), 43 (15.1%) and 37 (13.0%) patients receiving neoadjuvant immunotherapy with nivolumab, pembrolizumab, camrelizumab, tislelizumab and sintilimab, respectively. There were 84 (29.5%) patients achieved pCR, including 58 (29.0%) cases in the training cohort and 26 (30.6%) cases in the validation cohort. Among the patients, 69 (24.2%) cases received Ivor-Lewis procedure and 216 (75.8%) cases received McKeon procedure. There was no statistical difference between the two groups regarding clinical characteristics. Regarding the inflammatory and nutritional indicators, the values of LY (1.72 ± 0.67 10^9/L vs 1.58 ± 0.52 10^9/L, P = 0.049), LMR (4.25 ± 1.78 vs 3.64 ± 1.36, P = 0.006) and PNI (50.36 ± 4.22 vs 48.97 ± 4.71, P = 0.019) were significant higher in validation set than training set, respectively (Table 1).

IINS Construction and Risk Stratification

The flowchart for IINS construction based on LASSO logistic regression and risk stratification was shown in Figure 2. The correlation heatmap for 18 inflammatory and nutritional indicators was shown in Figure 3A. According to the LASSO regression model, 8 inflammatory and nutritional indexes including BMI, NEUT, NLR, LMR, HB, CAR, PLT and HALP were selected (Figure 3B and C). Finally, the IINS = −0.1888 × BMI −0.0563 × NEUT −0.1636 × NLR + 0.0201 × LMR + 0.0006 × PLT − 0.1021 × CAR + 0.0073 × HALP + 0.0089 × HB. According to the cutoff finder, the optimal cutoff value was −3.033 for pCR prediction, maintaining an optimum balance of sensitivity (67.2%) and specificity (66.9%) (Figure 4). Then, patients were stratified into two groups (low and high) for further analysis.

Table 1 Comparison of the Baseline Characteristics in the Training and Validation Cohorts

	Training Set (n=200)	Validation Set (n=85)	P value
Age (mean ± SD, years)	63.5 ± 6.6	63.2 ± 6.9	0.730
Sex (male/female, n)	186/14	81/4	0.466
Hypertension history (yes/no, n)	60/140	25/60	0.921
Diabetes history (yes/no, n)	9/191	2/83	0.389
Smoking history (yes/no, n)	141/59	59/26	0.854
Drinking history (yes/no, n)	147/53	60/25	0.614
Tumor location (U/M/L, n)	17/121/62	5/48/32	0.474
Differentiation (W/M/P, n)	30/91/79	13/39/33	0.994
cT stage (T2/T3/T4a, n)	28/129/43	16/59/10	0.125
cN stage (N0/N1/N2/N3, n)	40/104/46/10	10/57/17/1	0.066
cTNM stage (II/III/Iva, n)	56/101/43	24/51/10	0.132
ypT stage (T0/T1/T2/T3/T4a)	58/45/29/47/21	26/21/12/17/9	0.973
ypN stage (N0/N1/N2/N3)	133/37/25/5	48/27/8/2	0.106
ypTNM stage (0/I/II/III/IVa)	58/47/21/57/17	26/15/3/36/5	0.076
pCR (yes/no, n)	58/142	26/59	0.788
Surgery (Ivor-Lewis/McKeon, n)	51/149	18/67	0.436
Immunotherapy (N/P/C/T/S, n)	13/26/103/30/28	4/12/47/13/9	0.898
Inflammatory and nutritional scores			
BMI (mean ± SD, Kg/m^2)	21.6 ± 2.22	21.8 ± 2.35	0.334
NEUT (mean ± SD, 10^9/L)	4.78 ± 1.71	5.11 ± 1.59	0.134
MONO (mean ± SD, 10^9/L)	0.47 ± 0.16	0.44 ± 0.15	0.116
PLT (mean ± SD, 10^9/L)	234.8 ± 74.2	231.8 ± 78.8	0.757
LY (mean ± SD, 10^9/L)	1.58 ± 0.52	1.72 ± 0.67	0.049
HB (mean ± SD, g/L)	138.4 ± 14.8	141.2 ± 13.6	0.138
CRP (mean ± SD, mg/L)	5.13 ± 8.46	4.36 ± 5.72	0.440
ALB (mean ± SD, g/dL)	4.11 ± 3.58	4.17 ± 2.73	0.127
PALB (mean ± SD, mg/L)	265.9 ± 59.9	276.3 ± 56.3	0.172
LDH (mean ± SD, U/L)	195.3 ± 41.3	195.8 ± 32.2	0.911
NLR (mean ± SD)	3.31 ± 1.59	3.32 ± 1.62	0.950
PLR (mean ± SD)	162.8 ± 77.0	148.2 ± 63.6	0.125
LMR (mean ± SD)	3.64 ± 1.36	4.25 ± 1.78	0.006
CAR (mean ± SD)	0.13 ± 0.23	0.11 ± 0.14	0.346
SII (mean ± SD)	800.0 ± 550.5	775.7 ± 464.6	0.722
PNI (mean ± SD)	48.97 ± 4.71	50.36 ± 4.22	0.019
SIRI (mean ± SD)	1.62 ± 1.17	1.51 ± 1.08	0.455
HALP (mean ± SD)	43.2 ± 29.0	49.3 ± 29.6	0.108

Abbreviations: TNM, tumor node metastasis; U/M/L, upper/middle/lower; W/M/P, well/moderate/poor; pCR, pathological complete response; N/P/C/T/S, nivolumab/pembrolizumab/camrelizumab/tislelizumab/sintilimab; BMI, body mass index; NEUT, neutrophil; MONO, monocyte; PLT, platelet; LY, lymphocyte; HB, hemoglobin; CRP, c-reactive protein; ALB, albumin; PALB, prealbumin; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; CAR, c-reactive protein to albumin ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; HALP, hemoglobin albumin lymphocyte platelet; SD, standard deviation.

Patient Characteristics Grouped by IINS

The results revealed that baseline characteristics grouped by IINS were significantly associated with BMI (training cohort: $P < 0.001$; validation cohort: $P = 0.002$) and pCR (training cohort: $P < 0.001$; validation cohort: $P < 0.001$), respectively. IINS was also related to hypertension in the training set but not in the validation set (Table 2). The associations between IINS and ypT stage (training set: $P = 0.001$; validation set: $P = 0.003$), ypN stage (training set: $P = 0.024$; validation set: $P = 0.047$) and ypTNM stage (training set: $P = 0.001$; validation set: $P < 0.001$) are shown in

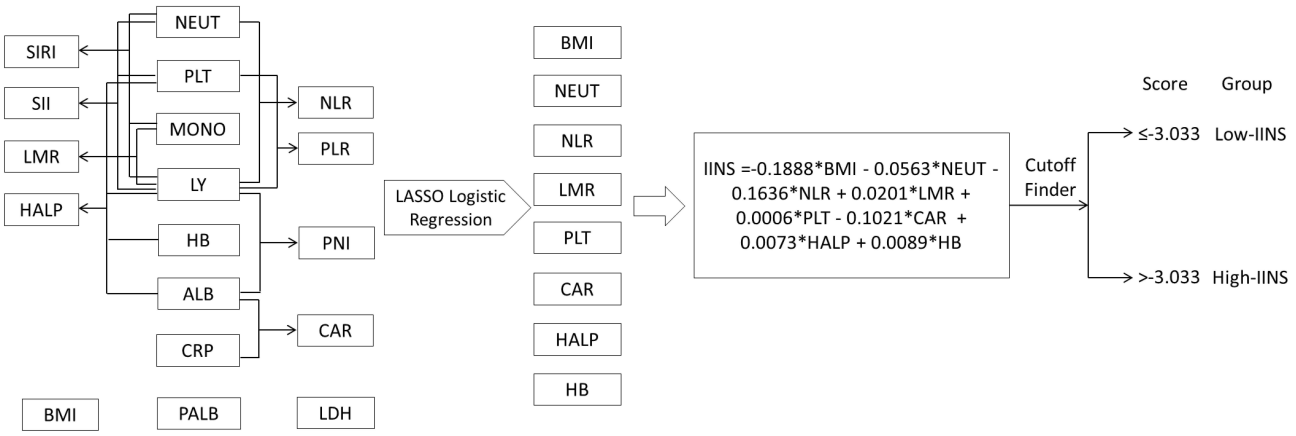

Figure 2 Process diagram for IINS construction and risk stratification. According to the LASSO logistic regression model, 8 indicators out of 18 variables including BMI, NEUT, NLR, LMR, HB, CAR, PLT and HALP were selected to construction IINS.

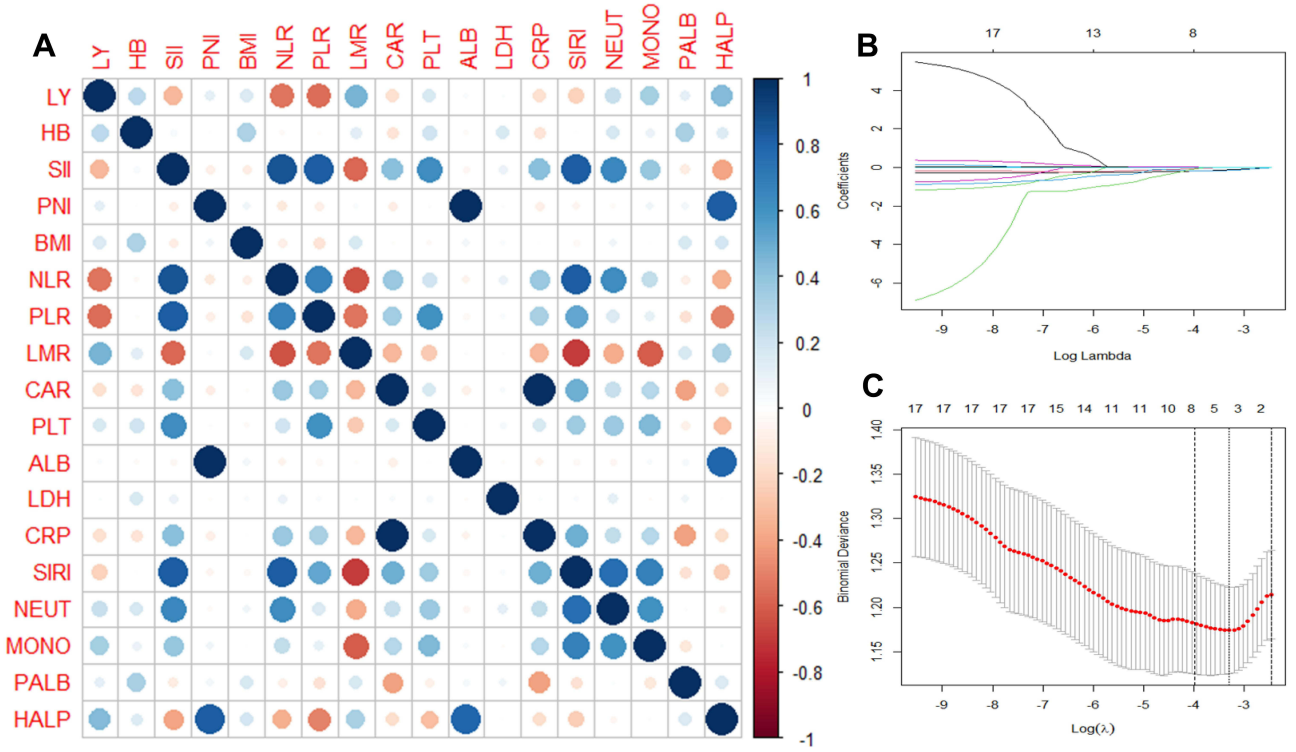

Figure 3 Construction of IINS by using LASSO logistic regression model and AUC comparisons between IINS and other variables. (**A**) A correlation matrix is represented regarding 18 indicators. (**B**) LASSO coefficient profiles of the 18 indicators. (**C**) Ten-fold cross-validation for tuning parameter selection in the LASSO model.

Table 2. The violin plots regarding IINS grouped by pCR or not in the training set and validation set are shown in Figure 5A and B, respectively. The value was significantly high in pCR group than non-pCR group in both training cohort (−2.84 ± 0.52 vs −3.25 ± 0.52, P < 0.001) and validation cohort (−2.94 ± 0.45 vs −3.20 ± 0.66, P = 0.038). The pCR rate was also significantly higher in the high-IINS group in both training (44.7% vs 17.4%, P < 0.001) and validation cohort (50.0% vs 13.3%, P < 0.001) (Figure 5C and D).

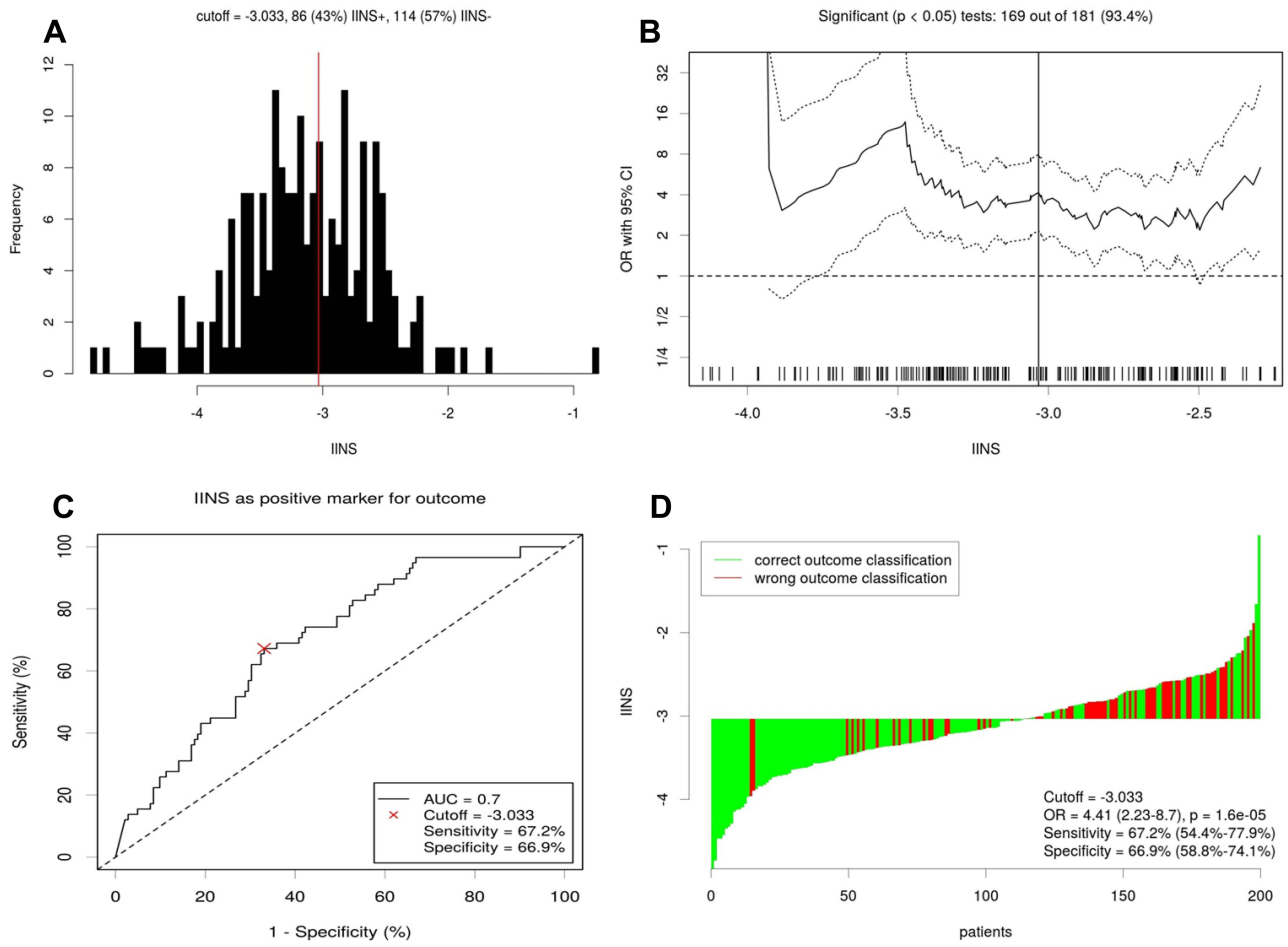

Figure 4 The optimal cutoff value achieved for IINS. (**A**) Distribution for IINS based cutoff optimization. (**B**) Cutoff optimization by correlation with pCR prediction. The vertical line denotes the optimal cutoff point, which was generated by Cutoff Finder. (**C**) ROC for IINS. A score of −3.033 was chosen as the cutoff point representing the optimal balance between sensitivity (67.2%) and specificity (66.9%). (**D**) Waterfall plot for IINS. Biologically effective dose values were stratified with the optimal threshold obtained.

Predictors to pCR with Logistic Analyses and ROC Analyses

The results regarding IINS and other clinical characteristics in univariate logistic regression analyses are shown in Table 3. Predictive factors associated with pCR of nICT for patients with LA-ESCC in univariate logistic regression included BMI, differentiation, cT stage, cN stage, cTNM and IINS. BMI and IINS were associated with nutrition and inflammatory status. In order to avoid collinearity, two models of multivariate logistic regression analyses were performed based on BMI or IINS, respectively (Table 4). According to the multivariate logistic regression analyses, the results indicated that IINS remained an independent predictor of pCR in patients with LA-ESCC treated with nICT (OR = 0.237, 95% CI = 0.117–0.480, P < 0.001). Besides IINS, cTNM was also an independent predictor of pCR (cTNM III vs II: OR=0.242, 95% CI=0.115–0.511, P < 0.001; cTNM IVa vs II: OR=0.071, 95% CI = 0.021–0.237, P < 0.001). To better understand the predictive value of IINS, we compared the AUCs between IINS and BMI. Based on the ROC curves of the three cohorts (total set, training set and validation set), IINS had a larger AUC than BMI, indicating a higher pCR predictive ability of IINS than BMI (Figure 6).

Nomogram Constructed to Predict pCR and Validated

A nomogram was established to predict pCR according to the independent predictors (cTNM and IINS) identified in the multivariate logistic regression analyses for patients with LA-ESCC who were treated with nICT (Figure 7A). The C-index was 0.759 and 0.812 in the training and validation cohort, respectively. Using a calibration plot with bootstrap

Table 2 Comparison of Baseline Characteristics Based on IINS in Training and Validation Sets

	Training (N=200)		P-value	Validation (N=85)		P-value
	High-IINS	Low-IINS		High-IINS	Low-IINS	
Age (years, ≤60/>60)	25/60	38/77	0.585	12/28	17/28	0.450
Sex (male/female)	81/4	105/10	0.274	1/39	3/42	0.365
BMI (Kg/m^2, ≤20/>20)	45/40	11/104	<0.001	15/25	4/41	0.002
Tumor location (U/M/L)	9/56/20	8/65/42	0.127	3/24/13	2/24/19	0.596
Differentiation (W/M/P)	15/39/31	15/52/48	0.595	6/18/16	7/21/17	0.978
Hypertension (Y/N)	18/67	42/73	0.019	10/30	15/30	0.400
Diabetes (Y/N)	1/84	7/108	0.080	0/40	2/43	0.177
Smoking history (Y/N)	62/23	79/36	0.515	31/9	28/17	0.127
Drinking history (Y/N)	64/21	83/32	0.621	26/14	34/11	0.286
cT stage (2/3/4a)	12/54/19	16/75/24	0.964	9/26/5	7/33/5	0.674
cN stage (0/1/2/3)	20/45/16/4	20/59/30/6	0.533	5/25/9/1	5/32/8/0	0.653
cTNM stage (II/III/IVa)	28/38/19	28/63/24	0.313	13/22/5	11/29/5	0.658
ypT stage (0/1/2/3/4a)	38/14/8/16/9	20/31/21/31/12	0.001	20/8/2/6/4	6/13/10/11/5	0.003
ypN stage (0/1/2/3)	65/8/10/2	68/29/15/3	0.024	25/12/1/2	23/15/7/0	0.047
ypTNM (0/I/II/III/IVa)	38/15/8/17/7	20/32/13/40/10	0.001	20/3/2/11/4	6/12/1/25/1	<0.001
pCR (Y/N)	38/47	20/95	<0.001	26/43	16/35	<0.001
Recurrence (Y/N)	9/76	16/99	0.482	3/37	5/40	0.569

Abbreviations: BMI, body mass index; TNM, tumor node metastasis; pCR, pathological complete response; U/M/L, upper/middle/lower; W/M/P, well/moderate/ poor; Y/N, yes/no; IINS, integrative inflammatory and nutritional score.

sampling (n = 1000), the calibration was carried out internally. An acceptable agreement regarding pCR prediction is based on the calibration curves in the two cohorts (Figure 7B and C). A good predictive ability regarding pCR according to the ROC analyses (training cohort: AUC = 0.769; validation cohort: AUC = 0.818) (Figure 7D and E). The DCA of the nomogram was performed and indicated a good clinical applicability of the model in predicting the probability of pCR in two cohorts (Figure 7F and G). These results confirmed that the IINS-based nomogram may serve as a simple and potential model in risk stratification regarding pCR prediction in LA-ESCC treated with nICT.

Discussion

In the present study, we initially constructed and verified a novel score of IINS based on various pretreatment inflammatory and nutritional indexes to predict pCR in patients with LA-ESCC who received nICT. In addition, a novel nomogram including IINS and cTNM was established to predict the pCR after nICT for patients with LA-ESCC. The present study is the largest study regarding nICT in ESCC. Compared with previous small sample studies, our study provides more authentic and reliable results of nICT in ESCC. Although this is not the first study to use inflammatory and nutritional indexes to predict pCR, to our knowledge, the present study is the first report focused on various inflammatory and nutritional indexes in predicting pCR in LA-ESCC patients who received nICT. This is also the first study to propose a nomogram model, which indicates an excellent pCR predictive effect both in the training and validation cohorts for LA-ESCC treated with nICT.

Neoadjuvant treatment combined with surgery was recommended by the NCCN guidelines and CSCO guidelines.[3,4] In recent years, immunotherapy represented by ICIs has become a research hotspot in cancer treatment. Immunotherapy significantly improved the long-time survival of advanced ESCC in the ATTRACTION and KEYNOTE studies.[5,6] Following encouraging conclusions from the advanced ESCC, ICIs have already been investigated for resectable LA-ESCC. Recently, more and more studies revealed that nICT is safe and feasible for patients with LA-ESCC.[8–10] The results demonstrated that nICT had manageable adverse effects, high R0 resection rate, promising pCR rate and limited postoperative complications.

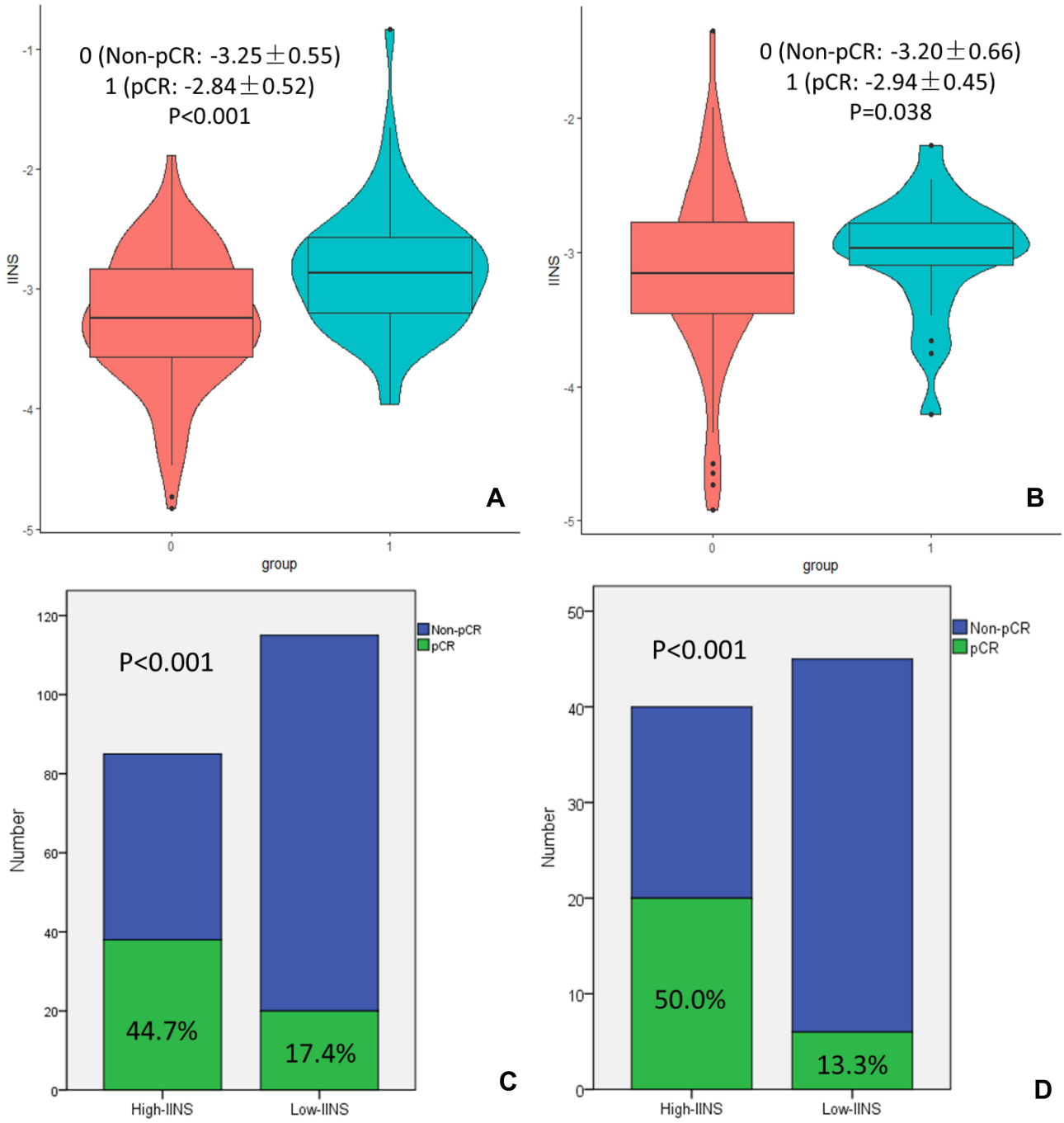

Figure 5 The violin plots and histograms regarding IINS. The violin plots regarding IINS values grouped by pCR in the (**A**) training and (**B**) validation cohort. The histograms regarding pCR rate grouped by pCR in the (**C**) training and (**D**) validation set.

Studies have indicated that patients with pCR in pathological results after neoadjuvant treatment have a significantly prolonged survival in ESCC. Therefore, predicting pCR to neoadjuvant therapy has been a focus of research for ESCC in recent years. However, at present no available and satisfactory clinical tools have been developed to confidently predict pCR in ESCC. Several studies revealed that a variety of inflammatory and nutritional indexes correlated with the response to nCRT.[14–18] However, the exact mechanisms of these indexes for pCR in ESCC received nICT remain unclear. NEUTs can promote tumor growth, and more and more data support the active role for NEUTs in cancer progression to distant metastasis. Recent study revealed that an increased interleukin-17 produced by NEUTs was associated with cancer

Table 3 Logistic Univariate Analysis of Predictors for pCR in Training Cohort

	OR (95% CI)	P value
Age (years, >60 vs ≤60)	1.156 (0.594–2.249)	0.670
Sex (male vs female)	0.517 (0.171–1.564)	0.243
BMI (Kg/m^2, >20 vs ≤20)	0.461 (0.239–0.887)	0.020
Tumor location (U/M/L)		
Middle vs Upper	1.488 (0.455–4.865)	0.511
Lower vs Upper	1.130 (0.322–3.972)	0.848
Differentiation (W/M/P)		
Moderate vs Well	0.379 (0.162–0.887)	0.025
Poor vs Well	0.295 (0.121–0.717)	0.007
Hypertension history (Y vs N)	0.511 (0.248–1.054)	0.069
Diabetes history (Y vs N)	0.689 (0.139–3.419)	0.648
Smoking history (Y vs N)	0.577 (0.301–1.104)	0.097
Drinking history (Y vs N)	0.925 (0.465–1.839)	0.824
cT stage (T2/T3/T4a)		
T3 vs T2	0.376 (0.163–0.863)	0.021
T4a vs T2	0.089 (0.025–0.316)	<0.001
cN stage (N+ vs N0)	0.485 (0.311–0.754)	0.001
cTNM stage (II/III/IVa)		
III vs II	0.238 (0.118–0.480)	<0.001
IVa vs II	0.083 (0.026–0.263)	<0.001
IINS (Low vs High)	0.260 (0.137–0.496)	<0.001

Abbreviations: pCR, pathological complete response; BMI, body mass index; U/M/L, upper/middle/lower; W/M/P, well/moderate/poor; Y/N, yes/no; TNM, tumor node metastasis; IINS, integrative inflammatory and nutritional score; OR, odds ratio; CI, confidence interval.

Table 4 Logistic Multivariate Analysis of Predictors for pCR in Training Cohort

Models	OR (95% CI)	P value
(1) BMI model		
BMI (Kg/m^2, >20 vs ≤20)	0.376 (0.181–0.779)	0.008
cTNM stage (II/III/IVa)		
III vs II	0.220 (0.107–0.455)	<0.001
IVa vs II	0.072 (0.022–0.236)	<0.001
(2) IINS model		
IINS (Low vs High)	0.237 (0.117–0.480)	<0.001
cTNM stage (II/III/IVa)		
III vs II	0.242 (0.115–0.511)	<0.001
IVa vs II	0.071 (0.021–0.237)	<0.001

Abbreviations: pCR, pathological complete response; BMI, body mass index; TNM, tumor node metastasis; IINS, integrative inflammatory and nutritional score; OR, odds ratio; CI, confidence interval.

progression, leading to immune escape.[30] Study also indicated that cancer progression was also associated with circulating activated LYs.[31] In addition, more and more evidence supports the idea that PLTs and MONOs play several roles in the progression of cancer.[32] These results indicated that peripheral blood indicators could be associated with immune response in several cancers.

Previous published studies including meta-analysis revealed that patients with lower BMI were associated with higher pCR rates in breast cancer receiving neoadjuvant chemotherapy (nCT).[33,34] Studies also reported that increased pCR rate

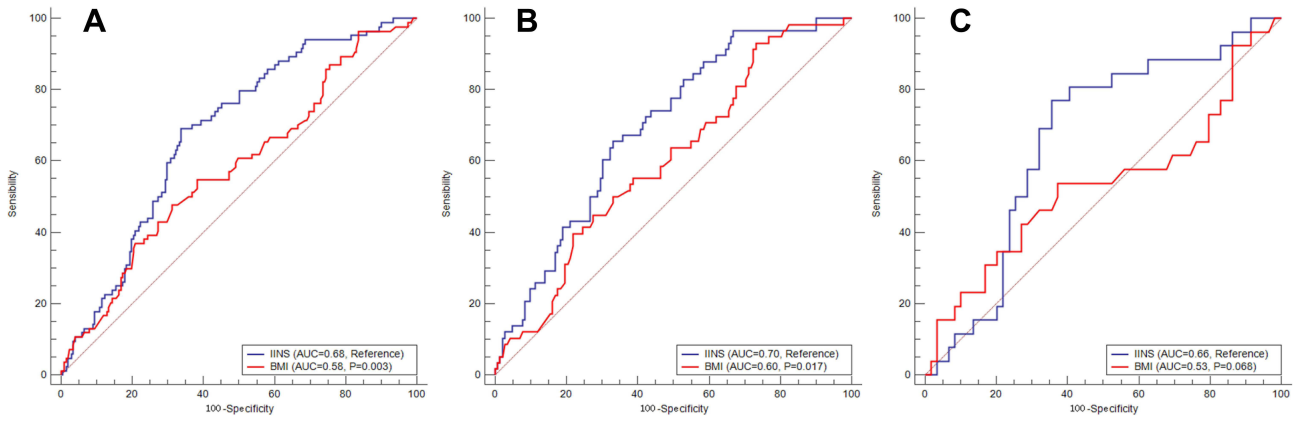

Figure 6 ROC curves for pCR prediction between IINS and BMI. Based on the ROC curves in (**A**) total set, (**B**) training set and (**C**) validation set, IINS had a larger AUC than BMI, indicating a higher pCR predictive ability of IINS than BMI.

was correlate to high levels of stromal tumor-infiltrating lymphocytes (sTIL). Therefore, BMI affected pCR by modifying sTIL in breast cancer patients who were treated with nCT.[35] In the current study, BMI and IINS were associated with nutrition and inflammatory status. In order to avoid collinearity, two models of multivariate logistic regression analyses were performed, respectively. Our study also revealed that a lower BMI was associated with a higher pCR rate. Based on the ROC curves, IINS had a larger AUC compared with BMI, indicating a higher pCR predictive ability.

Recently, a study including 64 LA-ESCC patients who received nICT analyzed the associations between several indicators (NLR, PLR, LMR and SII) and pCR.[19] The authors focused on the changes of these indicators between baseline and post-treatment in small sample. The authors used ROC to evaluate pCR sensitivity and indicated that the pretreatment indicators were not predictors between pCR and non-pCR patients. Our study revealed that the pCR prediction for a single pretreatment indicator is low, which was similar to the above study. However, the sample in the above study was small. Moreover, the authors in the above study used post-treatment indexes to predict pCR, but they ignored the fact that nICT may influence these blood indicators which will limit the application. In addition, the previous study did not analyze whether these blood indicators were predictive factors affecting pCR in logistic regression analyses. We hypothesized that an integrative indicator might be more valuable than a single indicator. Therefore, a novel predictor of IINS-based nomogram was initially constructed and verified for pCR prediction after nICT in patients with LA-ESCC.

In our study, we initially explored an integrative model to predict pCR after nICT in LA-ESCC. Recently, nomogram is considered to be a reliable tool for integrating and quantifying significant risk factors for cancer prognosis because of its ability to generate individual probabilities of clinical events by integrating different prognostic variables.[36,37] In the current study, a novel predictive nomogram based on two variables (IINS and cTNM) was firstly established and validated. The nomogram showed a good excellent risk stratification and predictive ability. To our knowledge, this is the first study to construct a nomogram to predict pCR efficacy in LA-ESCC patients treated with nICT.

Limitations should be noticed in our study. First, this was a single-center retrospective study. As a result, there may be potential data collection bias. Secondly, inflammatory and nutritional indexes may be affected by various conditions, although strict inclusion and exclusion criteria were adopted, which will limit the application of IINS in pCR prediction. Thirdly, the exact mechanisms regarding inflammation and nutrition in pCR prediction require further exploration. Finally, to date, there are no relevant guidelines for adjuvant treatment following nICT in EC. Therefore, adjuvant therapy mostly depended on published studies and clinical experience of each institute. Although the adjuvant therapy was not associated with the results of pCR in the current study, it was closely correlated to prognosis and recurrence. Therefore, more clinical trials are needed to explore the best adjuvant treatment for LA-ESCC after nICT. Although the above limitations exist, the IINS-based nomogram may serve as a simple and potential model for risk stratification regarding pCR prediction in LA-ESCC treated with nICT.

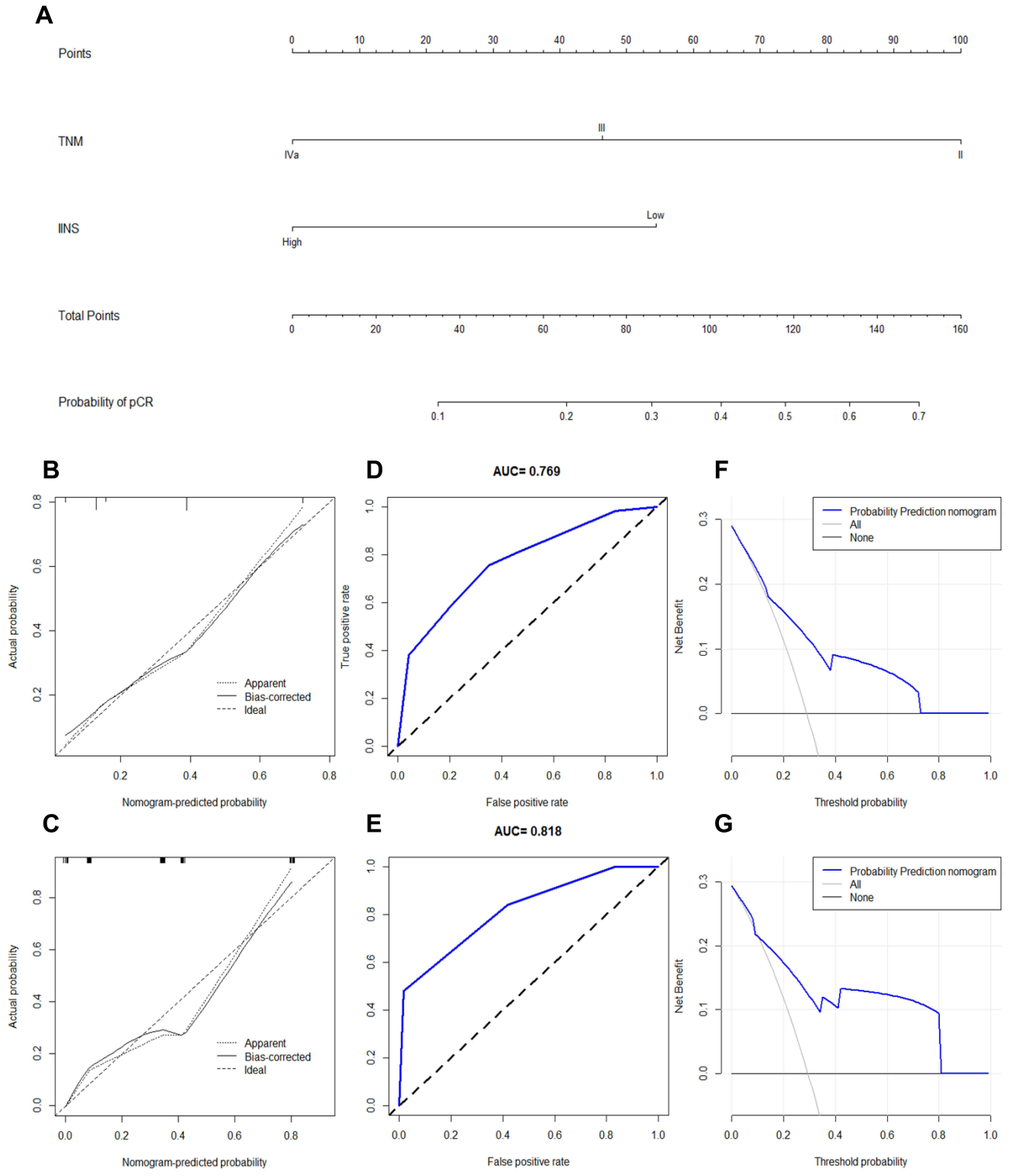

Figure 7 Nomogram established based on IINS and valeted. (**A**) A nomogram based on IINS and TNM was established to predict pCR. Calibration of the nomogram used to predict pCR after nICT in the (**B**) training and (**C**) validation cohort. ROC indicated an acceptable agreement regarding pCR prediction in the (**D**) training and (**E**) validation cohort. The DCA indicated a good clinical applicability of the model in predicting the probability of pCR in the (**F**) training and (**G**) validation cohort.

Conclusion

Pretreatment IINS was an independent predictor for pCR in LA-ESCC patients who received nICT. The IINS-based nomogram may serve as a potential model in risk stratification of pCR prediction in LA-ESCC treated with nICT, which may improve the application in daily clinical work and help clinicians provide a more personalized treatment.

Data Sharing Statement

The data analyzed in this study are available from the corresponding author (Qixun Chen or Xiangdong Cheng) on reasonable requests.

Ethics Approval and Consent to Participate

The present study was approved by the ethics committee of Zhejiang Cancer Hospital (IRB-2020-183) and conducted in accordance with the Declaration of Helsinki. Informed consent was achieved from each patient.

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Disclosure

The authors declare that they have no competing interests.

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