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Prognostic Significance of Preoperative Neutrophil-to-Lymphocyte Ratio in Surgically Resectable Pancreatic Neuroendocrine Tumors

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Background: The aim of this study was to evaluate the predictive and prognostic value of the preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in pancreatic neuroendocrine tumor (PNET) patients undergoing potentially curative resection.

Material/Methods: A retrospective review of 172 patients with PNETs was conducted. Kaplan-Meier curves and multivariate Cox proportional models were used to calculate overall survival (OS) and disease-free survival (DFS). The predictive performance of the NLR was compared with other inflammation-based scores and conventional stratification systems using receiver operating characteristic (ROC) curve analysis.

Results: Elevated NLR and PLR were both associated with advanced AJCC stage and high grade. In the univariate analysis, elevated NLR and PLR were both significantly associated with decreased OS and DFS. In the multivariate analysis, the preoperative NLR, but not the PLR, was an independent risk factor for OS (HR=4.471, 95% CI 1.531–13.054, p=0.006) and DFS (HR=2.531, 95% CI 1.202–5.329, p=0.015). The discriminatory capability of the NLR was superior to that of other inflammation-based scores in OS prediction. Furthermore, the predictive range was expanded by incorporating the NLR into the conventional stratification systems, including the AJCC stage and WHO classification systems.

Conclusions: As an independent prognostic factor, an elevated preoperative NLR is superior to the PLR with respect to predicting clinical outcomes in PNET patients undergoing potentially curative resection. The incorporation of the NLR into the existing conventional stratification systems improved the predictive accuracy.

MeSH Keywords: Multivariate Analysis • Neutrophils • Pancreatic Neoplasms

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Background

Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of neoplasms with multiple clinical characteristics. PNETs are considered more indolent tumors and are associated with better long-term survival rates than with tumors of the exocrine pancreas [1–3]. PNETs account for approximately 1–2% of all pancreatic neoplasms and 7.0% of all neuroendocrine tumors [4]. The annual incidence of PNETs in the United States is estimated to range between 2 and 5 cases per one million individuals but appears to be rising [5]. PNETs can be classified as either functional or nonfunctional. The majority (60%–90%) of PNETs are nonfunctional. Complete surgical resection of a PNET has been suggested to be the only potentially curative treatment for the disease, similar to pancreatic adenocarcinoma [6]. PNETs have a better prognosis than pancreatic ductal adenocarcinoma (PDAC). The 5-year survival rate after radical resection is approximately 86.4% [7]. Several studies have found that many host-related factors affect survival in PNETs. Intrinsic tumor characteristics, such as tumor sizes, stages, and grades; Ki-67 indices; and lymph node involvement, have long been shown to be associated with clinical outcomes [8–10]. Other clinical and pathologic factors used to predict disease progression include patient age at diagnosis, visceral pleural invasion status, and margin status [11]. Information regarding these factors is generally useful, but most of these factors are determined only after surgery. Therefore, it is necessary to search for potential prognostic indicators that are available before surgery.

Increasing evidence suggests that inflammatory cells are an essential component of the tumor microenvironment and play a role in tumor progression [12–15]. Inflammatory chemokines, including neutrophil-attracting cysteine-X-cysteine chemokines, can either be triggered by the tumor itself or be part of the host innate response to the cancer. Markers of systemic inflammation, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are generally appealing to clinicians, as these laboratory data are routinely collected prior to surgery and are therefore readily available. The NLR and PLR have been identified as prognostic factors. Elevated NLR and PLR have been shown to be correlated with advanced stages and poor prognoses in a variety of human tumors, including colorectal cancer [16], hepatocellular carcinoma [17], breast cancer [18], gastric neuroendocrine tumors [19], and pancreatic cancer [20]. However, the roles of NLR and PLR and the clinical significance of these parameters in PNETs remain under evaluation. The goal of this study was to assess the prognostic value of the NLR and PLR in patients with PNETs following potentially curative resection. Further, we compared the discriminative ability of the NLR with other inflammation-based scores to determine whether the NLR is a useful marker for predicting patient outcomes. Additionally, we refined the existing stratification systems by incorporating the NLR into the existing TNM staging system or WHO classification.

Material and Methods

Study population

Patients who underwent surgical resection for PNETs from November 2003 to August 2016 at the First Affiliated Hospital, Zhejiang University School of Medicine, were retrospectively reviewed. The diagnosis of PNET was made based on standard histologic criteria. The TNM stage of each PNET was determined based on the American Joint Committee on Cancer TNM Classification, while the grade of each PNET was determined according to the 2010 WHO classification of NETs of the GEP system. Patients were excluded if they: (1) showed clinical evidence of infection or evidence of hyperpyrexia at the time of diagnosis; (2) were treated for recurrent disease; (3) received preoperative radiochemotherapy prior to surgery; (4) had a history of cancer of any type; or (5) did not consent to the use of their medical records for research purposes. We included only those patients who had survived for at least 60 days after surgery to exclude perioperative mortality-related bias. All patients underwent potentially curative resection. Finally, 172 patients with PNETs were included (Figure 1). We also enrolled 172 healthy volunteers with similar age and sex distributions from the physical examination center in our hospital. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count, while the lymphocyte-to-monocyte ratio (LMR) was calculated by dividing the absolute lymphocyte count by the absolute monocyte count on preoperative routine blood tests. The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine.

Follow-up

Patient follow-up was performed by reviewing hospital records or contacting patient family members. Overall survival (OS) was defined as the time span extending from the date of initial diagnosis until the date of death from any cause or the date of last known contact. Disease-free survival (DFS) was defined as the time extending from the date of surgery to the date of PNET recurrence. Patients who did not have evidence of local recurrence or metastasis at the last follow-up and patients who had died of diseases unrelated to PNETs were censored in the analysis of DFS. Our department follows up with patients every 6 months for the first 5 years after surgery and then yearly thereafter. The following postoperative follow-up data were collected for each patient: clinical symptoms and signs, laboratory test results, and radiological examination

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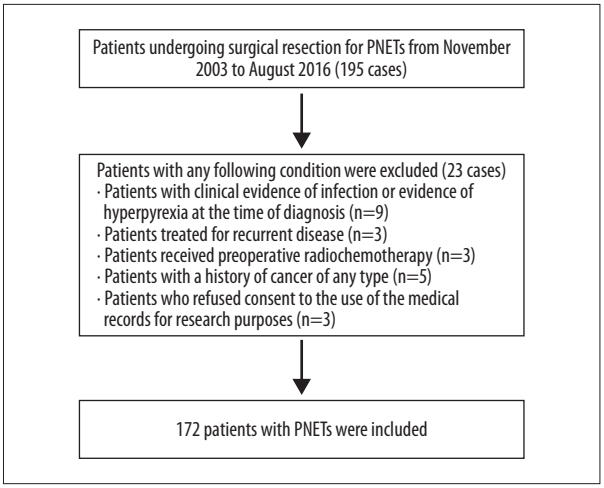

Figure 1. Flowchart of patient inclusion and exclusion.

results. Once recurrence was confirmed, patients were treated by repeat tumor resection, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), systemic chemotherapy, and somatostatin analogue therapy, according to the sizes, numbers, and locations of their recurrent tumors.

Statistical analysis

All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL, USA) for Windows. Differences in the NLR and PLR between patients and healthy subjects were evaluated by *t* tests in the case of normally distributed variables or by the Mann-Whitney U test in the case of abnormally distributed variables. Area under the curve (AUC) values obtained from the receiver operating characteristic (ROC) curve analysis were used to compare the predictive efficacies of the NLR and other inflammation-based scores. The associations between NLR and PLR and other prognostic factors were analyzed using chi-square and Fisher exact tests. The Kaplan-Meier method and the log-rank test were used to calculate OS and DFS. Prognostic analysis was performed using univariate and multivariate Cox regressions models. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 172 patients with histologically confirmed PNETs were included in the present analysis. These patients were diagnosed at a mean age of 52.92±12.55 years and were evaluated over a mean follow-up period of 48.04±35.2 months. Seventy-three (42.4%) of these patients had grade 1 disease, 76 (44.2%) had grade 2 disease, and the remaining 23 (13.4%) had grade 3 disease. The majority of patients (150/172, 87.2%) had stage I or II disease. A total of 166 patients underwent curative resections (R0 resection, 96.5%), while palliative surgery (R1 resection, 3.5%) was performed for only 6 patients. The operative procedures included the distal pancreatectomy (n=89), pancreaticoduodenectomy (n=53), enucleation (n=23), middle pancreatectomy (n=4), and total pancreatectomy (n=3). The pathology showed lymph node metastasis in 33 (19.2%) patients. At the time of the last follow-up visit, 46 patients had relapsed and 28 patients had died. The 1-, 3- and 5-y OS rates for the entire cohort were 98%, 90% and 78%, respectively, and the 1-, 3- and 5-y DFS rates for the entire cohort were 84%, 72%, and 71%, respectively.

Blood NLRs and PLRs were elevated in patients with PNETs

As shown in Table 1, platelet counts and lymphocyte counts were significantly lower in the blood of patients with PNETs than in the blood of normal volunteers (NVs) (both p<0.05). The PLR, NLR, and neutrophil counts were significantly higher in the patients with PNETs than in NVs (all p<0.05).

Correlations between the NLR and PLR and other PNET clinical parameters

Baseline patient demographic and clinicopathologic characteristics, which were stratified by NLR and PLR, are summarized in Table 2. Preoperatively, the NLR was >2.31 in 67 (39.0%) patients, while the PLR was >153.4 in 50 (29.1%) patients.

Table 1. Comparison of blood cell counts between PNET patients and NVs.

Variables	PNET (N=172)	NVs (N=172)	p Values
Neutrophil counts (10^9/l)	3.60±1.58	3.08±0.80	0.003
Platelet counts (10^9/l)	200.69±64.93	216.75±51.32	0.039
Lymphocyte counts (10^9/l)	1.64±0.56	2.08±0.58	<0.001
NLR	2.48±1.57	1.55±0.45	<0.001
PLR	133.39±58.71	110.48±35.68	<0.001

PNETs – pancreatic neuroendocrine tumours; NVs – normal volunteers; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio.

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Table 2. Baseline characteristics of the PNET patients stratified by the NLR and PLR.

Variables	NLR			PLR		
	≤2.31 (N=105)	>2.31 (N=67)	p Values	≤151.4 (N=122)	>151.4 (N=50)	p Values
Age (years)			0.576			0.947
≤56	61	36		69	28	
>56	44	31		53	22	
Albumin (g/l)			0.374			0.097
≤45	81	45		85	41	
>45	24	22		37	9	
Grade			0.003			0.045
G1	54	19		58	15	
G2	40	36		49	27	
G3	11	12		15	8	
AJCC stage			0.011			0.005
I–II	97	53		112	38	
III–IV	8	14		10	12	
LVSI			0.027			0.108
No	86	45		97	34	
Yes	19	22		25	16	
Tumour size			0.071			0.481
≤3.5 cm	67	33		73	27	
>3.5 cm	38	34		49	23	
Sex			0.068			0.802
Female	62	30		66	26	
Male	43	37		56	24	
Tumour location			0.139			0.048
Head/uncinate	31	28		35	24	
Neck	12	6		14	4	
Body/tail	62	33		73	22	
Symptomatic diagnosis			0.13			0.085
No	40	18		46	12	
Yes	65	49		76	38	
AKT (U/l)			0.011			<0.001
≤124	97	53		113	37	
>124	8	14		9	13	

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Table 2 continued. Baseline characteristics of the PNET patients stratified by the NLR and PLR.

Variables	NLR			PLR		
	≤2.31 (N=105)	>2.31 (N=67)	p Values	≤151.4 (N=122)	>151.4 (N=50)	p Values
Radical resection			0.002			0.039
R0	105	61		120	46	
R1	0	6		2	4	
Perineural invasion			0.038			0.070
No	96	54		110	40	
Yes	9	13		12	10	
Function			0.724			0.450
No	79	52		91	40	
Yes	26	15		31	10	

PNETs – pancreatic neuroendocrine tumours; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; LVSI – vascular lymph node invasion; AKT – alkaline phosphatase.

Univariate analysis revealed that an increased NLR and PLR were both associated with advanced AJCC stage, high grade, high alkaline phosphatase (AKT) level, and R1 resection (all p<0.05). Additionally, elevated NLR was associated with the presence of vascular lymph node invasion (LVSI) (p=0.027) and perineural invasion (p=0.038). In contrast, an elevated PLR was associated with tumor location (p=0.048).

Prognostic significance of variables and cut-off value determination

The results of the univariate survival analysis for each of the clinicopathologic variables are shown in Tables 3 and 4. Both a high NLR and a high PLR were significantly associated with a poor prognosis. Patients with a high NLR or PLR had shorter OS (HR=4.907, 95% CI 2.048–11.756, p<0.001 and HR=3.307, 95% CI 1.499–7.297, p=0.003, respectively) and DFS (HR=4.143, 95% CI 2.229–7.701, p<0.001 and HR=2.617, 95% CI 1.465–4.675, p=0.001, respectively) than patients with a low NLR or PLR (Figure 2). Furthermore, high tumor grade, presence of LVSI and perineural invasion, large tumor, high stage, increased AKT level, high LMR, nonfunctional tumor, and symptomatic tumor were prognostic factors for poor OS (p<0.05 for all). High grade, presence of LVSI and perineural invasion, large tumor, high stage, increased AKT level, high LMR, nonfunctional tumor, and male sex were associated with poor DFS (p<0.05 for all).

In multivariate analysis, NLR remained significantly associated with OS (HR=4.471, 95% CI 1.531-13.054, p=0.006) and DFS (HR=2.531, 95% CI 1.202-5.329, p=0.015) (Tables 3, 4). Furthermore, WHO grade, AJCC stage, perineural invasion, and radical resection were independent predictive factors for OS (p<0.05 for all measurements, Table 3), whereas WHO grade, AJCC stage, and perineural invasion were independent predictive factors for DFS (p<0.05 for all, Table 4).

ROC curve analysis showed that the AUCs of the NLR, PLR, LMR, and tumor size were 0.785, 0.67, 0.747, and 0.709, respectively, and that the best cut-off values for the above parameters were 2.31, 151.4, 3.22, and 3.5, respectively, as these values were both the most sensitive and the most specific in predicting survival (Figure 3).

Subgroup analyses of the parameters associated with the NLR

We investigated the prognostic value of the NLR relative to AJCC stage, grade, age, sex, LVSI, tumor size, and perineural invasion (Table 5). We noted a strong association between NLR and OS, which was independent of AJCC stage (p=0.002 for stage I/II; p=0.041 for stage III/IV), tumor size (tumor size ≤3.5 cm, p=0.016; tumor size >3.5 cm, p=0.006), and sex (male, p=0.021; female, p=0.007). We also noted a strong association between NLR and DFS, which was independent of age (age ≤56, p=0.017; age >56, p<0.001), tumor size (tumor size ≤3.5 cm, p=0.002; tumor size >3.5 cm, p=0.007), and sex (male, p=0.005; female, p=0.003). Furthermore, a high NLR was significantly associated with shorter OS in older (>56 y) (Figure 4A) patients with low-grade tumors (1 and 2) (Figure 4B), patients with tumors without perineural invasion (Figure 4C), and patients with tumors without LVSI (Figure 4D). Moreover, a high NLR was associated with poor DFS in patients with stage I/II

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Table 3. Variables associated with OS according to the Cox proportional hazards regression model.

Variables	Univariable analysis			Multivariable analysis		
	HR	95%CI	p Values	HR	95%CI	p Values
Age (years)			0.076			
≤56	Reference					
>56	2.085	0.926–4.696				
NLR			<0.001			0.006
≤2.31	Reference			Reference		
>2.31	4.907	2.048–11.756		4.471	1.531–13.054	
PLR			0.003			0.205
≤151.4	Reference			Reference		
>151.4	3.307	1.499–7.297		NA	NA	
LMR			<0.001			0.228
≤3.22				Reference		
>3.22	0.168	0.067–0.425		NA	NA	
Albumin (g/l)			0.249			
≤45	Reference					
>45	1.640	0.707–3.804				
Grade			<0.001			0.001
G1	Reference			Reference		
G2	6.666	1.491–29.805		0.851	0.114–6.367	
G3	45.599	9.676–214.977		5.360	0.616–46.666	
AJCC stage			<0.001			0.004
I–II	Reference			Reference		
III–IV	4.034	2.609–6.239		3.946	1.568–9.929	
LVSI			<0.001			0.531
No	Reference			Reference		
Yes	9.777	4.152–23.021		NA	NA	
Tumour size			0.023			0.782
≤3.5 cm	Reference			Reference		
>3.5 cm	2.557	1.135–5.760		NA	NA	
Sex			0.068			
Female	Reference					
Male	2.161	0.945–4.941				
Tumour location			0.084			
Head/uncinate	Reference					
Neck	1.553	0.201–11.996				

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Table 3 continued. Variables associated with OS according to the Cox proportional hazards regression model.

Variables	Univariable analysis			Multivariable analysis		
	HR	95%CI	p Values	HR	95%CI	p Values
Body/tail	0.398	0.177–0.896				
AKT (U/L)			<0.001			0.519
≤124	Reference			Reference		
>124	5.442	2.37–12.495		NA	NA	
Radical resection			0.006			0.025
R0	Reference			Reference		
R1	5.566	1.655–18.724		5.059	1.231–20.798	
Perineural invasion			<0.001			0.036
No	Reference			Reference		
Yes	6.943	3.027–15.925		2.683	1.065–6.763	
Function			0.03			0.245
No	Reference			Reference		
Yes	0.109	0.015–0.808		NA	NA	
Symptomatic diagnosis			0.044			0.069
No	Reference			Reference		
Yes	3.475	1.056–11.658		NA	NA	

PNETs– pancreatic neuroendocrine tumours; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; OS – overall survival; LVSI – vascular lymph node invasion; AKT – alkaline phosphatase; NA– not available.

disease (Figure 5A), patients with low-grade tumors (Figure 5B), patients with tumors without perineural invasion (Figure 5C), and patients with tumors without LVSI (Figure 5D) (p<0.01 for all measurements).

Comparative performance of the NLR and other predictive models

To further evaluate the prognostic values of the NLR, other inflammation-based scores and the conventional stratification systems, an ROC analysis was performed and the AUC values were compared. The NLR had a higher AUC value (0.736; p<0.001) than the PLR and LMR (Figure 6A). However, the conventional staging systems were superior to the inflammation-based scores in the OS prediction for PNETs (Table 6). In addition, the predictive ability of the AJCC staging system was superior to that of the WHO classification in our cohort (AUC value: 0.846 *vs.* 0.784).

The model integrating the NLR and the AJCC stage for OS prediction had higher AUC values than that of the AJCC stage alone (0.916 *vs.* 0.846), while the predictive abilities of the model integrating the NLR and the WHO classification was superior to that of the WHO classification alone (0.857 *vs.* 0.784) (Figure 6B).

Discussion

The results of the present study showed that the preoperative NLR, but not the PLR, was an independent risk factor for OS (HR=4.471, 95% CI 1.531–13.054, p=0.006) and DFS (HR=2.531, 95% CI 1.202–5.329, p=0.015) in PNET patients undergoing potentially curative resection. Furthermore, we observed that elevated preoperative NLR and PLR were both associated with advanced tumor stages and higher tumor grades. Finally, we showed that the NLR outperformed other inflammation-based scores in terms of its discriminatory capacity. The predictive models incorporating the NLR and conventional stratification systems, including the WHO classification and AJCC stage, showed improved predictive power relative to those of the stratification systems alone.

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Table 4. Variables associated with DFS according to the Cox proportional hazards regression model.

Variables	Univariable analysis			Multivariable analysis		
	HR	95%CI	p Values	HR	95%CI	p Values
Age (years)			0.087			
≤56	Reference					
>56	1.663	0.929–2.976				
NLR			<0.001			0.015
≤2.31	Reference			Reference		
>2.31	4.143	2.229–7.701		2.531	1.202–5.329	
PLR			0.001			0.275
≤151.4	Reference			Reference		
>151.4	2.617	1.465–4.675		NA	NA	
LMR			0.001			0.477
≤3.22	Reference			Reference		
>3.22	0.365	0.203–0.654		NA	NA	
Albumin (g/l)			0.426			
≤45	Reference					
>45	1.299	0.682–2.470				
Grade			<0.001			0.001
G1	Reference			Reference		
G2	10.426	3.16–34.398		1.659	0.413–6.663	
G3	42.931	12.345–149.297		5.632	1.303–24.349	
AJCC stage			<0.001			0.003
I–II	Reference				Reference	
III–IV	4.899	3.406–7.045		2.771	1.423–5.397	
LVSI			<0.001			0.163
No	Reference			Reference		
Yes	5.363	2.981–9.648		NA	NA	
Tumour size			0.001			0.611
≤3.5 cm	Reference			Reference		
>3.5 cm	2.812	1.547–5.112		NA	NA	
Sex			0.001			0.105
Female	Reference			Reference		
Male	2.856	1.54–5.297		NA	NA	
Tumour location			0.173			
Head/uncinate	Reference					
Neck	0.424	0.126–1.429				
Body/tail	0.615	0.338–1.121				

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Table 4 continued. Variables associated with DFS according to the Cox proportional hazards regression model.

Variables	Univariable analysis			Multivariable analysis		
	HR	95%CI	p Values	HR	95%CI	p Values
AKT (U/l)			<0.001			0.107
≤124	Reference			Reference		
>124	3.7	1.932–7.087		NA	NA	
Perineural invasion			<0.001			0.036
No	Reference			Reference		
Yes	5.423	2.884–10.197		1.989	1.001–3.95	
Function			0.003			0.43
No	Reference			Reference		
Yes	0.114	0.028–0.472		NA	NA	
Symptomatic diagnosis			0.109			
No	Reference					
Yes	1.741	0.883–3.430				

PNETs – pancreatic neuroendocrine tumours; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; DFS – disease-free survival; LVSI – vascular lymph node invasion; AKT – alkaline phosphatase; NA – not available.

Increasing evidence has confirmed that systemic inflammation is associated with poorer cancer-specific survival in patients with different types of cancer [21–24]. Among several prognostic scores, the NLR, the PLR, the Glasgow prognostic score (GPS) based on serum C-reactive protein (CRP) and albumin, the prognostic index (PI) based on CRP and WBC counts, and the prognostic nutritional index (PNI) based on albumin and lymphocyte count are recognized as useful for predicting outcomes after surgery in specific host subgroups [25,26]. More recently, the NLR, which can comprehensively reflect inflammatory and immune status in patients with cancer, has been shown to be a reliable marker for predicting the survival of patients with different types of cancer, such as lung cancer [27], colorectal cancer [21], liver cancer [17], breast cancer [18], PDAC [20], and renal cell carcinoma [22]. In addition, many studies have confirmed that the PLR is a marker of patient immune status and long-term survival. PLR is also a prognostic marker in several different tumor types [28,29]. However, Shirai et al. reported that an increased preoperative PLR was not associated with OS in patients undergoing elective pancreatic resection [30]. Another study reported that the PLR has no prognostic value in oesophageal cancer [31]. The heterogeneity across these studies may be attributed to several factors, such as differences in PLR cut-off values, differences in inclusion and exclusion criteria, differences in statistical analysis methodologies (univariate *vs.* multivariate analyses, differences in the covariates investigated in the multivariate analysis), and differences in treatment schedules. Regarding NETs, the report by Salman et al. revealed that elevated NLR and PLR were associated with a high tumor grade and advanced tumor stage. The study also verified that the NLR and PLR are simple laboratory parameters that can be used to identify NETs with worse outcomes [32]. Yucel et al. investigated 52 patients with NETs and demonstrated the prognostic importance of the NLR in their study [33]. Regarding gastric NET, blood NLRs can also be an independent prognostic factor for RFS and OS [19]. In the present study, we found that the NLR and PLR were significantly higher in patients with PNETs than in matched NVs. Furthermore, the NLR, but not the PLR, is an independent prognostic factor associated with both OS and DFS in patients with PNET. In addition, we found that a preoperative NLR >2.31 was predictive of significantly worse survival in the subgroup of patients with stage I/II or grade 1/2 tumors. Thus, the preoperative NLR may be able to predict a poor prognosis in patients with stage I/II or grade 1/2 tumors. However, the prognostic value of the PLR was limited in our study. Patients with a low PLR at diagnosis showed significantly prolonged OS and DFS compared to patients with a high PLR in the univariate analysis; however, PLR did not show prognostic significance in the multivariate analysis. Nevertheless, given the large number of patients enrolled in this study and the effect of the NLR on prognosis in PNET demonstrated herein, our study is an important addition to the relevant literature on this topic.

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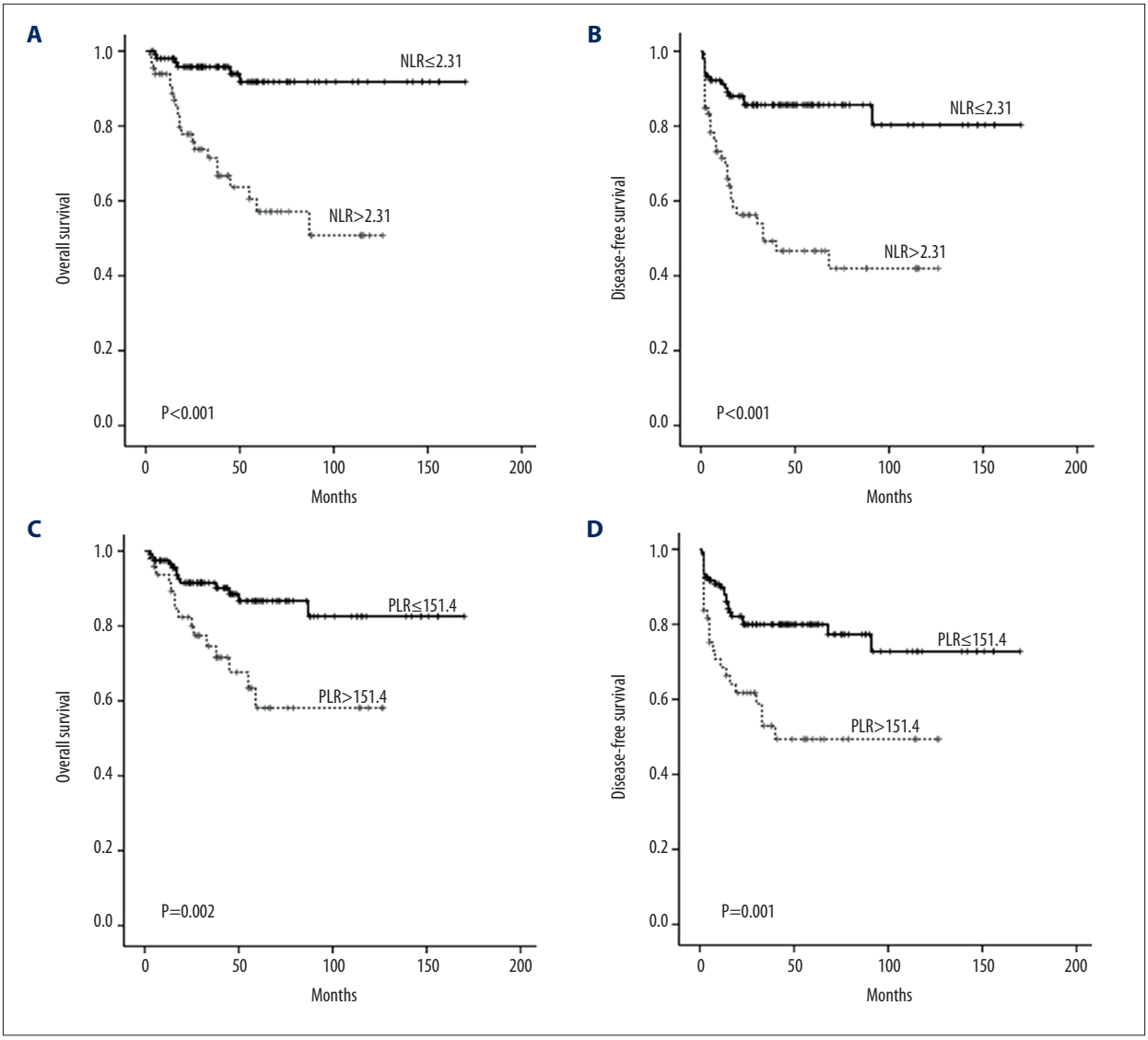

Figure 2. Kaplan-Meier survival curves showing OS (**A**) and DFS (**B**) stratified by NLR in patients who underwent surgery for PNETs and OS (**C**) and DFS (**D**) stratified by PLR.

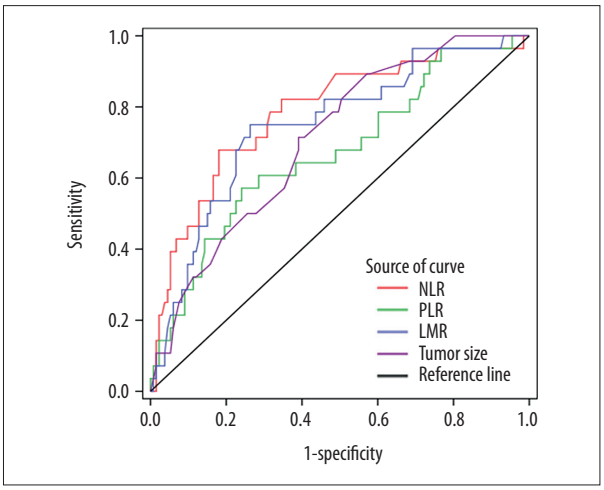

Figure 3. ROC curve for the NLR, PLR, LMR, and tumor size in resectable PNETs.

The cut-off values for the NLR and PLR were important in our analysis. The cut-off value for NLR that is commonly used many studies is 5.0 [30,31,33,34], while PLR cut-off values varying from 150 to 300 have been used in other studies [29–32]. In most of the above studies, the cut-off values for the NLR and PLR were set empirically. In contrast to those studies [31,33], our study used cut-off values for NLR and PLR that were calculated with an ROC curve based on survival predictions. Our results demonstrated that the best cut-off values for the NLR and PLR were 2.31 and 151.4, with AUCs of 0.785 and 0.67, respectively, indicating that the NLR was superior to the PLR as a predictive factor in patients with PNET undergoing potentially curative resection.

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Table 5. Subgroup analysis for OS and DFS according to NLR.

Variables	NLR	N (%)	OS			DFS		
			HR	95%CI	p Values	HR	95%CI	p Values
Age (years)								
≤56	≤2.31	61 (62.9)	Reference			Reference		
	>2.31	36 (37.1)	2.506	0.795–7.9	0.117	2.822	1.203–6.62	0.017
>56	≤2.31	44 (58.7)	Reference					
	>2.31	31 (41.3)	24.399	3.162–188.259	0.002	6.105	2.389–15.597	<0.001
Grade								
G1/G2	≤2.31	94 (63.1)	Reference			Reference		
	>2.31	55 (36.9)	11.078	2.454–50.012	0.002	5.856	2.588–13.252	<0.001
G3	≤2.31	11 (47.8)	Reference					
	>2.31	12 (52.2)	2.224	0.587–8.426	0.239	1.512	0.548–4.175	0.425
AJCC stage								
Stage I/II	≤2.31	97 (64.7)	Reference			Reference		
	>2.31	53 (35.3)	8.094	2.219–29.521	0.002	8.271	2.272–30.106	0.001
Stage III/IV	≤2.31	8 (36.4)	Reference			Reference		
	>2.31	14 (63.6)	2.902	1.047–8.042	0.041	1.783	0.87–3.655	0.114
LVSI								
No	≤2.31	86 (65.6)	Reference			Reference		
	>2.31	45 (34.4)	12.69	1.527–105.478	0.019	5.581	2.159–14.426	<0.001
Yes	≤2.31	19 (46.3)	Reference			Reference		
	>2.31	22 (53.7)	2.692	0.954–7.598	0.061	2.16	0.945–4.938	0.068
Tumour size								
≤3.5 cm	≤2.31	67 (67)	Reference			Reference		
	>2.31	33 (33)	7.129	1.434–35.454	0.016	5.519	1.912–15.930	0.002
>3.5 cm	≤2.31	38 (52.8)	Reference			Reference		
	>2.31	34 (47.2)	5.751	1.638–20.191	0.006	2.843	1.323–6.108	0.007
Sex								
Female	≤2.31	62 (67.4)	Reference			Reference		
	>2.31	30 (32.6)	18.263	2.243–148.732	0.007	5.238	1.772–15.479	0.003
Male	≤2.31	43 (53.8)	Reference			Reference		
	>2.31	37 (46.2)	3.806	1.226–11.812	0.021	2.979	1.4–6.339	0.005
Perineural invasion								
No	≤2.31	96 (64)	Reference			Reference		
	>2.31	54 (36)	12.837	2.871–57.394	0.001	5.685	2.611–12.38	<0.001
Yes	≤2.31	9 (40.9)	Reference			Reference		
	>2.31	13 (59.1)	1.34	0.345–5.206	0.673	0.887	0.315–2.497	0.821

NLR – neutrophil to lymphocyte ratio; OS – overall survival; DFS – disease-free survival; LVSI – vascular lymph node invasion.

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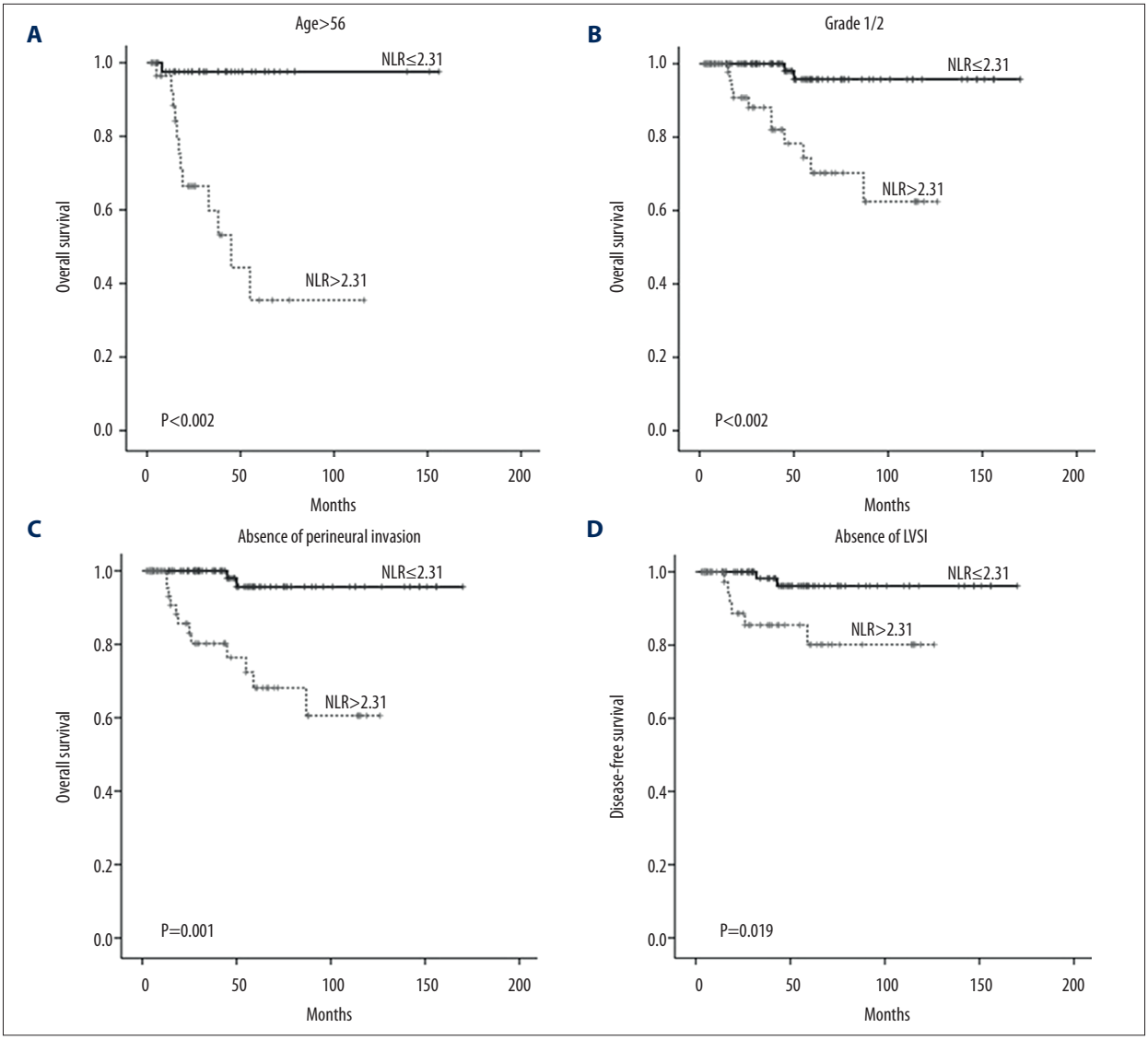

Figure 4. Kaplan-Meier survival curves for the different PNET subgroups. An NLR >2.31 was significantly correlated with shorter OS in older (>56 years) (**A**) patients with low-grade tumors (grade 1/2) (**B**), patients with tumors without perineural invasion (**C**), and patients with tumors without LVSI (**D**).

Although the biology underlying the abovementioned increases in the NLR and PLR remains unclear, it is widely accepted that tumor development is associated with inflammation and immunity. Inflammation plays an important role in tumor growth [35–37]. Inflammatory mediators and cytokines, such as epidermal growth factor (EGF), transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), fibroblast growth factors (FGFs), and interleukins (IL-4, IL-8, IL-10 and IL-13), which are produced by the tumor or as part of the host innate immune response, can promote angiogenesis, cause matrix degradation and cancer progression, and facilitate immunosuppression [38,39]. All of the above pathways converge to activate transcription factors, such as NF-kappaB and STAT3, leading to downstream recruitment of inflammatory mediators and leukocytes in the tumor environment [40]. This microenvironment also potentiates and enhances the neoplastic risk and ultimately promotes metastatic spread. Research has confirmed the existence of a relationship between the inflammatory microenvironments of tumors and the systemic responses induced by tumors. A variety of prognostic markers associated with the presence of a systemic inflammatory response have been described in a previous study [41].

In recent years, WHO classification, TNM stage, distant metastases, surgical margin status, tumor sizes, and Ki-67 indices have been suggested as valuable prognostic factors in patients with PNETs [8–11]. To the best of our knowledge, the existing stratification systems and predictive models for PNET,

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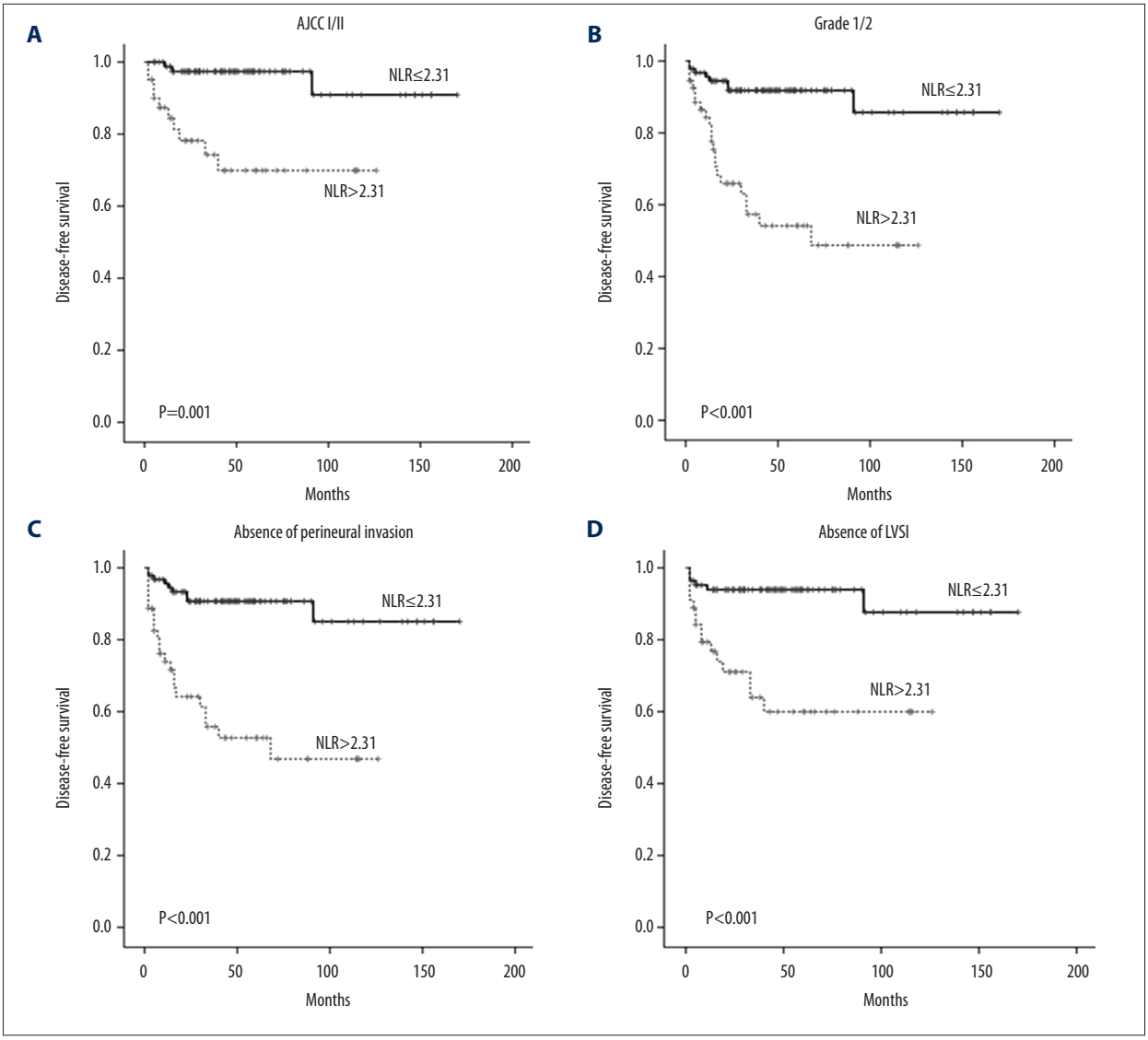

Figure 5. Kaplan-Meier survival curves for the different PNET subgroups. An NLR >2.31 was significantly correlated with poor DFS in patients with stage I/II disease (**A**), patients with low-grade tumors (**B**), patients with tumors without perineural invasion (**C**), and patients with tumors without LVSI (**D**).

including the abovementioned TNM staging system, WHO classification and 2 nomograms [42,43], lack indicators of systemic inflammation, which could offer additional information for prognostic evaluation. Herein, we incorporated the NLR into the AJCC stage and WHO classification and showed that the predictive ability of models integrating the NLR and the stratification systems for OS was superior to that of the stratification systems alone. The results support the integration of the NLR into the conventional stratification systems for an improved discriminative ability.

Our study had several limitations that must be considered. First, given its retrospective design, the current study was subject to possible selection bias and diagnostic bias. Second, the NLR, a marker of systemic inflammation, may be affected by many conditions, including chemotherapy toxicity, chronic inflammatory diseases, granulocyte colony-stimulating factor administration, pathogenic inflammation, and other diseases. Therefore, these conditions must be accounted for in clinical practice. Moreover, the present study was conducted at a single institution. The performance of multicentre studies of the markers used herein would strengthen our conclusions. Finally, only patients who underwent surgery were included in the study, and it does not cover most of the advanced cases; thus, our results may not apply to patients without indications for surgical resection due to advanced stage.

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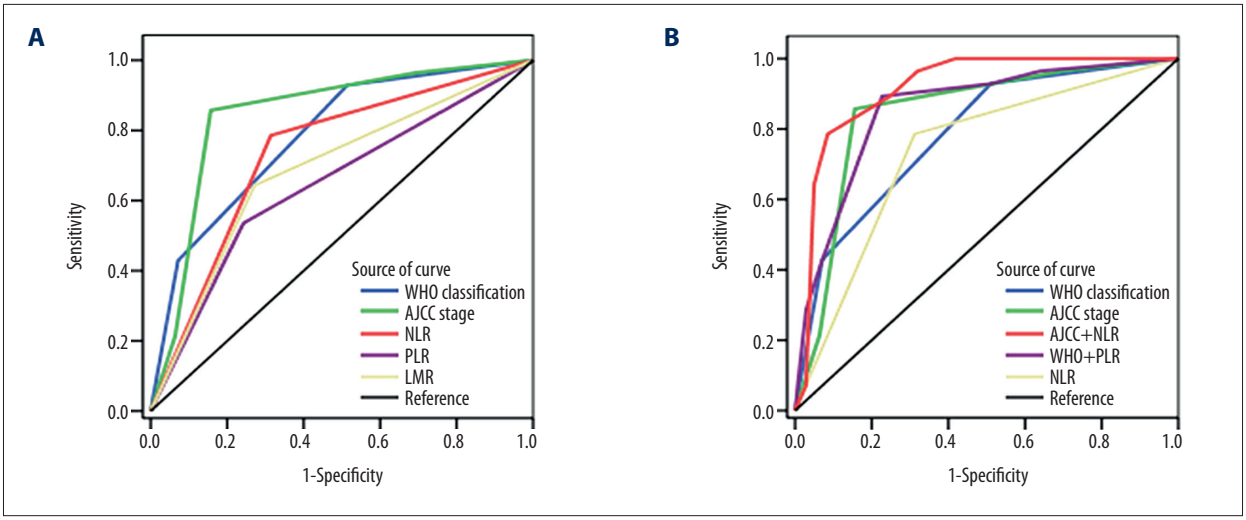

Figure 6. ROC curve for the NLR and other predictive models in resectable PNETs. The NLR had a higher AUC value than the PLR and LMR (**A**), while the prognostic models incorporating the NLR into the TNM staging system or WHO classification provided improved predictive accuracy compared with the prognostic models of the stratification systems alone (**B**).

Table 6. Areas under the ROC curves of the conventional staging systems and inflammation-based prognostic scores for predicting OS in PNET patients undergoing potentially curative resection.

Variables	Area under the ROC curve (95% CI)	p Values
Combined predictive models		
AJCC stage + NLR	0.916 (0.869–0.962)	<0.001
WHO classification + NLR	0.857 (0.782–0.932)	<0.001
Staging systems		
AJCC stage	0.846 (0.768–0.924)	<0.001
WHO classification	0.784 (0.694–0.874)	<0.001
Inflammation-based scores		
NLR (≤2.31/>2.31)	0.736 (0.636–0.835)	<0.001
PLR (≤151.4/>151.4)	0.646 (0.529–0.764)	0.015
LMR (≤3.22/>3.22)	0.686 (0.574–0.797)	0.002

ROC – receiver operating characteristic; OS – overall survival; PNETs – pancreatic neuroendocrine tumours; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; LMR – lymphocyte to monocyte ratio.

Conclusions

As an easily accessible inflammation-based biomarker, the preoperative NLR, but not the PLR, was an independent predictor of OS and DFS in patients who underwent potentially curative resection for PNETs. Furthermore, we confirmed that prognostic models incorporating the NLR into the TNM staging system or WHO classification provided improved predictive accuracy compared with those incorporating the stratification systems alone. Therefore, we recommend that surgeons develop a treatment plan that considers not only the TNM stage but also these prognosis-related serum biomarkers in order to improve personalized therapy for patients with PNETs.

Conflict of interests

None.

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References:

1. Klimstra DS, Modlin IR, Coppola D et al: The pathologic classification of neuroendocrine tumors: A review of nomenclature, grading, and staging systems. Pancreas, 2010; 39(6): 707–12
2. Fischer L, Kleeff J, Esposito I et al: Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumors of the pancreas. Br J Surg, 2008; 95(5): 627–35
3. Niederle MB, Hackl M, Kaserer K, Niederle B: Gastroenteropancreatic neuroendocrine tumors: The current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: An analysis based on prospectively collected parameters. Endocr Relat Cancer, 2010; 17(4): 909–18
4. Bilimoria KY, Talamonti MS, Tomlinson JS et al: Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: Analysis of 3851 patients. Ann Surg, 2008; 247(3): 490–500
5. Hauso O, Gustafsson BI, Kidd M et al: Neuroendocrine tumor epidemiology: Contrasting Norway and North America. Cancer, 2008; 113(10): 2655–64
6. Xiao J, Yu H: Gemcitabine conjugated chitosan and double antibodies (Abc-GC-Gemcitabine Nanoparticles) enhanced cytoplasmic uptake of gemcitabine and inhibit proliferation and metastasis in human SW1990 pancreatic cancer cells. Med Sci Monit, 2017; 23: 1613–20
7. Wang SE, Su CH, Kuo YJ et al: Comparison of functional and nonfunctional neuroendocrine tumors in the pancreas and peripancreatic region. Pancreas, 2011; 40(2): 253–59
8. Strosberg JR, Cheema A, Weber JM et al: Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: An analysis of the AJCC and ENETS staging classifications. Ann Surg, 2012; 256(2): 321–25
9. Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvols LK: Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. J Clin Oncol, 2011; 29(22): 3044–49
10. Bettini R, Boninsegna L, Mantovani W et al: Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumors. Ann Oncol, 2008; 19(5): 903–8
11. Yao JC, Hassan M, Phan A et al: One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol, 2008; 26(18): 3063–72
12. Moore MM, Chua W, Charles KA, Clarke SJ: Inflammation and cancer: Causes and consequences. Clin Pharmacol Ther, 2010; 87(4): 504–8
13. Hanahan D, Weinberg RA: Hallmarks of cancer: The next generation. Cell, 2011; 144(5): 646–74
14. Liao J, Hwang SH, Li H et al: Inhibition of chronic pancreatitis and murine pancreatic intraepithelial neoplasia by a dual inhibitor of c-RAF and soluble epoxide hydrolase in LSL-KrasG^{12}D/Pdx-1-Cre mice. Anticancer Res, 2016; 36(1): 27–37
15. Stark AP, Chang HH, Jung X et al: E-cadherin expression in obesity-associated, Kras-initiated pancreatic ductal adenocarcinoma in mice. Surgery, 2015; 158(6): 1564–72
16. Kwon HC, Kim SH, Oh SY et al: Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers, 2012; 17(3): 216–22
17. Mano Y, Shirabe K, Yamashita Y et al: Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma: A retrospective analysis. Ann Surg, 2013; 258(2): 301–5
18. Azab B, Bhatt VR, Phookan J et al: Usefulness of the neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. Ann Surg Oncol, 2012; 19(1): 217–24
19. Cao LL, Lu J, Lin JX et al: A novel predictive model based on preoperative blood neutrophil-to-lymphocyte ratio for survival prognosis in patients with gastric neuroendocrine neoplasms. Oncotarget, 2016; 7(27): 42045–58
20. Paramanathan A, Saxena A, Morris DL: A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumors. Surg Oncol, 2014; 23(1): 31–39
21. Li MX, Liu XM, Zhang XF et al: Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: A systematic review and meta-analysis. Int J Cancer, 2014; 134(10): 2403–13
22. Pichler M, Hutterer GC, Stoeckigt C et al: Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. Br J Cancer, 2013; 108(4): 901–7
23. Pan QX, Su ZJ, Zhang JH et al: A comparison of the prognostic value of preoperative inflammation-based scores and TNM stage in patients with gastric cancer. Onco Targets Ther, 2015; 8: 1375–85
24. Asher V, Lee J, Innamaa A, Bali A: Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol, 2011; 13(7): 499–503
25. Yamada S, Fujii T, Yabusaki N et al: Clinical implication of inflammation-based prognostic score in pancreatic cancer: Glasgow prognostic score is the most reliable parameter. Medicine (Baltimore), 2016; 95(18): e3582
26. Hu H, Yao X, Xie X et al: Prognostic value of preoperative NLR, dNLR, PLR and CRP in surgical renal cell carcinoma patients. World J Urol, 2017; 35(2): 261–70
27. Zhang H, Xia H, Zhang L et al: Clinical significance of preoperative neutrophil-lymphocyte *vs.* platelet-lymphocyte ratio in primary operable patients with non-small cell lung cancer. Am J Surg, 2015; 210(3): 526–35
28. Smith RA, Bosonnet L, Raraty M et al: Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg, 2009; 197(4): 466–72
29. Smith RA, Ghaneh P, Sutton R et al: Prognosis of resected ampullary adenocarcinoma by preoperative serum CA19-9 levels and platelet-lymphocyte ratio. J Gastrointest Surg, 2008; 12(8): 1422–28
30. Shirai Y, Shiba H, Sakamoto T et al: Preoperative platelet to lymphocyte ratio predicts outcome of patients with pancreatic ductal adenocarcinoma after pancreatic resection. Surgery, 2015; 158(2): 360–65
31. Dutta S, Crumley AB, Fullarton GM et al: Comparison of the prognostic value of tumour- and patient-related factors in patients undergoing potentially curative resection of oesophageal cancer. World J Surg, 2011; 35(8): 1861–66
32. Salman T, Kazaz SN, Varol U et al: Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for patients with neuroendocrine tumors: An Izmir Oncology Group Study. Chemotherapy, 2016; 61(6): 281–86
33. Yucel B, Babacan NA, Kacan T et al: Survival analysis and prognostic factors for neuroendocrine tumors in Turkey. Asian Pac J Cancer Prev, 2014; 14(11): 6687–92
34. Martin HL, Ohara K, Kiberu A et al: Prognostic value of systemic inflammation-based markers in advanced pancreatic cancer. Intern Med J, 2014; 44(7): 676–82
35. Shimizu T, Marusawa H, Endo Y, Chiba T: Inflammation-mediated genomic instability: Roles of activation-induced cytidine deaminase in carcinogenesis. Cancer Sci, 2012; 103(7): 1201–6
36. Grivennikov SI, Greten FR, Karin M: Immunity, inflammation, and cancer. Cell, 2010; 140(6): 883–99
37. Coussens LM, Werb Z: Inflammation and cancer. Nature, 2002; 420(6917): 860–67
38. Lippitz BE: Cytokine patterns in patients with cancer: A systematic review. Lancet Oncol, 2013; 14(6): e218–28
39. Popivanova BK, Kitamura K, Wu Y et al: Blocking TNF-alpha in mice reduces colorectal carcinogenesis associated with chronic colitis. J Clin Invest, 2008; 118(2): 560–70
40. Grivennikov SI, Karin M: Dangerous liaisons: STAT3 and NF-kappaB collaboration and crosstalk in cancer. Cytokine Growth Factor Rev, 2010; 21(1): 11–19
41. Elinav E, Nowarski R, Thaiss CA et al: Inflammation-induced cancer: Crosstalk between tumors, immune cells and microorganisms. Nat Rev Cancer, 2013; 13(11): 759–71
42. Han X, Zhang C, Tang M et al: The value of serum chromogranin A as a predictor of tumor burden, therapeutic response, and nomogram-based survival in well-moderate nonfunctional pancreatic neuroendocrine tumors with liver metastases. Eur J Gastroenterol Hepatol, 2015; 27(5): 527–35
43. Ellison TA, Wolfgang CL, Shi C et al: A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors: A validation of current staging systems and a new prognostic nomogram. Ann Surg, 2014; 259(2): 204–12

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