

Original Article

Development and validation of a nomogram based on multiple preoperative immunoinflammatory indexes for survival prediction in patients with stage IA-IB endometrial cancer

Nie Zhang^{1,4*}, Hong Liu^{2*}, Jiankang Yang³, Fei Zhong⁴

¹Graduate School of Anhui Medical University, Hefei, Anhui, China; ²Department of Cardiovascular, Fuyang Hospital of Anhui Medical University, Fuyang, Anhui, China; ³Department of Cardiac Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China; ⁴Department of Oncology, Fuyang Hospital of Anhui Medical University, Fuyang, Anhui, China. *Equal contributors and co-first authors.

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Abstract: Objectives: To evaluate the preoperative systemic immune-inflammation index (SII), advanced lung cancer inflammation index (ALI), neutrophil to lymphocyte ratio (NLR), and prognostic nutritional index (PNI) capacity to predict the prognosis of stage IA-IB endometrial carcinoma (EC) patients after operation, and establish a nomogram model to guide clinical practice. Methods: A total of 387 patients with EC (R0 resection, stage IA-IB) were assessed. Clinical information and the SII, NLR, ALI, and PNI values were obtained. The low and high ratio groups were separated using the receiver operating characteristic curve (ROC). Pearson's χ^2 -test or Fisher's exact test was used to determine their relationship with clinical variables. To determine the independent prognostic factors, Cox regression was utilized to do the univariate and multivariate survival analyses. The Kaplan-Meier method was used to draw the survival curve in our survival analysis. Depending upon the independent prognostic factors, the nomogram for Overall survival (OS) and Disease-free survival (DFS) nomogram was developed, and its discrimination ability was validated by the consistency index (C-index) and calibration curve. Results: Cox regression analysis revealed that FIGO staging, Ki-67 expression level, PNI, and ALI are independent prognostic factors for both OS and DFS. Then a novel predictive nomogram was developed, and its C-index value for OS and DFS was 0.829 and 0.814, respectively. The calibration curves demonstrated consistency amid the predicted prognosis using the developed nomogram and the actual observed outcomes. Conclusions: The ALI and PNI could serve as readily available prognostic indicators for OS and DFS prediction in stage IA-IB EC patients. The nomogram developed owned superior power for OS and DFS prediction in stage IA-IB EC patients, and it would assist clinical oncologists in accurately predicting the individual's OS and DFS.

Keywords: Endometrial cancer, preoperative immunoinflammatory index, prognostic prediction, nomogram

Introduction

Endometrial carcinoma (EC) is one of the most prevalent gynecological malignancies with increasing incidence and associated mortality [1, 2]. Since patients with EC tend to have abnormal vaginal bleeding in the early stage, which is easily detected at an early stage [3], more than 50% of EC patients are diagnosed at an early stage (stage IA-IB) [4, 5]. Although the prognosis of early EC is good, in our clinical work, we find that some patients with early endometrial cancer or low-grade early EC will

experience recurrence and metastasis after treatment, and their prognosis is poor. Therefore, early diagnosis and treatment are essential for improving patient survival rates and prolonging patient survival.

Despite the fact that conventional clinical characteristics like Federation International of Gynecology and Obstetrics (FIGO) stage, histologic type, lymph node metastasis, tumor grade, and muscle invasion are currently regarded as risk factors for prognosis prediction in EC patients [6, 7], the majority of these predictive

items are only available after surgical treatment, and their capacity to predict recurrence and estimate survival is insufficient. There is still a lack of practical hematological evaluation indexes with high sensitivity and specificity for EC. Therefore, the clinical study's core is finding the best EC predictive and prognostic markers.

Systemic immunological inflammation is implicated in the pathways of carcinogenesis, progression, and metastasis, according to earlier research. Inflammation has become a key mediator of malignant disease [8-10]. Because inflammation is a vital feature of the tumor microenvironment and there is a close association between systemic inflammation and cancer progression and metastasis [11], some hematological inflammatory parameters such as neutrophils, lymphocytes, monocytes, and platelets, to a certain extent, have important predictive value for the prognosis of cancers. Previous studies have demonstrated that the hematological immunoinflammatory parameters, including NLR, ALI, PNI, and SII, could accurately envisage the prognosis of several malignant tumors such as esophageal, pancreatic, colorectal, and lung cancer [12-19]. However, the predictive advantage of these indexes for the prognosis of stage IA-IB EC patients is currently unclear.

This study investigated the prognostic value of preoperative NLR, ALI, PNI, and SII in stage IA-IB EC patients. Then we developed a novel nomogram depending upon the independent prognostic factors, including multiple preoperative immunoinflammatory indexes, to efficiently predict the OS and DFS of stage IA-IB EC patients.

Materials and methods

General information

According to inclusion and exclusion criteria, patients pathologically diagnosed with EC in the Affiliated Hospital of Anhui Medical University from January 2013 to January 2017 were retrospectively enrolled in this study. Inclusion criteria: (1) patients who received R0 resection and had been pathologically diagnosed with early stage EC (stage IA-IB, according to FIGO staging system); (2) patients with no chemotherapy, radiotherapy, and other anti-

tumor treatments before surgery; (3) patients with comprehensive follow-up. Exclusion criteria: (1) patients with distant metastases; (2) patients with preoperative systemic infection, autoimmune disease, or hematologic disease; (3) patients with nutrition support therapy or blood transfusion within 1 month before blood collection; (4) patients with other malignant tumors; (5) patients who were lost to follow-up. All procedures of this study complied with the Helsinki Declaration.

Data collection

Clinical information of enrolled patients including age, body weight, height, menopausal status, history of hypertension and diabetes, histological type, histopathological grade, FIGO staging, estrogen receptor (ER) expression level, Ki-67 expression level, progesterone receptor (PR) expression level and depth of myometrial infiltration were collected from the hospital's electronic medical record management system. The need for further postoperative anti-tumor therapy was determined per the National Comprehensive Cancer Network Clinical Practice Guidelines for EC, and if necessary, the standard treatment was given. The standard formula was used to determine Body Mass Index (BMI). Blood samples were obtained within 7 days before surgery to measure the count of neutrophils, lymphocytes, platelet, and level of serum albumin. Inflammation-based indices were calculated as follows: SII = platelet count \times NLR; NLR = neutrophil count/lymphocyte count; ALI = BMI (kg/m²) \times albumin (g/dL)/NLR; PNI = 10 \times albumin (g/dL) + 5 \times lymphocyte count (10⁹/L).

Follow-up

Survivors were followed up via phone, in-patient reexamination, and outpatient reexamining. Routine gynecological examinations, hematological markers, computed tomography (CT), gynecological ultrasonography, and magnetic resonance imaging (MRI) were all part of the progress follow-up. Following surgery, all patients were checked on every three to four months, every six months after three years, and then once a year after five years, up until the end of the follow-up or loss of follow-up. The follow-up came to an end on December 31, 2021. OS was outlined as the duration from

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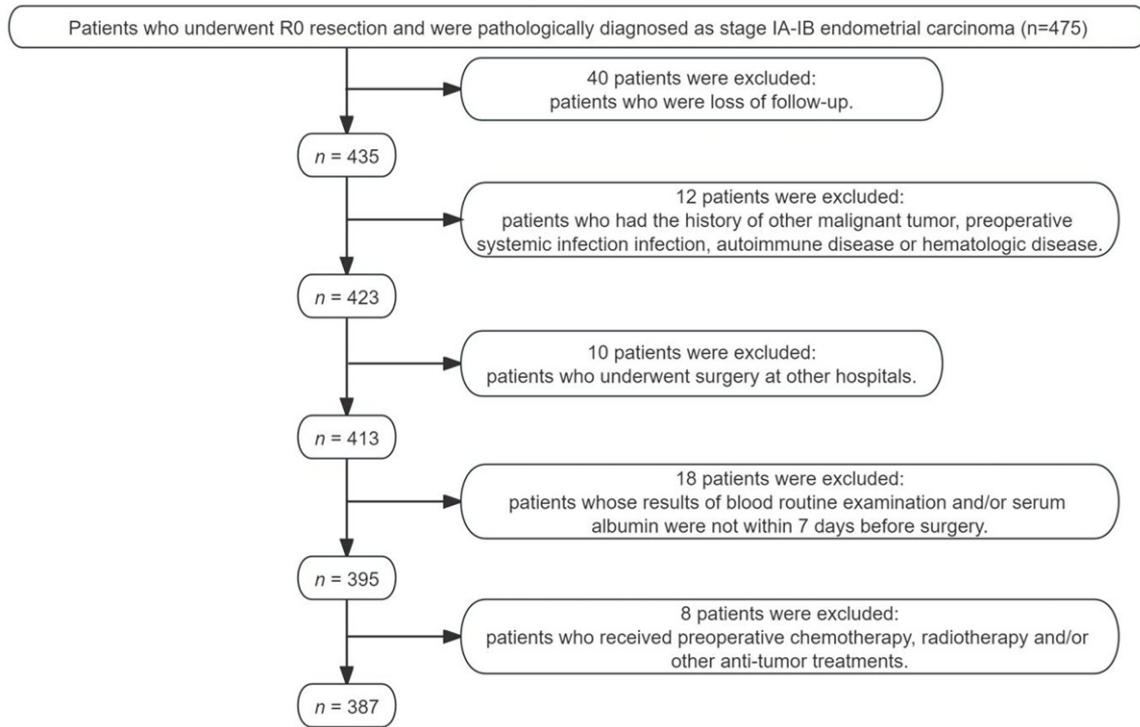


Figure 1. Workflow of patient selection.

the day of surgery to the study's conclusion or until the patient died. The interval between a postoperative pathology diagnosis and a physical examination suggested the development of distant metastases was used to determine DFS.

Statistical analysis

ROC curves were utilized to identify the optimal cut-off values of NLR, ALI, PNI, and SII. Patients were then grouped into the high or the low group based on each parameter's cut-off value, and Fisher's exact and Chi-square tests were used to explore the association between the above indexes and clinical characteristics. The survival curves were plotted using the Kaplan-Meier method, and their comparison was made using the log-rank test. Univariate and multivariate Cox regression analysis was performed to identify the independent prognostic predictors of OS and DFS. The OS and DFS prediction nomogram was created using R v4.1.2 (<https://www.r-project.org/>), and its discrimination ability was assessed using the C-index and calibration curve. It was deemed statistically significant at $P < 0.05$.

Results

Baseline characteristics of enrolled patients

The flow chart of the study is shown in **Figure 1**. In total, 88 patients were excluded, including 8 patients who received neoadjuvant therapy such as radiotherapy or chemotherapy before surgery, 18 patients whose routine blood examination results or serum albumin was not within 7 days of surgery, and 40 patients who were lost to follow-up. Additionally, 12 patients were found to have combined other cancers. Ultimately, 387 patients were included in the study.

The characteristics of 387 participants are shown in **Table 1**. The mean age of patients was 55.46 ± 8.42 years (range 26-84 years), and the mean follow-up time was 69.25 ± 10.56 months (range 38.7-100.0 months). There were 10 (2.60%) patients with BMI < 18.5 kg/m², 151 (39.00%) patients with BMI of 18.5-24.9, and 226 (58.40%) patients with BMI > 24.9 kg/m². Besides, 328 (84.80%) patients with stage IA and 59 (15.20%) patients were diagnosed with stage IB. A total of 369 (95.30%) patients with type I cancer and 18

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Table 1. Baseline characteristics of enrolled patients

| Characteristics | Number of cases (n; %) |
|-------------------------|------------------------|
| Age (years) | |
| < 55 | 196 (50.60%) |
| ≥ 55 | 191 (49.40%) |
| BMI | |
| < 18.5 | 10 (2.60%) |
| 18.5~24.9 | 151 (39.00%) |
| > 24.9 | 226 (58.40%) |
| History of hypertension | |
| No | 315 (81.40%) |
| Yes | 72 (18.60%) |
| History of diabetes | |
| No | 339 (87.60%) |
| Yes | 48 (12.40%) |
| Menopausal status | |
| No | 140 (36.20%) |
| Yes | 247 (63.80%) |
| Ki-67 expression level | |
| < 55 | 265 (68.50%) |
| ≥ 55 | 122 (31.50%) |
| Histopathological grade | |
| G1 | 157 (40.60%) |
| G2 | 178 (46.00%) |
| G3 | 52 (13.40%) |
| Histological type | |
| Type I | 369 (95.30%) |
| Type II | 18 (4.70%) |
| PR expression level | |
| Positive | 311 (80.40%) |
| Negative | 76 (19.60%) |
| FIGO staging | |
| IA | 328 (84.80%) |
| IB | 59 (15.20%) |
| ER expression level | |
| Positive | 356 (92.00%) |
| Negative | 31 (8.00%) |

(4.70%) patients were diagnosed with type II cancer. Also, 157 (40.60%) and 178 (46.00%) patients had a tumors, grade 1 and 2, respectively, and 52 (13.40%) patients had grade 3. There were 247 (63.80%) of the patients who were menopausal, while 72 (18.60%) and 48 (12.40%) patients had hypertension and diabetes, respectively. There were 356 (92.00%) and 311 (80.40%) patients who were ER and

PR positive, respectively. Finally, 122 (31.50%) patients had a Ki67 expression index ≥ 55.

The optimal cut-off values of preoperative NLR, ALI, PNI, and SII

ROC curve of OS and DFS was plotted and used to determine its optimal value. For OS, the optimum cut-off values for preoperative NLR, ALI, PNI, and SII were 3.13, 38.46, 51.55, and 763.1, respectively, and their area under the curve (AUC) was 0.702, 0.785, 0.711 and 0.765, respectively (**Figure 2**). While for DFS, the optimum cut-off values of 3.23, 38.46, 53.15, and 763.1 for preoperative NLR, ALI, PNI, and SII, respectively, and the AUC for preoperative NLR, ALI, PNI, and SII were 0.706, 0.782, 0.702 and 0.767, respectively (**Figure 3**). All patients were then dichotomized into the high and low groups per the optimum cut-off value of each index.

Association of preoperative NLR, ALI, PNI, and SII with clinicopathological characteristics

Next, we examined the association of preoperative NLR, ALI, PNI, and SII with clinicopathological factors. As depicted in **Table 2**, preoperative ALI was closely associated with FIGO staging ($P = 0.017$) and menopausal status ($P = 0.048$). In addition, preoperative SII ($P = 0.021$) and preoperative NLR ($P = 0.017$) were significantly correlated with menopausal status.

Relationship between preoperative NLR, ALI, PNI, and SII and postoperative OS and DFS in stage IA-IB EC patients

We then calculated each group's 5-year OS and DFS rates and analyzed the effect of the above preoperative immunoinflammatory indexes on the patient's OS and DFS. The results (**Figures 4, 5**) suggested that the high NLR group (OS: 94.50% vs. 78.13%; DFS: 89.90% vs. 63.33%), high SII group (OS: 96.57% vs. 77.60%; DFS: 92.75% vs. 64.80%), low ALI group (OS: 70.33% vs. 96.62%; DFS: 54.95% vs. 92.57%) and low PNI group (OS: 73.68% vs. 94.53%; DFS: 68.60% vs. 90.60%) were related to a shorter DFS and OS. As a whole, the survival gap between high ALI and low ALI groups was larger than other preoperative immunoinflammatory indexes, which implied that ALI might be more effective than other indexes in predicting DFS and OS in stage IA-IB EC patients.

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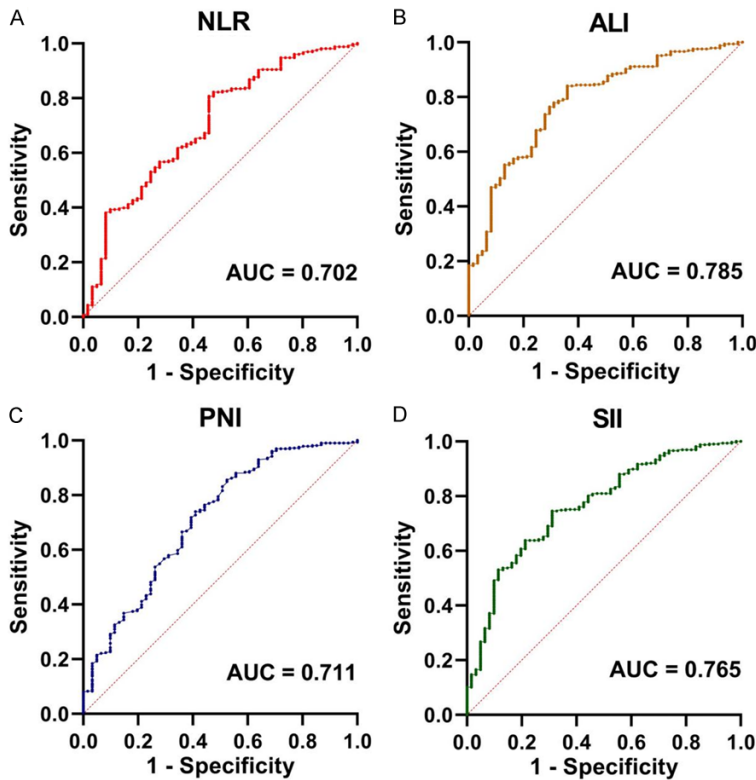


Figure 2. ROC curves of NLR (A), ALI (B), PNI (C) and SII (D) to predict OS in patients with stage IA-IB endometrial cancer. NLR: neutrophil to lymphocyte ratio; ALI: advanced lung cancer inflammation index; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

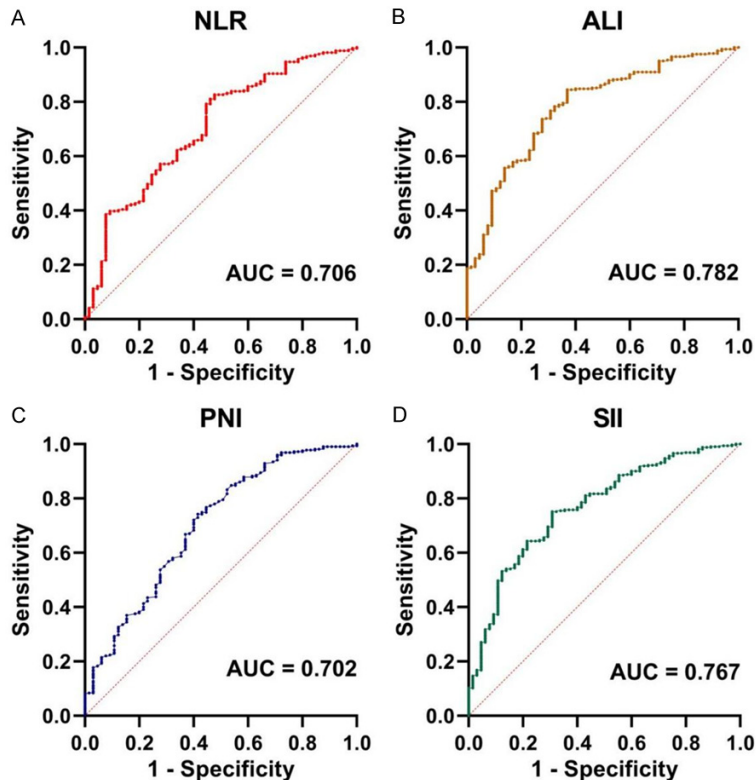


Figure 3. ROC curves of NLR (A), ALI (B), PNI (C) and SII (D) to predict DFS in patients with stage IA-IB endometrial cancer. NLR: neutrophil to lymphocyte ratio; ALI: advanced lung cancer inflammation index; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

In terms of univariate analysis, the results revealed that FIGO staging, NLR, PNI, ALI, SII ($P < 0.001$), and Ki-67 expression level ($P = 0.002$), were significantly related with OS in these patients. The FIGO staging, NLR, PNI, ALI, SII ($P < 0.001$), and Ki-67 expression level ($P = 0.011$) were significantly related to DFS in these patients. While age, BMI, menopause status, tumor grade, ER expression level, PR expression level, history of hypertension and diabetes, and histological type had no statistically significant association with OS or DFS. These significant risk factors were then incorporated into the multivariate Cox regression model, and the results demonstrated that FIGO staging (HR = 4.35, 95% CI: 2.56-7.39, $P < 0.001$), PNI (HR = 0.35, 95% CI: 0.19-0.57, $P < 0.001$), Ki-67 expression level (HR = 2.04, 95% CI: 1.22-3.41, $P = 0.006$) and ALI (HR = 0.27, 95% CI: 0.12-0.63, $P = 0.002$) were independent prognostic factors for OS in stage IA-IB EC patients. FIGO staging (HR = 2.31, 95% CI: 2.29-6.32, $P < 0.001$), PNI (HR = 0.42, 95% CI: 0.25-0.72, $P = 0.001$), Ki-67 expression level (HR = 1.84, 95% CI: 1.12-3.04, $P = 0.016$) and ALI (HR = 0.28, 95% CI: 0.12-0.67, $P = 0.004$) remained to be independent prognostic factors for DFS in stage IA-IB EC patients (Tables 3, 4; Figure 6).

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Table 2. The association of preoperative NLR, PNI, ALI and SII with clinicopathological characteristics of enrolled patients

| Characteristics | NLR | | | ALI | | | PNI | | | SII | | |
|-------------------------|-----------|------------|----------|-----------|------------|----------|-----------|------------|----------|-----------|------------|----------|
| | Low group | High group | <i>P</i> | Low group | High group | <i>P</i> | Low group | High group | <i>P</i> | Low group | High group | <i>P</i> |
| Age (years) | | | 0.745 | | | 0.223 | | | 0.160 | | | 0.422 |
| < 55 | 146 | 50 | | 41 | 155 | | 33 | 163 | | 129 | 67 | |
| ≥ 55 | 145 | 46 | | 50 | 141 | | 43 | 148 | | 133 | 58 | |
| BMI | | | 0.183 | | | 0.192 | | | 0.227 | | | 0.271 |
| < 18.5 | 10 | 0 | | 0 | 10 | | 0 | 10 | | 9 | 1 | |
| 18.5~24.9 | 113 | 38 | | 38 | 113 | | 33 | 118 | | 99 | 52 | |
| > 24.9 | 168 | 58 | | 53 | 173 | | 43 | 183 | | 154 | 72 | |
| History of hypertension | | | 0.243 | | | 0.226 | | | 0.708 | | | 0.235 |
| No | 233 | 82 | | 78 | 237 | | 63 | 252 | | 209 | 106 | |
| Yes | 58 | 14 | | 13 | 59 | | 13 | 59 | | 53 | 19 | |
| History of diabetes | | | 0.163 | | | 0.232 | | | 0.541 | | | 0.137 |
| No | 251 | 88 | | 83 | 256 | | 65 | 274 | | 225 | 114 | |
| Yes | 40 | 8 | | 8 | 40 | | 11 | 37 | | 37 | 11 | |
| Menopausal status | | | 0.017 | | | 0.048 | | | 0.893 | | | 0.021 |
| No | 115 | 25 | | 25 | 115 | | 28 | 112 | | 105 | 35 | |
| Yes | 176 | 71 | | 66 | 181 | | 48 | 199 | | 157 | 90 | |
| Histopathological grade | | | 0.890 | | | 0.899 | | | 0.404 | | | 0.557 |
| G1 | 120 | 37 | | 38 | 119 | | 36 | 121 | | 111 | 46 | |
| G2 | 132 | 46 | | 40 | 138 | | 31 | 147 | | 116 | 62 | |
| G3 | 39 | 13 | | 13 | 39 | | 9 | 43 | | 35 | 17 | |
| Histological type | | | 0.157 | | | 0.115 | | | 0.745 | | | 0.259 |
| Type I | 280 | 89 | | 84 | 285 | | 73 | 296 | | 252 | 117 | |
| Type II | 11 | 7 | | 7 | 11 | | 3 | 15 | | 10 | 8 | |
| FIGO staging | | | 0.153 | | | 0.017 | | | 0.224 | | | 0.135 |
| IA | 251 | 77 | | 70 | 258 | | 61 | 267 | | 227 | 101 | |
| IB | 40 | 19 | | 21 | 38 | | 15 | 44 | | 35 | 24 | |
| Ki-67 expression level | | | 0.749 | | | 0.551 | | | 0.266 | | | 0.924 |
| < 55 | 198 | 67 | | 60 | 205 | | 48 | 217 | | 179 | 86 | |
| ≥ 55 | 93 | 29 | | 31 | 91 | | 28 | 94 | | 83 | 39 | |
| ER expression level | | | 0.570 | | | 0.101 | | | 0.367 | | | 0.426 |
| Negative | 22 | 9 | | 11 | 20 | | 8 | 23 | | 19 | 12 | |
| Positive | 269 | 87 | | 80 | 276 | | 68 | 288 | | 243 | 113 | |
| PR expression level | | | 0.525 | | | 0.345 | | | 0.766 | | | 0.902 |
| Negative | 55 | 21 | | 21 | 55 | | 14 | 62 | | 51 | 25 | |
| Positive | 236 | 75 | | 70 | 241 | | 62 | 249 | | 211 | 100 | |

A novel nomogram based on multiple preoperative NLR, ALI, PNI, and SII for OS and DFS prediction was developed and validated

A unique predictive nomogram for OS (**Figure 7**) and DFS (**Figure 8**) in stage IA-IB EC patients was developed depending upon the aforementioned independent prognostic factors; the no-

mogram suggested that the higher the total points, the lower the 5 and 7-year OS and DFS rates. Then, the nomogram's effectiveness was assessed using the C-index and calibration curve. The C-index value of this developed nomogram was 0.829 (0.797-0.860) for OS and 0.814 (0.786-0.843) for DFS, which indicated that this nomogram's prediction accura-

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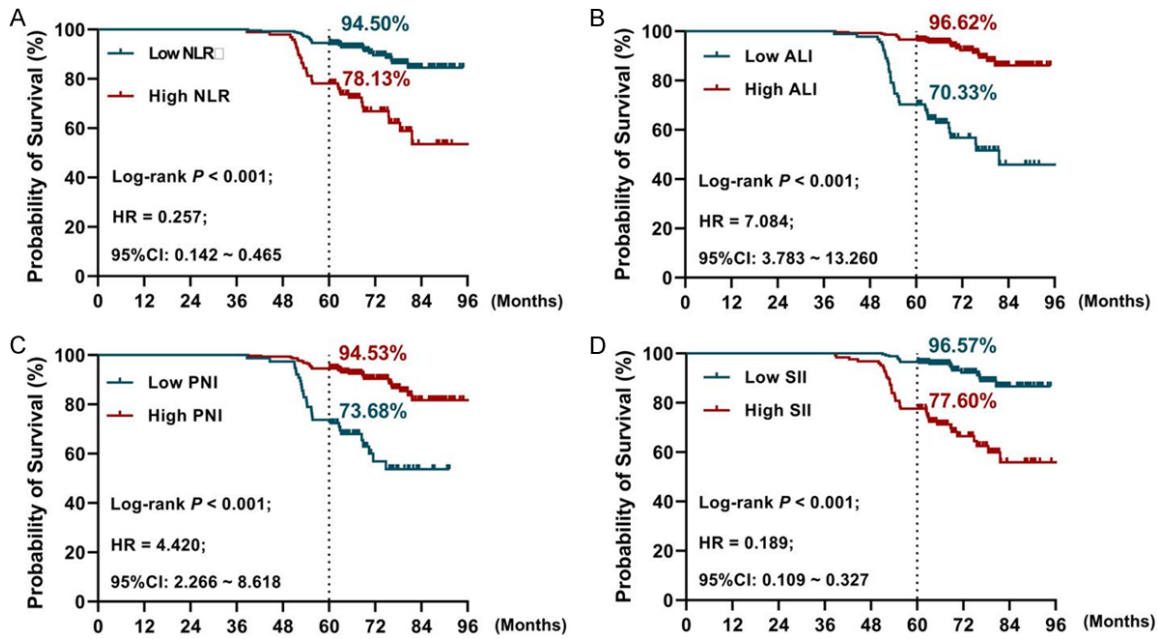


Figure 4. Kaplan-Meier curves of OS in patients with stage IA-IB endometrial cancer according to preoperative hematological immunoinflammatory parameters (A) NLR, (B) ALI, (C) PNI and (D) SII. NLR: neutrophil to lymphocyte ratio; ALI: advanced lung cancer inflammation index; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

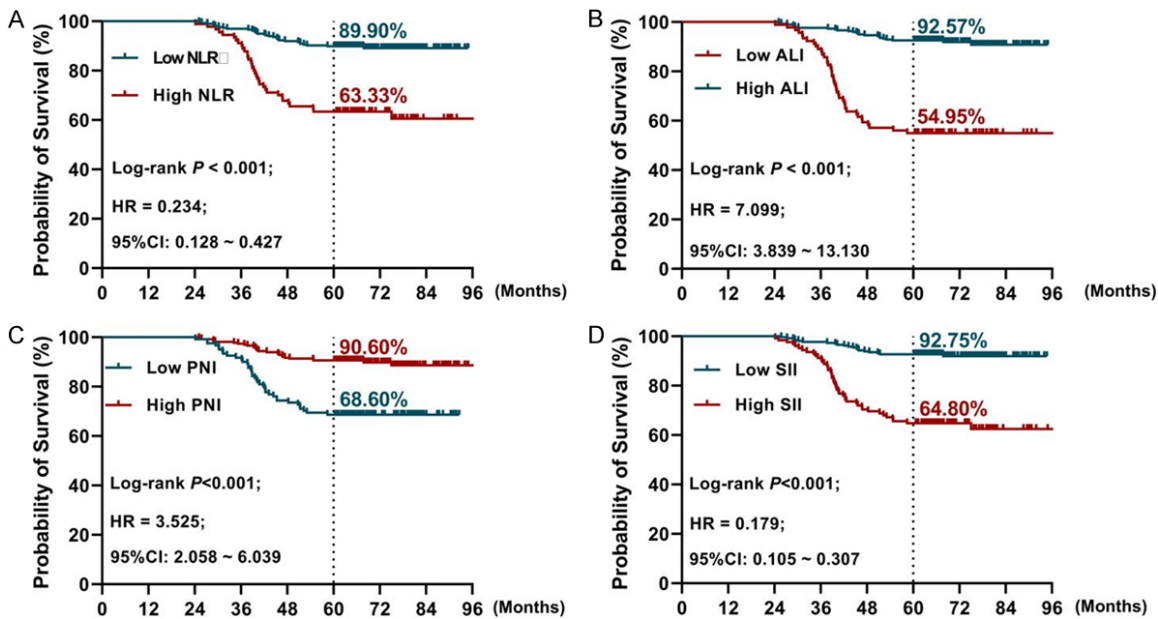


Figure 5. Kaplan-Meier curves of DFS in patients with stage IA-IB endometrial cancer according to preoperative hematological immunoinflammatory parameters (A) NLR, (B) ALI, (C) PNI and (D) SII. NLR: neutrophil to lymphocyte ratio; ALI: advanced lung cancer inflammation index; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

cy was good. Furthermore, the calibration curves demonstrated the consistency between the predicted prognosis from using the developed

nomogram and the actual observed outcomes, which further verified the superior predictive power of this nomogram.

Immunoinflammatory indexes in early stage EC

Table 3. Cox regression analysis of independent risk factors of OS

| Variables | Univariate analysis | | | Multivariate analysis | | |
|--|---------------------|-----------|---------|-----------------------|-----------|---------|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age at surgery (year, < 55 vs. ≥ 55) | 0.97 | 0.59~1.61 | 0.914 | | | |
| BMI | | | | | | |
| < 18.5 | Reference | | | | | |
| 18.5~24.9 | 1.17 | 0.75~1.83 | 0.497 | | | |
| > 24.9 | 1.09 | 0.65~1.81 | 0.746 | | | |
| Menopausal status (yes vs. no) | 0.71 | 0.41~1.23 | 0.222 | | | |
| History of hypertension (yes vs. no) | 0.90 | 0.44~1.84 | 0.776 | | | |
| History of diabetes (yes vs. no) | 1.74 | 0.88~3.46 | 0.115 | | | |
| Histological type (type I vs. type II) | 1.23 | 0.38~3.92 | 0.731 | | | |
| Histopathological grade | | | | | | |
| G1 | Reference | | | | | |
| G2 | 0.86 | 0.58~1.25 | 0.421 | | | |
| G3 | 1.06 | 0.46~2.42 | 0.900 | | | |
| ER expression level | 1.11 | 0.44~3.36 | 0.703 | | | |
| PR expression level | 0.74 | 0.41~1.33 | 0.313 | | | |
| FIGO staging (IA vs. IB) | 4.98 | 2.96~8.39 | < 0.001 | 4.35 | 2.56~7.39 | < 0.001 |
| Ki-67 expression level (< 55 vs. ≥ 55) | 2.22 | 1.34~3.67 | 0.002 | 2.04 | 1.22~3.41 | 0.006 |
| NLR (< 3.13 vs. ≥ 3.13) | 3.90 | 2.36~6.45 | < 0.001 | 1.11 | 0.53~2.33 | 0.779 |
| ALI (< 38.46 vs. ≥ 38.46) | 0.14 | 0.08~0.24 | < 0.001 | 0.27 | 0.12~0.63 | 0.002 |
| PNI (< 51.55 vs. ≥ 51.55) | 0.23 | 0.14~0.37 | < 0.001 | 0.35 | 0.19~0.57 | < 0.001 |
| SII (< 763.1 vs. ≥ 763.1) | 5.31 | 3.09~9.13 | < 0.001 | 1.64 | 0.78~3.42 | 0.189 |

Table 4. Cox regression analysis of independent risk factors of DFS

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---------------------|-----------|---------|-----------------------|-----------|---------|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age at surgery (year, < 55 vs. ≥ 55) | 1.07 | 0.66~1.74 | 0.794 | | | |
| BMI | | | | | | |
| < 18.5 | Reference | | | | | |
| 18.5~24.9 | 1.17 | 0.74~1.84 | 0.505 | | | |
| > 24.9 | 1.01 | 0.61~1.66 | 0.977 | | | |
| Menopausal status (yes vs. no) | 0.82 | 0.49~1.38 | 0.448 | | | |
| History of hypertension (yes vs. no) | 0.81 | 0.41~1.59 | 0.535 | | | |
| History of diabetes (yes vs. no) | 1.37 | 0.70~2.69 | 0.363 | | | |
| Histological type (type I vs. type II) | 1.04 | 0.33~3.32 | 0.946 | | | |
| Histopathological grade | | | | | | |
| G1 | Reference | | | | | |
| G2 | 0.94 | 0.66~1.35 | 0.743 | | | |
| G3 | 1.10 | 0.50~2.40 | 0.811 | | | |
| ER expression level (negative vs. positive) | 1.37 | 0.50~3.77 | 0.542 | | | |
| PR expression level (negative vs. positive) | 0.80 | 0.45~1.42 | 0.444 | | | |
| FIGO staging (IA vs. IB) | 4.75 | 2.89~7.80 | < 0.001 | 2.31 | 2.29~6.32 | < 0.001 |
| Ki-67 expression level (< 55 vs. ≥ 55) | 1.89 | 1.16~3.09 | 0.011 | 1.84 | 1.12~3.04 | 0.016 |
| NLR (< 3.23 vs. ≥ 3.23) | 3.80 | 2.64~7.00 | < 0.001 | 1.11 | 0.52~2.36 | 0.796 |
| ALI (< 38.46 vs. ≥ 38.46) | 0.14 | 0.08~0.23 | < 0.001 | 0.28 | 0.12~0.67 | 0.004 |
| PNI (< 53.15 vs. ≥ 53.15) | 0.28 | 0.17~0.46 | < 0.001 | 0.42 | 0.25~0.72 | 0.001 |
| SII (< 763.1 vs. ≥ 763.1) | 5.60 | 3.31~9.49 | < 0.001 | 1.67 | 0.76~3.67 | 0.200 |

Immunoinflammatory indexes in early stage EC

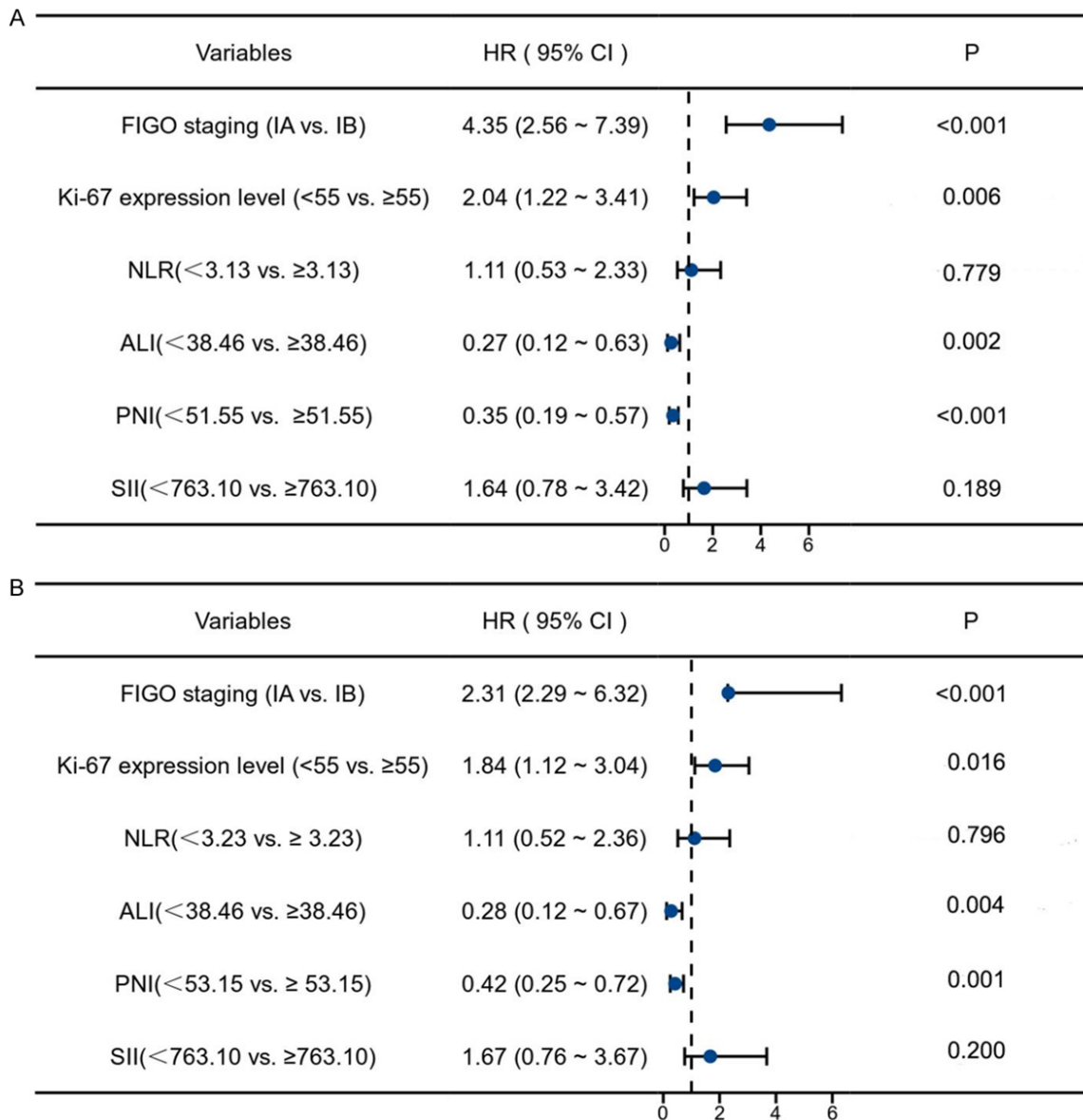


Figure 6. Forest plots of independent risk factors for OS (A) and DFS (B) in patients with stage IA-IB endometrial cancer.

Discussion

Cancer is closely associated with systemic inflammation, which promotes cancer proliferation, invasion, and metastasis [20, 21]. Numerous inflammatory markers have been demonstrated to aid in predicting and tracking the prognosis of cancer patients as a result of substantial research into the prognostic importance of inflammatory markers in cancer patients in recent years. The association between preoperative immunological and inflammatory indicators and the prognosis of stage IA-IB EC

patients has only been briefly studied. Based on the many clinical composite markers published, we examined the predictive value of the ALI, SII, PNI and NLR.

In this retrospective study, we analyzed the prognostic effect of several hematological immunoinflammatory parameters including ALI, SII, PNI and NLR on OS and DFS in patients with stage IA-IB EC, and the results indicated that there was significant relationship between the above preoperative immunoinflammatory indexes and OS as well as DFS, among them, ALI

Immunoinflammatory indexes in early stage EC

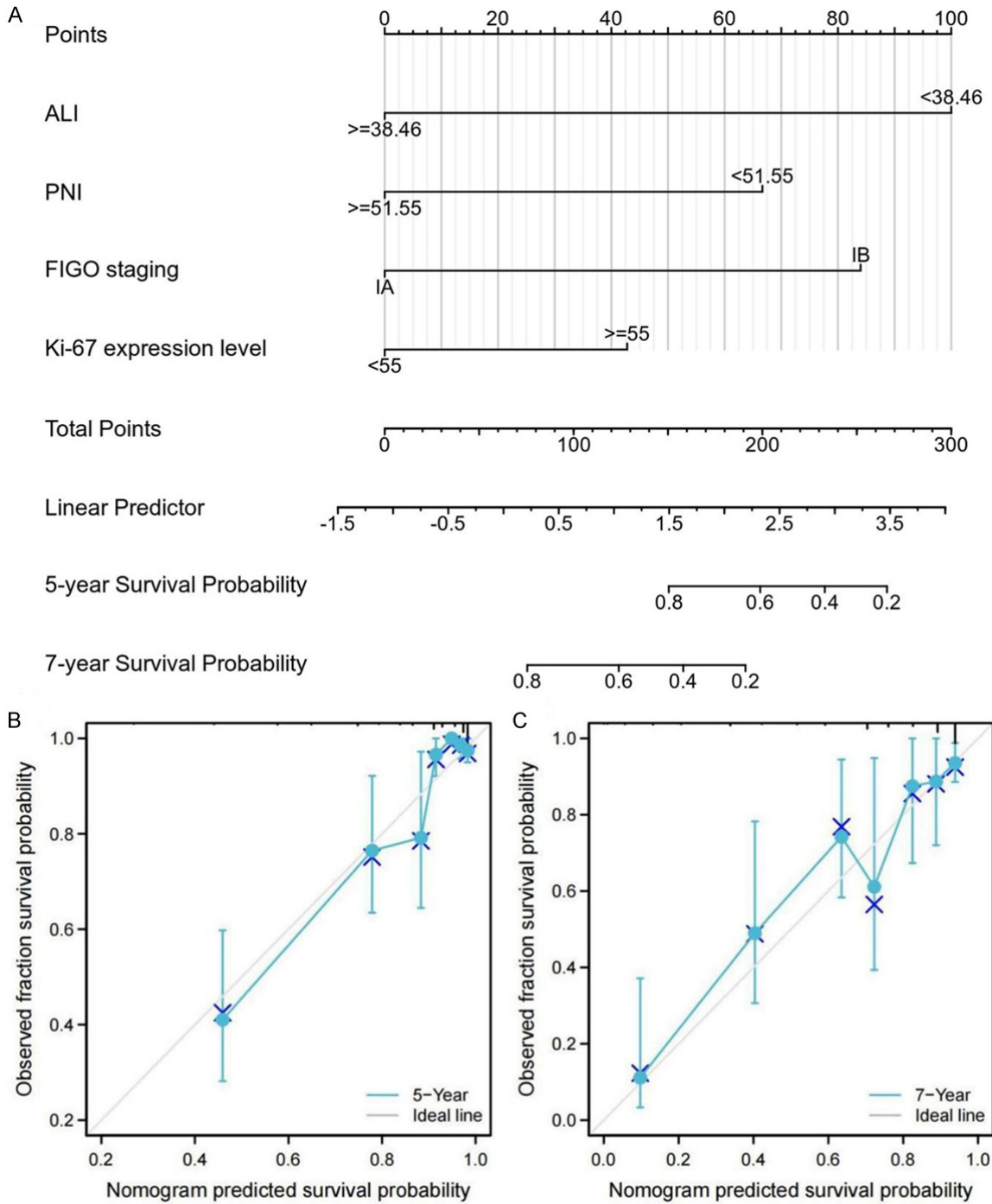


Figure 7. (A) Nomogram based on ALI and independent prognostic factors for OS prediction. The point for each variable is achieved by drawing a line straight upward to the point axis, and then the points of all variables are summed. The final sum is located on the total point axis, then a line is drawn down to find out the 5/7-year overall survival and progression free survival probability. (B, C) Calibration plots of the nomogram for (B) 5-year and (C) 7-year OS prediction. The overall survival and progression free survival estimated by the developed nomogram is plotted on the x-axis, and the actual overall survival and progression free survival is plotted on the y-axis, the gray diagonal line represents the reference line showing the “ideal” prediction, the blue line represents the performance of the developed nomogram in prognostic prediction, the closer the blue line is to the gray diagonal line, the higher the consistency between the predicted results and the actual results.

Immunoinflammatory indexes in early stage EC

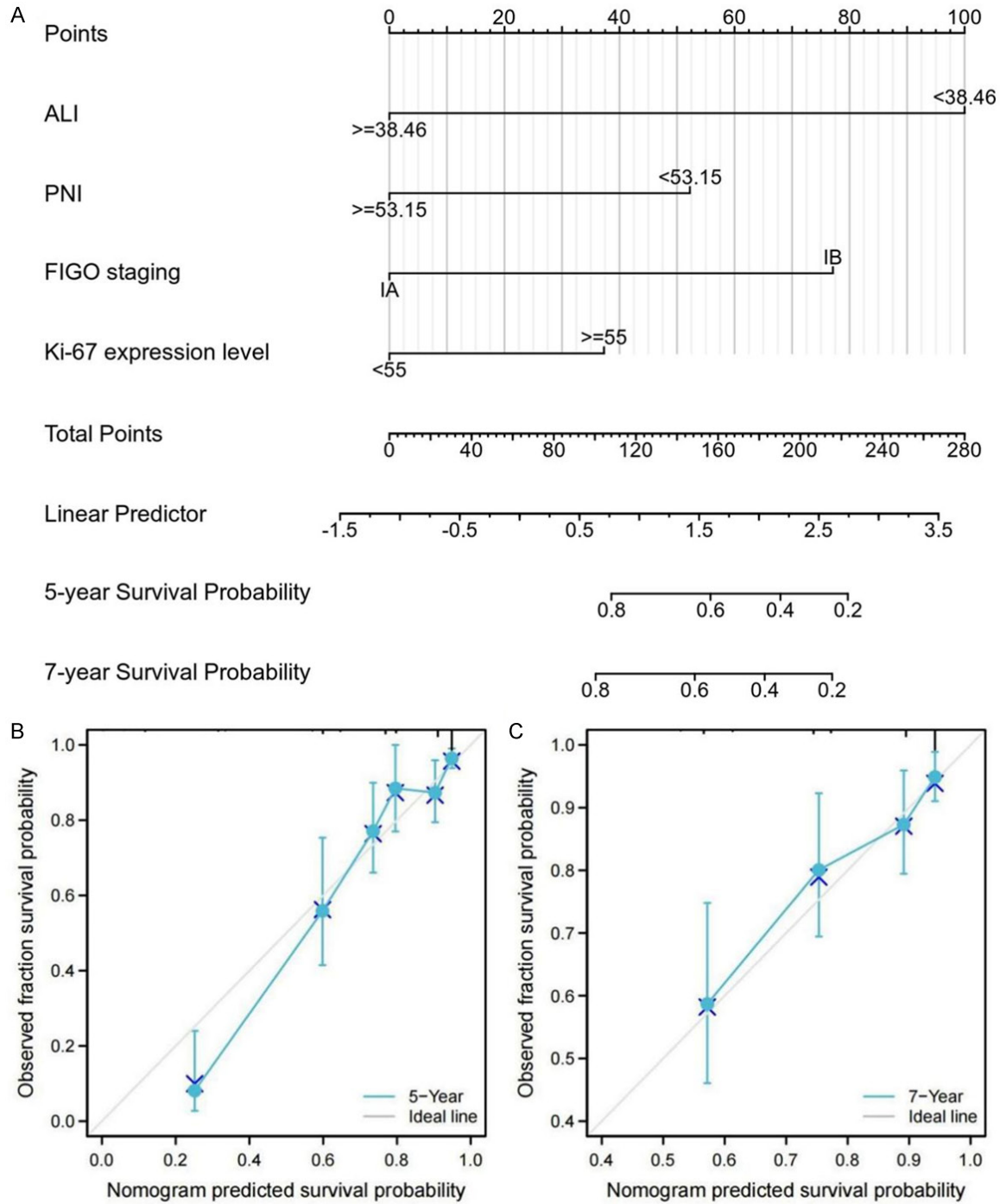


Figure 8. (A) Nomogram based on ALI and independent prognostic factors for DFS prediction. (B, C) Calibration plots of the nomogram for (B) 5-year and (C) 7-year DFS prediction.

was most closely associated with the survival of patients, the higher the level of preoperative ALI, the better the patients' prognosis. In the last few years, ALI, a novel inflammation and nutritional index by combining BMI, preopera-

tive serum albumin and NLR [22], has been proposed as a prognostic factor of some cancers, and cancer patients with low ALI suffered poor prognosis [22-25], which was consistent with our results.

Since predicting the prognosis of cancer patients based on a single indicator is not entirely reliable, we then identified the independent risk factors for OS in stage IA-IB EC patients, the results showed that, in addition to ALI, FIGO staging, Ki-67 expression level and PNI were independent prognostic factors for OS. PNI, which is initially used to evaluate the nutritional status in patients undergoing surgery [26], has also been demonstrated to be played important role in predicting the survival of some cancers such as malignant melanoma, glioblastoma, pancreatic cancer, ovarian cancer [19, 27-29], the above studies and our study consistently revealed that higher PNI was related to longer OS in cancer patients. In addition, we further investigated the relationship between various immunological indicators and clinical parameters and DFS in patients with early EC, and the results showed that ALI and PNI was likewise an independent prognostic factor for DFS in patients.

Nomograms have become increasingly employed in recent years for prognosis of cancer prediction because they can condense statistical predictive models into a single numerical estimate of the probability of an event suited to a specific patient's profile. Taking into account the recognized independent risk factors, we developed a nomogram to predict the OS and DFS of stage IA-IB EC patients. The results suggested that the nomogram had high degrees of discrimination and calibrated accuracy, which meant that it had a specific value for clinical applications.

We acknowledge several potential limitations of this study. First, selection bias was inevitable since this was a single-center, nonrandomized retrospective study. Second, there was a pretty limited sample size. Third, a subgroup analysis of stage IA-IB EC patients was not performed due to the limited number of enrolled cases. Hence, this study's findings must be confirmed in additional larger, multicenter, prospective clinical trials.

Conclusion

Low preoperative ALI and PNI are independent risk factors that affect the prognosis of stage IA-IB endometrial cancer patients, and the prognosis can be accurately predicted by nomograms based on ALI, PNI, and other clinicopathological data.

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Disclosure of conflict of interest

None.

Address correspondence to: Fei Zhong, Department of Oncology, Fuyang Hospital of Anhui Medical University, Fuyang 236000, Anhui, China. E-mail: zhongfei@ahmu.edu.cn

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