ORIGINAL RESEARCH

Comparison and validation of the value of preoperative inflammation marker-based prognostic scores in resectable pancreatic ductal adenocarcinoma

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Purpose: We aimed to compare and validate the prognostic value of inflammation-based prognostic scores for patients with resectable pancreatic ductal adenocarcinoma (PDAC) and to establish a novel, effective nomogram incorporating inflammation-based prognostic scores to predict disease-free survival (DFS) in these patients.

Patients and methods: Clinicopathological characteristics and follow-up data were retrieved from our prospective database. A total of 420 patients with PDAC who underwent radical resection were evaluated between January 2007 and December 2016. Blood samples were obtained within 7 days prior to surgical intervention. Time-dependent receiver operating characteristic curves were generated to determine optimal cutoff values for independent prognostic factors. Nomograms for DFS were established based on multivariate Cox proportional hazard models, and the results were internally validated using bootstrap resampling.

Results: Neutrophil-lymphocyte ratio (NLR) >2.13 and platelet-lymphocyte ratio (PLR) >140 were independent prognostic factors for DFS and overall survival. Stratified analyses indicated that these associations were not present among patients with stage III disease. Independent predictors of DFS, including Eastern Cooperative Oncology Group performance status score, tumor stage, differentiation, adjuvant treatment, NLR, and PLR, were incorporated into two nomograms for prediction of DFS in a cohort of PDAC patients after curative surgery. The area under receiver operating characteristic curve of the nomogram including NLR and PLR (0.804) was higher than that without NLR and PLR (0.711). The bootstrap-corrected AUC for the model including NLR and PLR was 0.803, while that for the model without NLR and PLR was 0.711.

Conclusion: Our study demonstrates that high NLR and high PLR are important clinical predictors of poor survival in patients with resectable PDAC. Additionally, a nomogram including NLR and PLR can objectively and reliably predict DFS among patients with PDAC following curative surgery.

Keywords: neutrophil-lymphocyte ratio, NLR, platelet-lymphocyte ratio, PLR, nomogram, disease-free survival

Introduction

Pancreatic ductal adenocarcinoma (PDAC) ranks third among the causes of cancer-related death, with approximately 338,000 new cases annually worldwide.[1] Prognosis remains poor, and the 5-year cumulative survival rates for PDAC are estimated at less than 10%.[2] Surgical resection offers the only chance of cure; however, over 80% of patients experience local or distant recurrence after radical surgery.[3] Current predictions

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of tumor recurrence depend primarily on the histopathological characteristics of resected tumor specimens, including tumor size, histological grade, the depth of infiltration, and lymph node involvement; however, patients with equivalent pathological status often exhibit highly heterogeneous survival rates, suggesting that conventional characteristics are insufficient for optimal prediction of an individual's prognosis.[4–6] Hence, the identification of novel prognostic factors to enable a better risk stratification for follow-up schedules and individualized treatment of PDAC, has become critical.

Inflammation is a recognized hallmark of various malignant solid tumors, including PDAC.[7] Chronic inflammation contributes substantially to the development and progression of malignancies, through its influence on tumor angiogenesis, invasion, and metastasis.[8] Conversely, malignancies can also trigger regional inflammatory responses and the release of pro-inflammatory cytokines, leading to the formation of an inflammatory tumor microenvironment which favors tumor progression.[8,9] Several prognostic factors based on analysis of systemic inflammation scores, including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and prognostic nutritional index (PNI), have been proposed to estimate the magnitude of systemic inflammation in patients with cancer.[10,11] These proposed biomarkers are potentially useful prognostic indicators for stratification of patients with good and poor prognosis.[10,12,13] The results of published studies that have examined the relationship between inflammation-based prognostic indices and resectable PDAC have been somewhat inconsistent to date.[12,14,15] Possible explanations for these inconsistencies may include the relatively small numbers included in these studies (n<100), differences in inclusion criteria and clinical endpoints, unclear selection of cutoff values, and concomitant evaluation of resectable and unresectable disease; these limitations would affect the reproducibility and reliability of these markers. Furthermore, inflammation-based prognostic indices have yet to be appropriately validated for clinical decision-making. Therefore, the aim of this study was to compare the prognostic values of NLR, PLR, LMR, and PNI and to develop a nomogram incorporating inflammation-based prognostic indices to predict the disease-free survival (DFS) in a large cohort of 420 patients with PDAC who underwent curative resection.

Materials and methods
Study population
We conducted a retrospective study of patients with PDAC who underwent potentially radical resection from January 2007 to December 2016 at the Chinese PLA General Hospital, Beijing, China. Patients were excluded from the study if they met the following criteria: 1) without pathologically confirmed PDAC; 2) positive surgical margins; 3) presence of distant metastasis; 4) preoperative chemotherapy or radiotherapy for PDAC; 5) other malignancies diagnosed within 5 years; 6) clinical evidence of acute infection or other inflammatory conditions; 7) previous hematological or autoimmune disease; and 8) no complete record of preoperative hematological variables and follow-up data. Following these exclusions, a total of 420 patients with PDAC were eligible for the present study. Approval for the study was granted by the ethics committee of the Chinese PLA General Hospital, and the requirement to obtain written informed consent from patients was waived due to the retrospective nature of the investigation. To protect patient privacy, all personal information was appropriately anonymized and de-identified prior to analysis.

Data collection and clinical definition
Information regarding the clinicopathological characteristics, sociodemographic data, and lifestyle factors were retrieved from medical records. Laboratory data, including routine blood examination, albumin concentration, and levels of the tumor markers, CA19-9, CA125, and CEA, were obtained within 7 days prior to surgical intervention. Pathological data included tumor size, histological type, grade, the presence of micro-invasion (of nerves, lymphatics, and vessels), number of cancer positive lymph nodes, and microscopic status of all evaluated resection margins. Pathological staging was performed according to the tumor-node-metastasis (TNM) classification system; as the TNM classification system for PDAC changed during the study period, tumors were uniformly staged according to the eighth edition of this system. Alcohol intake was classified as either currently drinking almost/more than once a week or not. Smoking habit was defined as either smoking more than once a day or not. Body mass index (BMI) was calculated as weight divided by height squared (in kg m²). NLR was defined as the absolute neutrophil count divided by absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. LMR was determined as the absolute lymphocyte count divided by absolute monocyte count. PNI was calculated as 10× albumin (g/dL) +0.005× total lymphocyte count (per mm³).

Follow-up data were collected prospectively, and all patients were followed-up every 3 months during the first and second postoperative year, every 6 months in the third to fifth

years, and annually thereafter. If recurrence was confirmed, the follow-up interval was 3 months. The closing date for follow-up was February 30, 2018. The primary endpoint of the study was DFS. The secondary endpoint was overall survival (OS). DFS was defined as the time from surgical resection to local recurrence or distant metastasis. OS was defined as the interval between the date of a definitive diagnosis and cancer-related death. Patients were censored at the date of last follow-up.

Statistical analysis

Continuous variables are expressed as median (25th, 75th percentile) and categorical variables as frequency and percentage. Differences in the distribution of categorical variables were evaluated using the chi-squared test. Time-dependent receiver operating characteristic (ROC) curves were generated to determine the optimal cutoff values of independent prognostic factors. Kaplan–Meier analyses with log-rank tests were used to compare survival outcomes between patients with systemic inflammatory marker values above vs below optimal cutoff points. Cox proportional hazard models were used to assess the relationships between systemic inflammatory markers and survival outcomes. Unadjusted and multivariate adjusted models were applied, and HR and 95% confidence intervals (CIs) calculated. Nomograms for predicting 1-year DFS were established based on the results of multivariate Cox proportional hazard regression models. A backward model selection technique was used for the final model selection, and predictive accuracy was evaluated by calculation of the area under the ROC curve. The performance of the models was internally validated using bootstrapping (500 samples). Statistical significance was defined as a two-tailed P-value <0.05.

All statistical analyses were undertaken using the statistical software packages, R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA).

Results

Table 1 summarizes the detailed clinical characteristics of the 420 eligible patients. The median follow-up time was 38 months (range 1–75 months). Of the 420 resectable PDAC patients, 382 (91%) developed tumor recurrence and 346 (82.4%) died within the follow-up period. The median DFS and OS were 9.2 and 14.4 months, respectively.

The AUCs of the time-dependent ROC curve analyses are presented in Table 2 and ROC curves are shown in Figure 1. The AUCs for NLR and PLR were 0.743 and 0.715,

Table 1 Baseline characteristics of patients

Characteristic	Total patients (n=420)
Age (years), n (%)	
≤50	64 (15.2)
51–70	308 (73.3)
>70	48 (14.4)
Sex, n (%)	
Female	156 (37.1)
Male	264 (62.9)
BMI (kg/m²), n (%)	
<18.5	47 (11.2)
18.5–24	318 (75.7)
≥24	55 (13.1)
Smoking, n (%)	
Yes	74 (17.6)
No	346 (82.4)
Alcohol consumption, n (%)	
Yes	126 (30)
No	294 (70)
ECOG PS, n (%)	
0–1	356 (84.8)
≥2	64 (15.2)
Tumor location, n (%)	
Head	286 (68.1)
Body and/or tail	134 (31.9)
Operation	
Pancreaticoduodenectomy	286 (68.1)
Distal pancreatectomy	132 (31.4)
Total pancreatectomy	2 (0.05)
Maximum diameter (cm), n (%)	
<2	31 (7.4)
2–4	257 (61.2)
>4	132 (31.4)
Differentiation, n (%)	
Well	225 (53.6)
Poor	195 (46.4)
T stage, n (%)	
T1	45 (10.7)
T2	232 (55.3)
T3	132 (31.4)
T4	11 (2.6)
N stage, n (%)	
N0	281 (66.9)
N1	103 (24.5)
N2	36 (8.6)
pTNM stage, n (%)	
I	186 (44.3)
II	188 (44.8)
III	46 (10.9)
Tumor extension, n (%)	
Choledochal duct	150 (35.7)
Duodenum	146 (34.8)
Peripheral tissue	158 (37.6)
Nerve	124 (29.5)
Vessel	28 (6.7)
Tumor thrombus, n (%)	
Yes	50 (11.9)
No	370 (11.9)

(*Continued*)

Table 1 (*Continued*)

Characteristic	Total patients (n=420)
Adjuvant treatment	
Yes	117 (27.9)
No	303 (72.1)
NLR, median (IQR)	2.12 (1.53–3.11)
PLR, median (IQR)	127.94 (92.10–175.56)
LMR, median (IQR)	4.53 (3.20–5.70)
PNI, median (IQR)	48.39 (45.45–51.84)
CA19-9 (U/mL), n (%)	
≤37	89 (21.2)
>37	331 (78.8)
CA125 (U/mL)	
≤35	341 (81.2)
>35	79 (18.8)
CEA (ng/mL)	
≤5	284 (67.6)
>5	136 (32.4)

Note: Continuous data are presented as median (interquartile range) and categorical data are shown as frequency (%).
Abbreviations: CA19-9, carbohydrate antigen 19–9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index.

respectively. The optimal cutoff value for NLR was 2.13, with a sensitivity of 61.7% and a specificity of 74.1% for 1-year DFS. For PLR, the optimal cutoff value was 140 with a sensitivity of 54.1% and a specificity of 80.6%. LMR and PNI were not suitable for inclusion in subsequent analyses since their AUC values were <0.5.

Patients were divided into low or high groups based on NLR and PLR cutoff values. Comparisons of the baseline characteristics of patients stratified by NLR and PLR are presented in Table 3. Compared to low NLR (<2.13), high NLR (>2.13) was significantly associated with unfavorable tumor characteristics including higher T stage, more positive lymph nodes, and advanced stage. Similar significant differences were also observed when the two groups were stratified by PLR.

Kaplan–Meier analyses demonstrated that high preoperative NLR and PLR were associated with worse DFS and OS. The median DFS and OS of patients with an NLR of ≤2.13 was 12.4 and 23.1 months, respectively, whereas for patients with an NLR of >2.13 the equivalent values were 6.0 and 10.7 months, respectively (both *P*<0.01; Figure 2A and C). Patients with PLR ≤140 had superior DFS (12.1 vs 5.9 months, *P*<0.001) and OS (23.5 vs 10.6 months, *P*<0.001) compared to those with PLR >140 (Figure 2B and D).

The results of univariate and multivariable Cox regression analyses are presented in Table 4. Both high NLR and high

PLR were identified as independently associated with inferior DFS and OS in unadjusted analysis. The adjusted HR (95% CI), *P*-value of worse DFS and OS for patients with high NLR were 1.59 (1.27–2.00), <0.001 and 1.70 (1.33–2.16), <0.001, respectively. Patients with high PLR had inferior DFS (HR [95% CI]: 1.93 [1.53–2.45], *P*<0.001) and OS (HR [95% CI]: 2.23 [1.74–2.85], *P*<0.001) compared to their counterparts with low PLR.

Given the close relationship between survival outcomes and tumor stage, we also performed an analysis with data stratified by tumor stage subgroups (Table 5). Both high NLR and high PLR remained independent risk factors for inferior DFS and OS in patients with stage I and II tumors; however, for patients with stage III disease, these associations were lost after adjustment for confounding factors.

To predict the 1-year DFS of patients with resectable PDAC, nomograms (Figure 3A and B) were established using a multivariate Cox regression model incorporating all significant independent predictors of DFS. Eastern Cooperative Oncology Group performance status (ECOG PS) score, stage, differentiation, adjuvant treatment, NLR, and PLR were incorporated into the DFS nomograms. The AUCs of the nomograms, either including or excluding NLR and PLR, were 0.804 and 0.711, respectively (Figure 3C and D). The respective C-indices of the nomograms including or excluding NLR and PLR were 0.750 and 0.679. The discriminative performance of the nomogram (bootstrap-corrected AUC) was 0.803 for the model including NLR and PLR, and 0.711 for that excluding NLR and PLR.

Discussion

In the present study, we demonstrated that NLR >2.13 and PLR >140 can be reliable predictive markers for shorter DFS and OS in a large and homogenous population of patients with resectable PDAC. After adjustment for a wide range of potential confounding factors, NLR >2.13 and PLR >140 remained independent unfavorable prognostic factors with clinically relevant HR values; however, these associations were not consistent among the patient subgroup with stage III tumors. Additionally, we presented a nomogram including NLR and PLR that predicts the 1-year DFS with good discriminative performance. To the best of our knowledge, this is the first nomogram for patients with resected PDAC incorporating inflammation-based prognostic indices to effectively predict DFS.

It is well-established that cancer progression is determined not only by oncogenes or tumor suppressor genes within the tumor itself but also by host-related factors such as

Table 2 ROC curve analyses of the NLR, PLR, LMR, and PNI for 1-year DFS

Variable	Cutoff	AUC	Sensitivity	Specificity	Harrell's C index
NLR	2.13	0.743	0.617	0.741	0.699
PLR	140	0.715	0.541	0.806	0.668
LMR	–	0.297	1	0	0.652
PNI	64.96	0.397	0.006	0.998	0.599

Abbreviations: AUC, area under the curve; DFS, disease-free-survival; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; ROC, receiver operating characteristic.
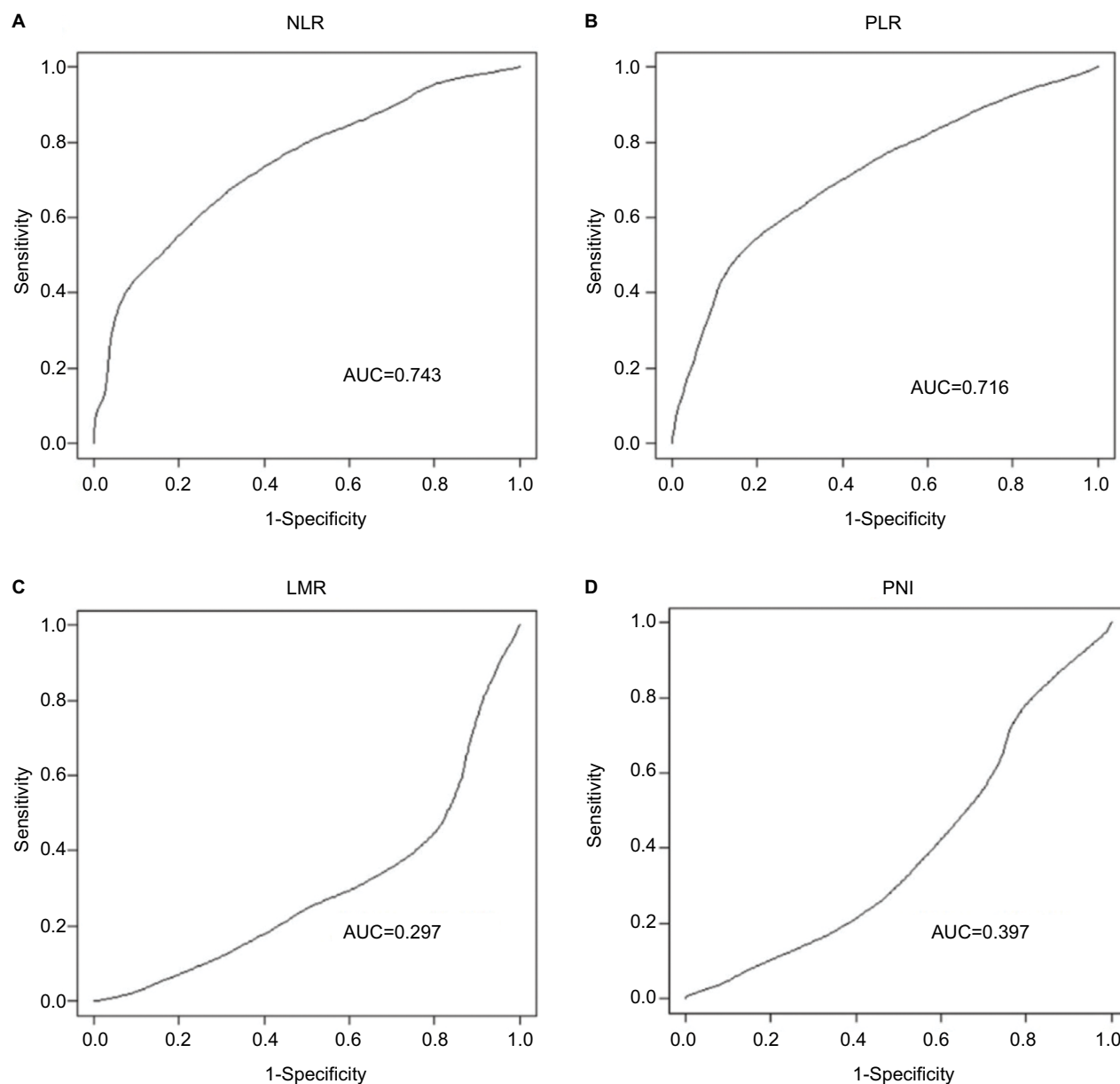
Figure 1 ROC curves of NLR, PLR, LMR, and PNI for 1-year DFS.
Note: (**A**) NLR, (**B**) PLR, (**C**) LMR, and (**D**) PNI.
Abbreviations: AUC, area under the curve; DFS, disease-free survival; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; ROC, receiver operating characteristic.

age, sex, performance status, and inflammatory responses.[16] The relationship between systemic inflammation and cancer progression has been subject to increasing attention in investigation of various gastrointestinal malignancies, including PDAC.[17,18] Cancer-related inflammation involves crosstalk of inflammatory cells and mediators, such as cytokines

Table 3 Baseline characteristics stratified by NLR and PLR

Characteristic	NLR			PLR		
	≤2.13 (n=215)	>2.13 (n=205)	*P*-value	≤140 (n=245)	>140 (n=175)	*P*-value
Age (years), n (%)						
≤50	25 (11.6)	39 (19)	**0.043**	41 (16.7)	23 (13.1)	**0.003**
51–70	160 (74.4)	148 (72.2)		166 (67.8)	142 (81.1)	
>70	30 (14)	18 (8.8)		38 (15.5)	10 (5.8)	
Sex, n (%)						
Female	83 (38.6)	73 (35.6)	0.525	86 (35.1)	70 (40)	0.306
Male	132 (61.4)	132 (64.4)		159 (64.9)	105 (60)	
BMI (kg/m²), n (%)						
<18.5	32 (14.9)	15 (7.3)	<0.001	35 (14.3)	12 (6.9)	<0.001
18.5–24	144 (67)	174 (84.9)		167 (68.2)	151 (86.3)	
≥24	39 (18.1)	16 (7.8)		43 (17.6)	12 (6.8)	
Smoking, n (%)						
Yes	37 (17.2)	37 (18)	0.821	46 (18.8)	28 (16)	0.462
No	178 (82.8)	168 (82)		199 (81.2)	147 (84)	
Alcohol consumption, n (%)						
Yes	62 (28.8)	64 (31.2)	0.594	79 (32.2)	47 (26.9)	0.235
No	153 (71.2)	141 (68.8)		166 (67.8)	128 (73.1)	
ECOG PS, n (%)						
0–1	202 (94)	154 (75.1)	<0.001	223 (91)	133 (76)	<0.001
≥2	13 (6)	51 (24.9)		22 (9)	42 (24)	
Tumor location, n (%)						
Head	147 (68.4)	139 (67.8)	0.901	151 (61.6)	135 (77.1)	<0.001
Body and/or tail	68 (31.6)	66 (32.2)		94 (38.4)	40 (22.9)	
Operations						
Pancreaticoduodenectomy	147 (68.4)	139 (67.8)	0.876	151 (61.6)	135 (77.1)	<0.001
Distal pancreatectomy	66 (30.7)	66 (32.2)		93 (38)	39 (22.3)	
Total pancreatectomy	2 (0.9)	0 (0)		1 (0.4)	1 (0.6)	
Maximum diameter (cm), n (%)						
<2	18 (8.4)	13 (6.3)	0.707	20 (8.2)	11 (6.3)	0.271
2–4	129 (60)	128 (62.4)		142 (58)	115 (65.7)	
>4	68 (31.6)	64 (31.3)		83 (33.8)	49 (28)	
Differentiation, n (%)						
Well	120 (55.8)	105 (51.2)	0.345	129 (52.7)	96 (54.9)	0.655
Poor	95 (44.2)	100 (48.8)		116 (47.3)	79 (45.1)	
T stage, n (%)						
T1	28 (13)	17 (8.3)	**0.003**	31 (12.7)	14 (8)	<0.001
T2	119 (55.3)	113 (55.1)		131 (53.5)	101 (57.7)	
T3	68 (31.7)	64 (31.2)		83 (33.9)	49 (28)	
T4	0 (0)	11 (5.4)		0 (0)	11 (6.3)	
N stage, n (%)						
N0	154 (71.6)	127 (62)	**0.019**	173 (70.6)	108 (61.7)	**0.03**
N1	50 (23.3)	53 (25.9)		58 (23.7)	45 (25.7)	
N2	11 (5.1)	25 (12.1)		14 (5.7)	22 (12.6)	
pTNM stage, n (%)						
I	105 (48.8)	81 (39.5)	<0.001	114 (46.5)	72 (41.1)	<0.001
II	99 (46)	89 (43.4)		117 (47.8)	71 (40.6)	
III	11 (5.1)	35 (17.1)		14 (5.7)	32 (18.3)	
Tumor extension, n (%)						
Choledochal duct	85 (39.5)	65 (31.7)	0.094	96 (39.2)	54 (30.9)	0.079
Duodenum	80 (37.2)	66 (32.2)	0.281	88 (35.9)	58 (33.1)	0.556
Peripheral tissue	72 (33.5)	86 (42)	**0.074**	86 (35.1)	72 (41.1)	0.208
Nerve	68 (31.6)	56 (27.3)	0.333	78 (31.8)	46 (26.3)	0.219
Vessel	17 (7.9)	11 (5.4)	0.297	22 (9)	6 (3.4)	0.025

(Continued)

Table 3 (*Continued*)

Characteristic	NLR			PLR		
	≤2.13 (n=215)	>2.13 (n=205)	*P*-value	≤140 (n=245)	>140 (n=175)	*P*-value
Tumor thrombus, n (%)						
Yes	27 (12.6)	23 (11.2)	0.672	31 (12.7)	19 (10.9)	0.575
No	188 (87.4)	182 (88.8)		214 (87.3)	156 (89.1)	
CA19-9 (U/mL), n (%)						
≤37	46 (21.4)	43 (21)	0.916	59 (24.1)	30 (17.1)	0.086
>37	169 (78.6)	162 (79)		186 (75.9)	145 (82.9)	
CA125 (U/mL)						
≤35	171 (79.5)	170 (82.9)	0.374	199 (81.2)	142 (81.1)	0.983
>35	44 (20.5)	35 (17.1)		46 (18.8)	33 (18.9)	
CEA (ng/mL)						
≤5	141 (65.6)	143 (69.8)	0.361	161 (65.7)	123 (70.3)	0.324
>5	74 (34.4)	62 (30.2)		84 (34.3)	52 (29.7)	

Note: Bold values (*P*<0.05).
Abbreviations: CA19-9, carbohydrate antigen 19–9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.

and chemokines; however, systemic levels of cytokines and chemokines are some way from routine clinical use. Therefore, several prognostic scores, based on shifts in the cellular components that occur during systemic inflammation have been proposed.[19–21]

Neutrophils, major components of the leukocyte population, can migrate from the venous system to tumors and may be triggered in the presence of cancer-related inflammatory factors, such as interleukin-6 (IL-6), granulocyte colony-stimulating factor, and by myeloid growth factors produced during neoplastic processes.[22] Neutrophils can release various factors, such as reactive oxygen species, leading to DNA damage, genetic instability, and tumor growth.[23,24] In contrast, neutrophils interact with various other cell populations, leading to generation of numerous cytokines and effector molecules, particularly vascular endothelial growth factor (VEGF), which is important for tumor angiogenesis, growth, and metastasis.[25] In addition, neutrophil subpopulations in the vicinity of the tumor microenvironment may suppress the antitumor immune responses of natural killer cells and activated T cells mediated by integrin Mac-1 and hydrogen peroxide.[26]
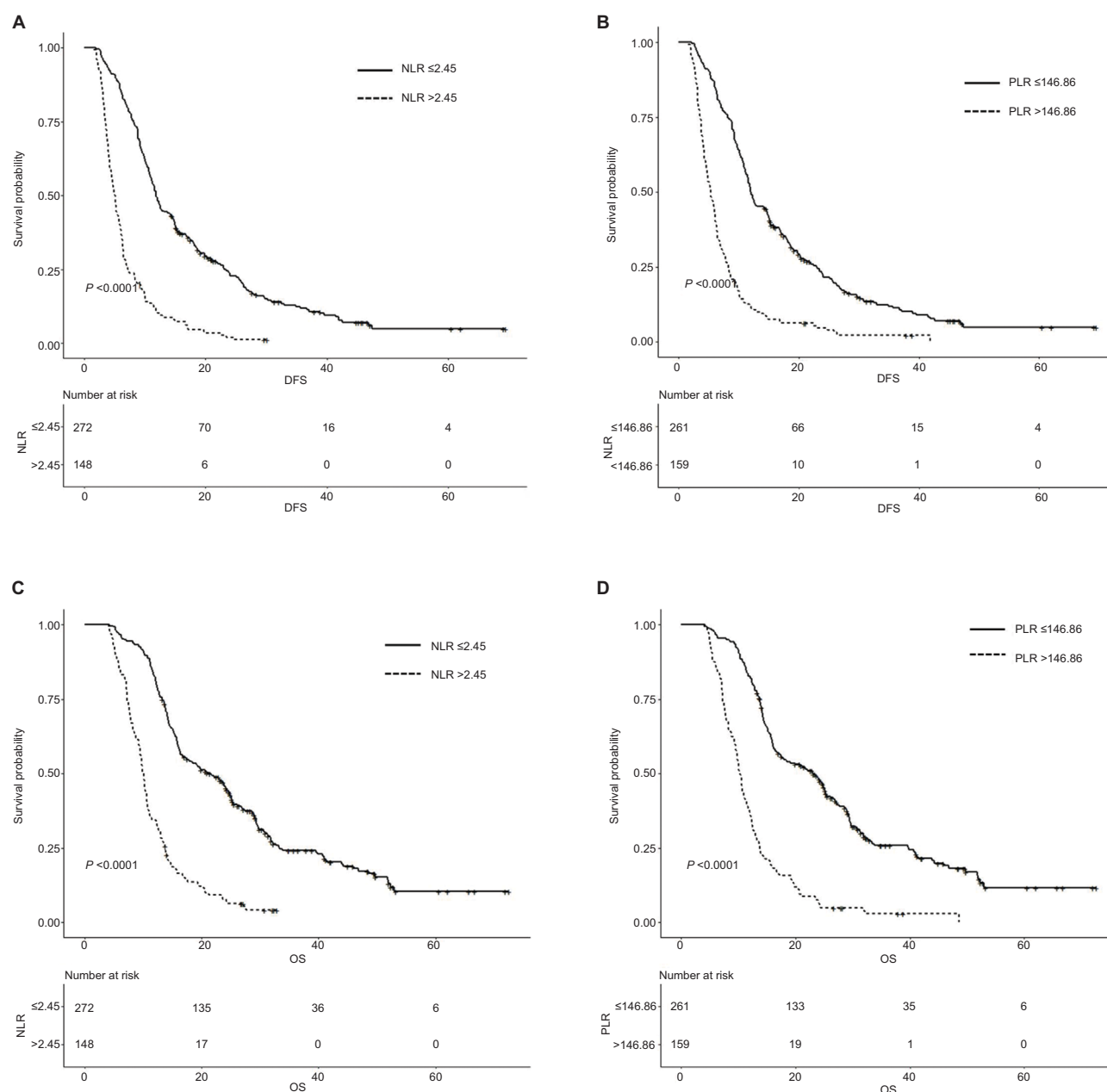
Lymphocytes, which are the cellular mediators of immunosurveillance and immunoediting, have crucial roles in antitumor reactions through induction of cytotoxic cell death and inhibition of tumor cell proliferation and migration.[8] During cancer-related inflammation, the presence of tumor-infiltrating lymphocytes with high CD4+/CD8+ and Th2/Th1 ratios is indicative of poor prognosis.[27]

Platelets, the major transporter of VEGF, are regulated by pro-inflammatory cytokines, such as IL-1, IL-6, IL-11, and TNF-α.[28] Platelets can also contribute substantially to tumor vascular growth through secretion of a number of proangiogenic cytokines, including VEGF, platelet-derived growth factor, and thymidine phosphorylase.[29,30] Platelet aggregation also facilitates tumor cell adhesion to the vascular endothelium, which can act as a physiological shield, protecting tumor cells against NK cell-mediated lysis.[31] Additionally, tumor cell infiltration and metastasis are induced via platelet-mediated activation of the TGFb/Smad pathway.[32]

Overall, neutrophilia, thrombocytosis, and lymphopenia tend to contribute to cancer-related inflammatory responses, and the NLR and PLR, simple derivatives of routine blood counts, can reflect the dynamic balance between anti- and pro-tumor functions of the immune system.[33]

Currently, there is no consensus on the appropriate cut-off values for NLR and PLR for prediction of prognosis in patients with PDAC; thus, various thresholds have been used in previous studies. For NLR, many studies have used a cutoff value of 5.0,[34–36] while others used values varying from 2.2 to 4.0.[15,37–39] PLR cutoff values of 150, 160, and 300 have been used in previous studies.[14,15,36,40,41] In some studies, patients were even categorized according to quartiles or mean values of NLR or PLR;[42] however, despite these differences in cutoff values, all studies reported worse survival when NLR or PLR exceeded the threshold. Unlike studies that set cutoff values for NLR and PLR empirically, we used time-dependent ROC to determine the values, and calculated optimal thresholds of 2.13 for NLR and 140 for PLR. The AUCs of NLR and PLR were 0.743 and 0.715, respectively, indicating that both indices are promising predictors of DFS in patients with resectable PDAC. In contrast, the AUCs of LMR and

A

B

C

D

Figure 2 Kaplan–Meier curves of NLR and PLR for DFS and OS.
Notes: (**A**) NLR for DFS, (**B**) PLR for DFS, (**C**) NLR for OS, (**D**) PLR for OS.
Abbreviations: DFS, disease-free survival; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PLR, platelet-lymphocyte ratio.

PNI were both <0.5, demonstrating no prognostic power for predicting DFS. Further survival analyses showed that high NLR and high PLR (above the threshold values) were significantly associated with impaired DFS and OS, independent of a wide range of potential confounding factors. These results are consistent with previous publications.[15,37] Interestingly, in analysis stratified by TNM stage, we demonstrated that patient subgroups with stage I–II tumors presented different DFS and OS according to their NLR or PLR values; however,

these associations were not observed for patients with stage III tumors. The small number of patients with stage III disease may be an important factor contributing to this phenomenon. Although these results are insufficient to directly influence clinical practice at present, they provide valuable information regarding clinical risk stratification to facilitate improved personalized medical care, such as a closer follow-up once high NLR and/or high PLR are identified, even among patients with the same stage tumor.

Table 4 Multivariate analyses for DFS and OS

Characteristic	DFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years), n (%)								
≤50	1 (ref)		_		1 (ref)		_	
51–70	1.11 (0.83–1.47)	0.492			1.12 (0.83–1.51)	0.45		
>70	0.97 (0.65–1.44)	0.879			0.91 (0.60–1.38)	0.643		
Sex, n (%)								
Female	1 (ref)	0.193	_		1 (ref)	0.64	_	
Male	0.87 (0.71–1.07)				1.05 (0.85–1.32)			
Smoking, n (%)								
Yes	1 (ref)	0.175	_		1 (ref)	0.061	_	
No	1.20 (0.92–1.56)				1.30 (0.99–1.70)			
Alcohol consumption, n (%)								
Yes	1 (ref)	0.557	_		1 (ref)	0.512	_	
No	0.94 (0.75–1.17)				0.93 (0.73–1.17)			
ECOG PS, n (%)								
0–1	1 (ref)	<0.001	1 (ref)	**<0.001**	1 (ref)	<0.001	1 (ref)	**<0.001**
≥2	2.84 (2.15–3.76)		2.44 (1.81–3.29)		2.61 (1.96–3.47)		2.09 (1.54–2.84)	
Tumor location, n (%)								
Head	1 (ref)	0.561	_		1 (ref)	0.216	_	
Body and/or tail	1.07 (0.86–1.32)				0.86 (0.68–1.09)			
Maximum diameter (cm), n (%)								
<2	1 (ref)		_		1 (ref)		_	
2–4	1.29 (0.85–1.96)	0.2349			1.05 (0.70–1.55)	0.825		
>4	1.36 (0.87–2.11)	0.173			1.19 (0.79–1.81)	0.403		
Differentiation, n (%)								
Well	1 (ref)	**0.04**	1 (ref)	**0.003**	1 (ref)	0.116	1 (ref)	**0.027**
Poor	1.23 (1.01–1.51)		1.36 (1.11–1.67)		1.19 (0.96–1.46)		1.28 (1.03–1.58)	
T stage, n (%)								
T1	1 (ref)		_		1 (ref)		_	
T2	1.21 (0.85–1.72)	0.288			1.01 (0.72–1.42)	0.958		
T3	1.32 (0.91–1.92)	0.139			1.21 (0.85–1.74)	0.292		
T4	18.22 (8.77–37.83)	<0.001			12.72 (6.24–-25.93)	<0.001		
N stage n (%)								
N0	1 (ref)		_		1 (ref)		_	
N1	1.10 (0.86–1.39)	0.45			1.23 (0.97–1.58)	0.092		
N2	4.05 (2.80–5.85)	<0.001			3.27 (2.25–4.75)	<0.001		
pTNM stage, n (%)								
I	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
II	1.29 (1.04–1.60)	**0.02**	1.42 (1.14–1.77)	0.002	1.42 (1.13–1.78)	**0.002**	1.47 (1.17–1.85)	0.001
III	5.71 (4.02–8.09)	<0.001	4.69 (3.26–6.76)	**<0.001**	4.72 (3.31–6.75)	<0.001	3.25 (2.25–4.68)	**<0.001**
Tumor extension, n (%)								
Choledochal duct	0.90 (0.73–1.11)	0.334	_		0.90 (0.72–1.13)	0.364	_	
Duodenum	1.15 (0.93–1.42)	0.194	_		1.04 (0.83–1.30)	0.744	_	
Peripheral tissue	1.16 (0.98–1.24)	0.058	_		1.33 (1.07–1.66)	**0.009**	1.25 (0.99–1.56)	0.054
Nerve	1.09 (0.87–1.36)	0.446	_		1.07 (0.85–1.35)	0.585	_	
Vessel	0.73 (0.48–1.10)	0.136	_		0.82 (0.53–1.26)	0.356	_	
Tumor thrombus, n (%)								
Yes	1 (ref)	0.151	_		1 (ref)	0.137	_	
No	0.79 (0.57–1.09)				0.77 (0.54–1.09)			
CA19-9 (U/mL). n (%)								
≤37	1 (ref)	0.768	_		1 (ref)	0.502	_	
>37	1.04 (0.81–1.32)				1.09 (0.85–1.41)			
CA125 (U/mL)								
≤35	1 (ref)	0.362	_		1 (ref)	0.134	_	
>35	1.13 (0.87–1.45)				1.22 (0.94–1.58)			

(*Continued*)

Table 4 (*Continued*)

Characteristic	DFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CEA (ng/mL)								
≤5	I (ref)	0.503	_		I (ref)	0.439	_	
>5	1.08 (0.87–1.33)				1.09 (0.87–1.37)			
Adjuvant treatment								
No	I (ref)	<0.001	I (ref)	<0.001	I (ref)	<0.001	I (ref)	<0.001
Yes	0.63 (0.50–0.79)		0.6 (0.48–0.76)		0.62 (0.49–0.79)		0.61 (0.47–0.78)	
NLR								
≤2.13	I (ref)	<0.001	I (ref)	<0.001	I (ref)	<0.001	I (ref)	<0.001
>2.13	2.43 (1.98–2.99)		1.59 (1.27–2.00)		2.65 (2.14–3.29)		1.70 (1.33–2.16)	
PLR								
≤140	I (ref)	<0.001	I (ref)	<0.001	I (ref)	<0.001	I (ref)	<0.001
>140	2.54 (2.06–3.13)		1.93 (1.53–2.45)		2.93 (2.35–3.64)		2.23 (1.74–2.85)	

Note: Bold values (*P*<0.05).
Abbreviations: CA19-9, carbohydrate antigen 19–9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CI, confidence interval; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PLR, platelet-lymphocyte ratio.

Table 5 Multivariate analyses of NLR and PLR for DFS and OS stratified by pTNM stage

Stage	Survival	NLR		*P*-value	PLR		*P*-value
		≤2.13	>2.13 HR (95% CI)		≤140	>140 HR (95% CI)	
I	DFS	I (ref)	2.57 (1.83–3.60)	<0.001	I (ref)	3.82 (2.69–5.41)	<0.001
	OS	I (ref)	2.80 (1.95–4.00)	<0.001	I (ref)	5.06 (3.40–7.53)	<0.001
II	DFS	I (ref)	2.01 (1.44–2.81)	<0.001	I (ref)	2.06 (1.41–3.00)	<0.001
	OS	I (ref)	2.06 (1.46–2.92)	<0.001	I (ref)	2.24 (1.54–3.28)	<0.001
III	DFS	I (ref)	0.80 (0.34–1.88)	0.609	I (ref)	1.46 (0.67–3.18)	0.344
	OS	I (ref)	1.60 (0.65–3.95)	0.305	I (ref)	2.11 (0.98–4.55)	0.058

Note: Model adjusted for age, sex, ECOG PS score, smoking status, alcohol consumption, differentiation, and adjuvant treatment.
Abbreviations: CI, confidence interval; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PLR, platelet-lymphocyte ratio.

Accurate information on prognostication is useful for medical decision-making and clinical counseling. Nomograms, statistical instruments that can evaluate multiple relevant clinical factors and predict the continuous probability of a particular outcome for an individual patient, have been used in an extensive array of applications, including cancer.[43] To allow physicians to tailor prognostication for patients with resectable PDAC who maintain an underlying constant systemic inflammatory status, we established a nomogram incorporating NLR and PLR and compared its discriminatory ability to an instrument not incorporating NLR and PLR. In our study, the independent predictors, ECOG PS score, tumor stage, differentiation, adjuvant treatment, NLR, and PLR, were incorporated into the two nomograms. The AUCs of the nomograms including or excluding NLR and PLR were 0.804 and 0.711, respectively, indicating that the former had superior discrimination ability for prediction of

clinical outcomes. In addition, the nomogram incorporating NLR and PLR performed well on bootstrap validation, with a bootstrap-corrected AUC of 0.803. Thus, for example, a patient with an ECOG PS score of 0–1 (0 points), stage II tumor (65 points), well-differentiated tumor (0 points), NLR >2.13 (90 points), PLR ≤140 (0 points), and no adjuvant treatment (95 points) would score 250 total points, which converts to a probability for 1-year DFS of <10%. The predictors included in our nomogram are all available in routine clinical practice; therefore, we believe that it can be easily used by clinicians to make accurate individualized estimates of prognosis.

The strengths of our study are the large sample size and the long follow-up period. Moreover, our prediction model enables surgical PDAC patients to be monitored easily on an individual basis. Nevertheless, the investigation had several limitations that merit emphasis. First, although the
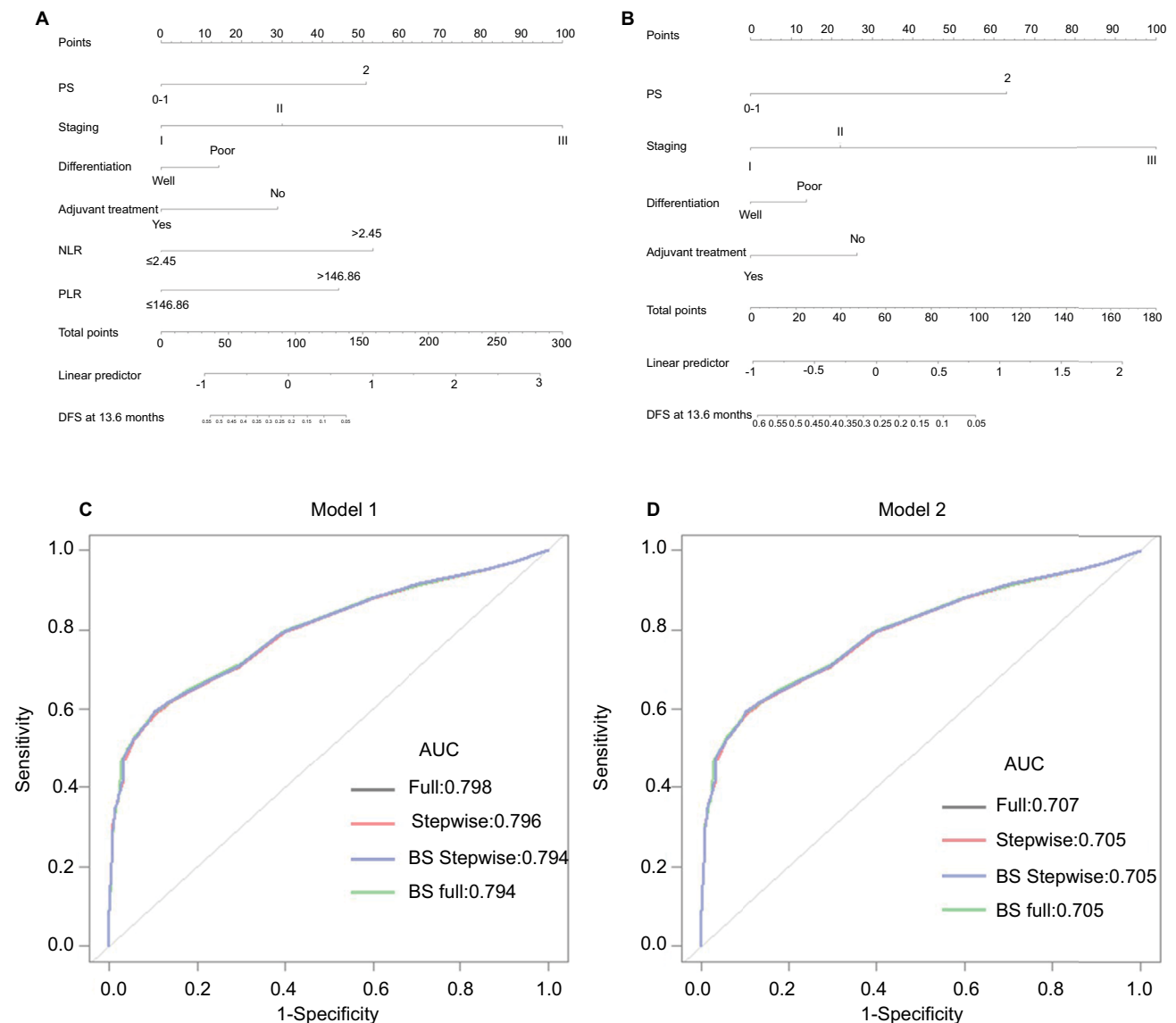
Figure 3 Nomograms and their accuracy for predicting 1-year DFS in patients with resectable PDAC.
Notes: (**A**) Nomogram including NLR and PLR, (**B**) nomogram without NLR and PLR, (**C**) bootstrap-corrected AUCs for model including NLR and PLR, (**D**) bootstrap-corrected (BS) AUCs for model without NLR and PLR.
Abbreviations: AUCs, areas under the curve; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil-lymphocyte ratio; PDAC, pancreatic ductal adenocarcinoma; PLR, platelet-lymphocyte ratio.

current study adjusted for a considerable number of potential confounders, we cannot rule out the possibility that the results may have been affected by other variables that were not included in the analyses. Second, patients were included in the database over a period of 10 years; therefore, it is possible that advances in surgical techniques and medical oncology have combined to improve survival of patients with resected PDAC. Hence, we used the bootstrapping technique to obtain an almost unbiased internal assessment of accuracy. Although the results of the bootstrapping correction procedure are promising, they do not negate the need for future

studies to externally validate whether our nomograms can be generalized to new patient populations. Furthermore, our conclusions were solely drawn from the objective clinical data, as it was beyond the scope of our study to elucidate the potential mechanism underlying the prognostic value of inflammatory markers.

Conclusion

In the present study, we demonstrated that high NLR and high PLR are clinically important predictors of poor survival in patients with resectable PDAC. Additionally, our

predictive nomogram including NLR and PLR can objectively and reliably predict DFS among PDAC patients after curative surgery, and performed well on internal validation. Therefore, with their advantages of cost-effectiveness and simplicity, NLR and PLR may be useful for stratification of high-risk subpopulations of patients with resectable PDAC in terms of recurrence and poor survival, even where tumors are the same stage. A further large-scale prospective validation study is needed to determine whether these results are widely applicable.

Author contributions

Both authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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