# The prognostic significance of inflammation-based scores in patients with ampullary carcinoma after pancreaticoduodenectomy

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**Research article**

**Keywords:** neutrophil-to-lymphocyte ratio, prognostic index, progress-free survival, overall survival, ampullary cancer, pancreaticoduodenectomy

**Posted Date:** May 1st, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-23444/v1



**Version of Record:** A version of this preprint was published on October 10th, 2020. See the published version at https://doi.org/10.1186/s12885-020-07482-0.

# Abstract

**Background:**

Growing evidence indicates that systemic inflammatory response plays an important role in cancer development and progression. Several inflammatory markers have been reported to be associated with the clinical outcomes in patients with various types of cancer. This study was designed to evaluate the prognostic value of the inflammatory indexes in patients suffering from ampullary cancer (AC) who underwent pancreaticoduodenectomy (PD).

**Methods:**

We retrospectively reviewed a database of 358 patients with AC who underwent PD between 2009 and 2018. R software was used to compare the area under the time-dependent receiver operating characteristic (ROC) curves (AUROCs) of the inflammation-based indexes, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), modified Glasgow Prognostic Score (mGPS), prognostic nutritional index (PNI) and prognostic index (PI), in terms of their predictive value of survival. The survival differences of these indexes were compared by Kaplan-Meier method and univariate and multivariate analyses were performed to determine the prognostic factors of progress-free survival (PFS) and overall survival (OS).

**Results:**

The estimated 1-, 2-, and 3-year OS and PFS rates were 83.9%, 65.8%, 55.2% and 58.0%, 42.8%, 37.8%, respectively, for the entire cohort. The survival differences were significant in terms of OS and PFS when they were stratified by these inflammation-based indexes. The comparisons of AUROCs of these inflammation-based indexes illustrated that NLR and PI displayed highest prognostic value, compared to other indexes. When NLR and PI were combined, NLR-PI showed even higher AUROC values and was identified as a significant prognostic factor in terms of OS and PFS.

**Conclusion:**

Specific inflammatory indexes, such as NLR, PLR and PI, were found to be able to predict the OS or PFS of patients. As a novel inflammatory index, the level of NLR-PI, which can be regarded as a more useful prognostic index, exhibited strong predictive power for predicting prognosis of patients with AC after PD procedure.


# Introduction

The malignancies arising within 2-cm of the major papilla in the duodenum were defined as the periampullary cancers (PACs) which general encompass four different anatomical subtypes: pancreatic, ampullary, biliary, or duodenal cancers, respectively[1]. A majority of PACs are pancreatic adenocarcinomas, which is one of the most aggressive and highly lethal malignancy. Afterwards,

ampullary cancer (AC) are the second most common type, approximately accounting for 16% to 28% of PACs[2-4]. AC is the term employed for the malignant epithelial tumor arised from the ampulla of Vater and due to an improved diagnostic endoscopic and radiological methods, their incidence has increased in the last years[5]. Distinctive clinical symptoms of patients usually arise in an early stage because of the specific anatomical structure and biliary obstruction. In the earlier disease course, operative treatments for AC are available and typically pancreaticoduodenectomy (PD) will be selected[6]. Although the resection rate is much higher than other periampullary adenocarcinomas, the majority of patients eventually succumb to recurrent disease. Unfortunately, both chemotherapy and radiotherapy only have limited efficacy and so the prognosis is not satisfactory[7].

Due to the lack of large-scale prospective studies, it is difficult to accurately predict the prognosis of the AC patients treated by Whipple procedure. Although several studies have reported that few parameters such as symptoms and general state of patients, tumor size, pathological grade, lymphatic metastasis and the level of carbohydrate antigen 19-9 (CA19-9) are related to the survival rate, they are not sufficiently powerful. Therefore, a better predicted index of the survival time and the risk of recurrence of patients with postoperative ampullary carcinoma is essential[8, 9].

Growing evidence indicates that there is intimate relationship between inflammation and malignancy[10, 11]. The inflammatory reaction induced by the tumor even contributes to the cancer progression. In addition, the current understanding suggests that the systemic inflammatory response of the host could be a promising indicator for the prognosis. Actually, after Virchow firstly described the presence of leukocytes in tumor tissue in 1863, the connection between inflammation and cancer has drawn great attention in various malignancies and several inflammatory markers have been verified[12]. Recently, inflammation-based indexes, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), have been widely used as evaluation indexes for the inflammatory and immune responses in kinds of malignant tumour[13, 14]. Lv et. al reported preoperative NLR was superior to the systemic immune inflammation index (SII) in predicting prognosis in patients with glioblastoma and Kim et. al confirmed that NLR, together with Glasgow prognostic score and serum level of PIVKA, offered significant prognostic information associated with early recurrence for hepatocellular carcinoma patients with liver cirrhosis after curative resection[15, 16].

However, few reports have addressed the prognostic value of a comprehensive systemic inflammatory factors, including NLR, PLR, prognostic index (PI), modified glasgow prognostic score (mGPS) and so on, in patients with AC who received PD as a curative resection. In this study, we aimed to elucidate the prognostic impact of these parameters and compare the power of these indexes in predicting overall survival (OS) or progress-free survival (PFS) of patients with AC after PD procedure. Moreover, we innovatively combined NLR with PI and this new inflammation-based score, NLR-PI, showed a superior discriminative capacity.

# Patients And Methods

## Patients

A series of 358 patients were enrolled in this study. Patient who underwent PD as a curative resection and was confirmed histopathologically as AC after resection at the Sun Yat-sen University Cancer Center between January 2009 and December 2018, were enrolled.

To be more specific, the inclusion criteria were as following: (1) all patients with histopathological diagnosis of adenocarcinoma anatomically located in the ampulla of Vater, (2) the patient received routine analyses of blood before and after surgery and (3) the patient received PD according to standard surgical procedures. On the other hand, the exclusion criteria were as following: (1) patients who are diagnosed as carcinoid histopathologically; (2) diagnosis of second tumors and (3) lost to follow-up. This study was reviewed and approved by the Institutional Review Board (IRB) of the Sun Yat-sen University Cancer Center. All the patients participated in our study were informed detailedly and the informed written consent had been obtained from each individual. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All data were analyzed retrospectively.

## Clinical management

A conventional therapeutic treatment was performed for each patient. Based on the medical examination results, including Computed Tomography (CT) or Magnetic Resonance (MR) imaging, blood biochemistry, tumor biomarker level, Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA), once the patient were diagnosed with AC and the tumor was resectable for Whipple procedure, which was assessed by the Multi-Disciplinary Treatment (MDT), the standard PD would be performed and suitable adjuvant therapy would be followed.

## Clinical data extraction

Serological examination, radiological and clinicopathologic factors that were potentially associated with survival and recurrence were selected in this study, including age, sex, tumor markers carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), tumor diameter and location, pathological pattern, white blood cell count, platelet (PLT) count, neutrophil cell count, lymphocyte cell count, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, gamma-glutamyl transpeptidase (GGT), albumin (ALB), C-reactive protein (CRP), NLR, derived neutrophil-to-lymphocyte ratio (dNLR), PLR, PI and so on. Clinical and radiological data were retrieved at the time of diagnosis before and after operation[11, 17]. All of the inflammation-based prognostic scores determined in this study are described in Table 1.

**Table 1** Inflammation-based prognostic scores

| Scoring systems | Score |
|---|---|
| NLR | |
| Neutrophil count:lymphocyte count ≤ 3.32 | 0 |
| Neutrophil count:lymphocyte count ＞ 3.32 | 1 |
| PLR | |
| Platelet count:lymphocyte count ≤ 99.02 | 0 |
| Platelet count:lymphocyte count ＞ 99.02 | 1 |
| dNLR | |
| Neutrophil count:lymphocyte count ≤ 1.94 | 0 |
| Neutrophil count:lymphocyte count ＞ 1.94 | 1 |
| PI | |
| CRP (≤10 mg/L) and WBC (≤11 × $10^9$/L) | 0 |
| CRP (≤10 mg/L) and WBC (＞11 × $10^9$/L) | 1 |
| CRP (＞10 mg/L) and WBC (≤11 × $10^9$/L) | 1 |
| CRP (＞10 mg/L) and WBC (＞11 × $10^9$/L) | 2 |
| mGPS | |
| CRP (≤10 mg/L) and ALB (≥35 g/L) | 0 |
| CRP (≤10 mg/L) and ALB (＜35 g/L) | 0 |
| CRP (＞10 mg/L) and ALB (≥35 g/L) | 1 |
| CRP (＞10 mg/L) and ALB (＜35 g/L) | 2 |
| PNI | |
| ALB (g/L) × total lymphocyte count × $10^9$/L≥45 | 0 |
| ALB (g/L) × total lymphocyte count × $10^9$/L＜45 | 1 |

NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; dNLR, drive neutrophil-to-lymphocyte ratio; PI, prognostic index; mGPS, modified glasgow prognostic score; WBC, white blood cell counts; CRP, C-reactive protein; PNI, Prognostic Nutritional Index; ALB, albumin.

## Follow-up

After discharge from the hospital, all patients were followed up at least once every 3 months during the first years and once every 6 months thereafter. The blood routine examination and the serological examination, imageological examination were selectively performed as needed. A routine follow-up was conducted by the follow-up department of Sun Yat-Sen University Cancer Center. OS was defined as the time from diagnosis to death from any cause or censored at the date of the last follow-up. PFS was calculated from the time of diagnosis to the date of tumour progression discovered for the first time or death.

### Statistical analysis

Statistical analysis was performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Continuous data are expressed as the means and ranges, and categorical data are shown as frequencies and proportions. Student's t-test was used to compare continuous variables. The chi-squared test and Fisher's exact test were used to compare the categorical variables. Univariate and multivariate analyses were performed to assess the significance of the differences in the clinical or radiological data. The associated 95% CI was calculated. The Kaplan–Meier method was used to analyze OS. Significant differences between the groups were identified using the log-rank test. The survival curves were performed using MedCalc software version 11.4.2.0 (http://www.medcalc.be). A two tailed P-value <0.05 was considered statistically significant.

Time-dependent receiver operating characteristic (ROC) curves were performed to determine the optimal cutoff values and to assess the predictive power of these inflammation-based indexes in predicting long-term survival[18, 19]. The analyses of ROC curves and comparisons of the areas under the ROC curves (AUROCs) were performed using R software version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org) with the "survival ROC" package and the "survival ROC.C" package.

## Results

### Optimal cutoff values for the variables

The NLR score was calculated by dividing the neutrophil counts by the lymphocyte counts. The PLR score was calculated by dividing the platelet counts by the lymphocyte counts. The dNLR score was calculated by dividing the neutrophil counts by the counts of white blood cell subtracting neutrophil. The optimal cut-off values for the NLR, PLR and dNLR scores were determined using an analysis of the time-dependent ROC. The NLR, PLR and dNLR scores were associated with the strongest Youden index for the OS and PFS prediction, with cut-off values of 3.32, 1.94 and 99.02 respectively. The threshold for each clinical and radiological dataset was utilized as the cut-off value for these variables.

### Patient characteristics

The baseline characteristics of the patients are summarized in Table 2. A total of 358 patients who were diagnosed with AC and had received Whipple procedure as a curative resection were included in the final analysis. The median age was 58 years (range: 25 to 85) and there were 216 (60.3%) male patients and 142 (39.7%) female patients in the whole study cohort. Additionally, according to the TNM grading criteria, 165 patients (46.1%) were in stages I, 138 patients (38.6%) were in stages II, and 55 patients (15.4%) were in stage III. Furthermore, 159 (44.4%) patients were sorted into the lymphatic metastasis group. The median values of lymphocytes, neutrophils, platelets were $1.60\times10^9$/L (range: $0.4\times10^9$/L to $4.7\times10^9$/L), 4.4×109/L (range: $1.3\times10^9$/L to $9.6\times10^9$/L) and $305.56\times10^9$/L (range: $84\times10^9$/L to $720\times10^9$/L), respectively. Moreover, the tumor differentiation degree can be classified into high (7, 2.0%), moderate (188, 52.5%) and poor (163, 45.5%) groups and 166 (46.4%) patients underwent the followed chemotherapy.

The NLR, PLR and dNLR scores were divided into two groups: ≤ 3.32 and ＞ 3.32, ≤ 99.02 and ＞ 99.02, ≤ 1.94 and ＞ 1.94, respectively. Among the 358 patients, 132 (36.9%) patients had an elevated NLR score; 327 (91.3%) patients had an elevated PLR score; and 154 (43.0%) patients had an elevated dNLR score; 136 (38%) patients had an mGPS > 0; 277 (77.4%) patients had a PNI ≥45; and 142 (39.6%) patients were allocated to PI 1 or 2.

**Table 2** Clinical and radiological characteristics of the study cohort

| Characteristics | Parameter | N (%) |
|---|---|---|
| **Age(years)** | <60/ ≥60 | 212 (59.2)/146 (40.8) |
| **Gender** | Female / Male | 142 (39.7) /216 (60.3) |
| **WBC(×$10^9$/L)** | <10/≥10 | 329 (91.9) /29 (8.1) |
| **Neutrophil count(×$10^9$/L)** | <7/≥7 | 289 (80.7) /69(19.3) |
| **Lymphoeyte count(×$10^9$/L)** | <4/≥4 | 348 (97.2)/10 (2.8) |
| **HGB(g/L)** | <100/≥100 | 170 (47.5) /188 (52.5) |
| **PLT(×$10^9$/L)** | <300/≥300 | 191 (53.4) /167 (46.6) |
| **ALT(U/L)** | <40/≥40 | 91 (25.4)/267 (74.6) |
| **AST(U/L)** | <45/≥45 | 96 (26.8) /262 (73.2) |
| **ALB(g/L)** | <35/≥35 | 70 (19.6) /288 (80.4) |
| **TBIL(mmol/L)** | <20.5/≥20.5 | 80 (22.3) /278 (77.7) |
| **IBIL(mmol/L)** | <15/≥15 | 182 (50.8) /176 (49.2) |
| **CRP(mg/L)** | <8/≥8 | 108 (30.2) /250 (69.8) |
| **mGPS** | 0 / 1 / 2 | 222 (62.0) /87 (24.3) /49 (13.7) |
| **CA19-9(U/ml)** | <35/≥35 | 90 (25.1) /268 (74.9) |
| **CEA (μg/L)** | <5/≥5 | 261 (72.9) / 97 (27.1) |
| **TNM** | IA/IB/IIA/IIB/III | 72 (20.1) / 93 (26.0) / 34 (9.5) / 104 (29.1) / 55 (15.4) |
| **LN metastasis** | absent/present | 199 (55.6) /159 (44.4) |
| **Tumor differentiation** | high/ moderate / poor | 7 (2.0) / 188 (52.5) / 163 (45.5) |
| **NLR** | ≤3.3 /<3.32 | 226 (63.1) /132 (36.9) |
| **PLR** | ≤99.02/<99.02 | 31 (8.7) / 327 (91.3) |
| **dNLR** | ≤1.94/<1.94 | 204 (57.0)/154 (43.0) |
| **mGPS** | 0/1/2 | 222 (62.0) /87 (24.3) /49 (13.7) |
| **PNI** | 0 / 1 | 277 (77.4) /81 (22.6) |
| **PI** | 0 / 1 / 2 | 216 (60.3) / 119 (33.2) / 23 (6.4) |
| **Chemotherapy** | No / Yes | 192 (53.6) / 166 (46.4) |

HGB, hemoglobin; PLT, Platelets; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total serum bilirubin; IBIL, Indirect serum bilirubin; AFP, Alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9; TNM,Tumor-node-metastasis; CEA, carcinoembryonic antigen; LN, lymph node.Other Abbreviations as in Table1.

## OS and prognostic factors

The median OS for the entire cohort was 44.3 months and the estimated 1-, 2-, and 3-year OS rates were 83.9%, 65.8%, and 55.2%, respectively. The long-term survival rates were signifcantly higher for patients with lower values of NLR than those with higher values of NLR (P<0.05, Fig.1a). Moreover, patients with dNLR ≤ 1.94 also had better long-term survival than patients with dNLR 1.94 (P<0.05, Fig.1b). However, as for other inflammatory indexes include PLR, PI, mGPS and PNI, can't be used to distinguish the long-term survival rates of patients in both relative group (Fig.1c-f).

In the univariate survival analysis, the NLR and dNLR were signifcantly associated with OS (NLR: Hazard Ratio (HR) 1.599, 95% CI 1.104-2.317, P<0.05; dNLR: HR 1.451, 95% CI 1.002-2.101, P<0.05). Other signifcant prognostic parameters included the age, neutrophilic granulocyte, IBIL, tumor differentiation, macrovascular or microvascular invision, lymph node metastasis, TNM Stage, CEA, CA199 and lymph node metastasis stage. According to the multivariate Cox proportional hazards model, the tumor differentiation can be viewed as independent prognostic indicator of OS ( HR 1.669, 95% CI 1.126-2.476, P<0.05) (Table 3).

**Table 3** Univariate and multivariate analyses of OS

| Characteristic | Parameter | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | HR(95% CI) | *P* | HR(95% CI) | *P* |
| **Gender** | Female / Male | 0.712(0.492-1.032) | 0.073 | — | NI |
| **Age**(years) | 60/ ≥60 | 1.570(1.083-2.277) | 0.017 | 1.492(0.994-2.240) | 0.054 |
| **NE**($\times10^9$/L) | 7/≥7 | 1.764(1.171-2.657) | 0.007 | 1.080(0.620-1.883) | 0.785 |
| **LY**($\times10^9$/L) | 4/≥4 | 0.788(0.250-2.482) | 0.684 | — | NI |
| **HGB**(g/L) | 100/≥100 | 0.869(0.600-1.258) | 0.458 | — | NI |
| **PLT**($\times10^9$/L) | 300/≥300 | 1.012(0.699-1.466) | 0.948 | — | NI |
| **ALT**(U/L) | 40/≥40 | 1.424(0.894-2.270) | 0.137 | — | NI |
| **AST**(U/L) | 45/≥45 | 1.279(0.825-1.983) | 0.272 | — | NI |
| **ALP**(U/L) | 100/≥100 | 1.171(0.680-2.017) | 0.568 | — | NI |
| **GGT**(U/L) | 50/≥50 | 0.953(0.545-1.664) | 0.867 | — | NI |
| **ALB**(g/L) | 35/≥35 | 0.976(0.629-1.514) | 0.914 | — | NI |
| **TBIL**(mmol/L) | 20.5/≥20.5 | 1.088(0.701-1.688) | 0.706 | — | NI |
| **IBIL**(mmol/L) | 15/≥15 | 1.493(1.030-2.166) | 0.035 | 1.345(0.895-2.021) | 0.154 |
| **CRP**(mg/L) | 8/≥8 | 1.189(0.779-1.814) | 0.422 | — | NI |
| **Tumor differentiation** | high/ moderate / poor | 2.029(1.421-2.895) | 0.001 | 1.669(1.126-2.476) | 0.011 |
| **Tumor size** (cm) | 2/≥2 | 1.082(0.837-1.397) | 0.548 | — | NI |
| **Macrovascular Invision** | Absent/Present | 1.998(1.010-3.954) | 0.047 | 1.521(0.639-3.621) | 0.344 |
| **Microvascular Invision** | Absent/Present | 1.592(1.080-2.347) | 0.019 | 1.098(0.708-1.703) | 0.678 |

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|---|---|---|---|---|---|
| **LN metastasis** | Absent/Present | 1.545(1.066-2.240) | 0.022 | 0.640(0.276-1.487) | 0.299 |
| **TNM Stage** | IA/IB/IIA/IIB/III | 1.208(1.051-1.388) | 0.008 | 1.035(0.777-1.379) | 0.814 |
| **CEA**(μg/L) | <5/≥5 | 1.356(1.030-2.289) | 0.035 | 1.172(0.771-1.283) | 0.457 |
| **CA199**(U/mL) | <35/≥35 | 2.075(1.289-3.339) | 0.003 | 1.250(0.745-2.096) | 0.398 |
| **Chemotherapy** | Absent/Present | 0.816(0.562-1.186) | 0.286 | — | NI |
| **LNMS** | N0/N1/N2 | 1.574(1.199-2.067) | 0.001 | 1.786(0.882-3.618) | 0.107 |
| **PLNR** | ≤0.167/>0.167 | 1.367(0.870-2.150) | 0.176 | — | NI |
| **NLR** | ≤3.32/>3.32 | 1.599(1.104-2.317) | 0.013 | 0.820(0.399-1.683) | 0.588 |
| **dNLR** | ≤1.94/>1.94 | 1.451(1.002-2.101) | 0.049 | 0.894(0.478-1.673) | 0.726 |
| **PLR** | ≤99.02/>99.02 | 1.389(0.676-2.853) | 0.371 | — | NI |
| **PI** | 0 / 1 / 2 | 1.216(0.906-1.633) | 0.193 | — | NI |
| **PNI** | 0 / 1 | 1.063(0.693-1.632) | 0.778 | — | NI |
| **mGPS** | 0/1/2 | 0.996(0.784-1.264) | 0.971 | — | NI |
| **NLR-PI** | 1 / 2 / 3 | 1.570(1.192-2.068) | 0.001 | 1.684(1.015-2.796) | 0.044 |

NE, neutrophilic granulocyte; LY, lymphocyte; GGT, glutamyltranspeptidase; ALP, alkaline phosphatase; LNMS, lymph node metastasus stage; PLNR, positive lymph node ratio. Other Abbreviations as in Table 1 and Table 2 .

### PFS and prognostic factors

The estimated 1-, 2-, and 3-year PFS rates for all patients were 58.0%, 42.8%, and 37.8%, respectively. The median PFS was 16.9 months. Correlations between the inflammation-based elements and PFS are shown in Fig. 2. Elevated NLR (P<0.05, Fig. 2a), PLR (P<0.05, Fig. 2c) were associated with a reduced

PFS. Nevertheless, the dNLR, PI, mGPS and PNI failed to tell patients with longer PFS from the other with shorter PFS (Fig. 2b, 2d-f).

The univariate survival analysis for PFS revealed significant associations between an unfavorable PFS and higher pretreatment NLR (HR 1.406, 95% CI 1.051-1.879, P < 0.05) and PLR (HR 2.432, 95% CI 1.197-4.942, P < 0.05). Other significant prognostic parameters related to PFS included tumor differentiation, macrovascular invision, lymph node metastasis, TNM Stage, lymph node metastasis stage, CEA, CA199 and whether followed chemotherapy was carried. After the multivariate Cox proportional hazards analysis, we found that tumor differentiation (HR 1.593, 95% CI 1.185-2.141, P < 0.05) and whether patients received the followed chemotherapy (HR 1.427, 95% CI 1.056-1.928, P < 0.05) were independent predictors of PFS (Table 4).

**Table 4** Univariate and multivariate analyses of PFS

| Characteristic | Parameter | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | HR(95% CI) | *P* | HR(95% CI) | *P* |
| **Gender** | Female / Male | 1.042(0.776-1.399) | 0.706 | — | NI |
| **Age**(years) | <60/ ≥60 | 1.160(0.866-1.555) | 0.319 | — | NI |
| **NE**(×$10^9$/L) | <7/≥7 | 1.218(0.864-1.717) | 0.260 | — | NI |
| **LY**(×$10^9$/L) | <4/≥4 | 0.804(0.330-1.955) | 0.630 | — | NI |
| **HGB**(g/L) | <100/≥100 | 1.019(0.765-1.358) | 0.897 | — | NI |
| **PLT**(×$10^9$/L) | <300/≥300 | 1.017(0.763-1.356) | 0.907 | — | NI |
| **ALT**(U/L) | <40/≥40 | 1.395(0.973-1.999) | 0.070 | — | NI |
| **AST**(U/L) | <45/≥45 | 1.224(0.875-1.712) | 0.238 | — | NI |
| **ALP**(U/L) | <100/≥100 | 1.225(0.798-1.881) | 0.353 | — | NI |
| **GGT**(U/L) | <50/≥50 | 0.926(0.598-1.433) | 0.729 | — | NI |
| **ALB**(g/L) | <35/≥35 | 0.940(0.665-1.330) | 0.728 | — | NI |
| **TBIL**(mmol/L) | <20.5/≥20.5 | 1.118(0.790-1.582) | 0.529 | — | NI |
| **IBIL**(mmol/L) | <15/≥15 | 1.365(1.024-1.821) | 0.034 | — | NI |
| **CRP**(mg/L) | <8/≥8 | 1.291(0.925-1.801) | 0.133 | — | NI |
| **Tumor differentiation** | high/ moderate / poor | 1.704(1.296-2.240) | < 0.001 | 1.593(1.185-2.141) | 0.002 |
| **Tumor size** (cm) | <2/≥2 | 1.116(0.914-1.363) | 0.281 | — | NI |
| **Macrovascular Invision** | Absent/Present | 2.216(1.260-3.896) | 0.006 | 1.758(0.834-3.704) | 0.138 |
| **Microvascular Invision** | Absent/Present | 1.806(0.897-1.245) | 0.060 | — | NI |

| | | | | | |
|---|---|---|---|---|---|
| **LN metastasis** | Absent/Present | 1.874(1.404-2.500) | 0.001 | 0.678(0.363-1.266) | 0.223 |
| **TNM Stage** | IA/IB/IIA/IIB/III | 1.074(1.181-1.467) | 0.001 | 1.074(0.848-1.361) | 0.553 |
| **CEA**(μg/L) | 5/≥5 | 1.291(1.179-2.172) | 0.003 | 1.291(0.935-1.782) | 0.121 |
| **CA199**(U/mL) | 35/≥35 | 1.416(1.351-2.848) | 0.001 | 1.416(0.959-2.093) | 0.080 |
| **Chemotherapy** | Absent/Present | 1.527(1.145-2.036) | 0.004 | 1.427(1.056-1.928) | 0.021 |
| **LNMS** | N0/N1/N2 | 1.639(1.432-2.161) | 0.001 | 1.639(0.966-2.782) | 0.067 |
| **PLNR** | ≤0.167/0.167 | 1.178(0.807-1.717) | 0.396 | — | NI |
| **NLR** | ≤3.32 /3.32 | 1.406(1.051-1.879) | 0.022 | 1.450(0.970-1.780) | 0.078 |
| **dNLR** | ≤1.94/1.94 | 1.207(0.905-1.609) | 0.200 | — | NI |
| **PLR** | ≤99.02/99.02 | 2.432(1.197-4.942) | 0.014 | 2.040(0.994-4.185) | 0.052 |
| **PI** | 0 / 1 / 2 | 1.179(0.941-1.479) | 0.153 | — | NI |
| **PNI** | 0 / 1 | 1.021(0.726-1.436) | 0.906 | — | NI |
| **mGPS** | 0/1/2 | 1.077(0.894-1.298) | 0.436 | — | NI |
| **NLR-PI** | 1 / 2 / 3 | 1.304(1.047-1.624) | 0.018 | 1.285(1.014-1.630) | 0.038 |

Abbreviations as in Table 3.

### Prognostic value of inflammatory indexes

Moreover, the prognostic capacities of the inflammation-based elements for both OS and PFS were compared by analyzing the AUROC values. The ROC curves for OS and PFS prediction were calculated for the patients at 1, 2, and 3 years of follow-up. To be more specific, as for OS, the AUROC values of the NLR or dNLR score were consistently higher than most of the other inflammatory indexes and, in addition, NLR or dNLR score were higher for the patients at 1 year and NLR or PLR were higher for the patients at 2, and 3 years of follow-up for PFS (Fig. 3)(Table 5).

**Table 5** The comparison of the AUROC values among each inflammation-based scores

| Characteristic | OS | | | PFS | | |
|---|---|---|---|---|---|---|
| | Time | | | Time | | |
| | Year=1 | Year=2 | Year=3 | Year=1 | Year=2 | Year=3 |
| **NLR** | 0.642 | 0.659 | 0.619 | 0.664 | 0.651 | 0.656 |
| **dNLR** | 0.64 | 0.626 | 0.60 | 0.646 | 0.632 | 0.632 |
| **PLR** | 0.542 | 0.578 | 0.586 | 0.63 | 0.653 | 0.654 |
| **PNI** | 0.596 | 0.56 | 0.556 | 0.629 | 0.59 | 0.595 |
| **mGPS** | 0.578 | 0.578 | 0.528 | 0.612 | 0.623 | 0.615 |
| **PI** | 0.607 | 0.593 | 0.546 | 0.621 | 0.638 | 0.628 |
| **NLR-PI** | 0.712 | 0.704 | 0.704 | 0.724 | 0.719 | 0.72 |

Abbreviations as in Table 1.

In order to further enhance the diagnostic efficiency, a new inflammation-based score system was generated. The NLR-PI score was defined as follow: (1) NLR-PI=1: NLR=0 and PI=0; (2) NLR-PI=2: NLR=0 and PI=1, 2NLR=1 and PI=0; (3) NLR-PI=3: NLR=1 and PI=1, 2. Among the 358 patients, 217 (60.6%) patients had a low NLR-PI score (NLR-PI=1) and 141 (39.4%) patients were allocated to NLR-PI 2 or 3. As shown in table 5, the AUROC value of NLR-PI is the maximal among these indexes mentioned above under any conditions. When the NLR score was combined with PI, the NLR-PI score showed a better distinguishing power for predicting the prognosis of patients with AC who were treated with Whipple procedure compared with the other inflammation-based elements alone. In other words, with regard to both OS and PFS, the NLR-PI score divided patients into subgroups more precisely. Additionally, the concordance index (C-index) of each inflammatory parameters were calculated (Table 6) and compared with each other (Table 7), this result also verified that the NLR-PI score had a superior discriminative capacity.

**Table 6** The C-index value of each inflammation-based score

| Characteristic | | NLR | dNLR | PLR | PI | PNI | mGPS | NLR-PI |
|---|---|---|---|---|---|---|---|---|
| c-index Value (95% CI) | OS | 0.674 (0.624-0.724) | 0.663 (0.613-0.713) | 0.614 (0.589-0.639) | 0.632 (0.577-0.687) | 0.619 (0.572-0.666) | 0.59 (0.539-0.641) | 0.7 (0.647-0.753) |
| | PFS | 0.651 (0.613-0.689) | 0.603 (0.573-0.634) | 0.627 (0.608-0.646) | 0.634 (0.594-0.674) | 0.609 (0.576-0.642) | 0.627 (0.587-0.667) | 0.657 (0.617-0.697) |

Abbreviations as in Table 1.

**Table 7** The pairwise comparison of C-indexes of each inflammation-based C-index valuescores for OS and PFS prediction

| Characteristic | | | NLR | dNLR | PLR | PI | mGPS | PNI | NLR-PI |
|---|---|---|---|---|---|---|---|---|---|
| *P* value | OS | NLR | — | 0.3357 | 0.0138 | 0.0857 | 0.0013 | 0.0197 | 0.1976 |
| | | dNLR | 0.3357 | — | 0.0368 | 0.1643 | 0.0053 | 0.0611 | 0.0902 |
| | | PLR | 0.0138 | 0.0368 | — | 0.2635 | 0.1817 | 0.4145 | 0.0011 |
| | | PI | 0.0857 | 0.1643 | 0.2635 | — | 0.0659 | 0.3406 | 0.0104 |
| | | mGPS | 0.0013 | 0.0053 | 0.1817 | 0.0659 | — | 0.1511 | 0.0001 |
| | | PNI | 0.0197 | 0.0611 | 0.4145 | 0.3406 | 0.1511 | — | 0.0018 |
| | | NLR-PI | 0.1976 | 0.0902 | 0.0011 | 0.0104 | 0.0001 | 0.0018 | — |
| | PFS | NLR | — | 0.3357 | 0.0101 | 0.0857 | 0.0150 | 0.0197 | 0.1976 |
| | | dNLR | 0.3357 | — | 0.0303 | 0.1643 | 0.0335 | 0.0611 | 0.0902 |
| | | PLR | 0.0101 | 0.0303 | — | 0.2573 | 0.4440 | 0.4145 | 0.0006 |
| | | PI | 0.0857 | 0.1643 | 0.2573 | — | 0.2195 | 0.3406 | 0.0092 |
| | | mGPS | 0.0150 | 0.0335 | 0.4440 | 0.2195 | — | 0.3799 | 0.0009 |
| | | PNI | 0.0197 | 0.0611 | 0.4145 | 0.3406 | 0.3799 | — | 0.0018 |
| | | NLR-PI | 0.1976 | 0.0902 | 0.0006 | 0.0092 | 0.0009 | 0.0018 | — |

Abbreviations as in Table 1.

Furthermore, patients with low NLR-PI also had better long-term survival or PFS than patients belonging to higer NLR-PI score groups (P<0.05, Fig. 4). In the univariate survival analysis, NLR-PI score were also signifcantly associated with OS or PFS (OS: HR 1.570, 95% CI 1.192-2.068, P < 0.05; PFS:HR 1.304, 95% CI 1.047-1.624, P < 0.05). As for multivariate Cox proportional hazards analysis, NLR-PI score also can be viewed as independent predictors of both OS and PFS (OS: HR 1.684, 95% CI 1.015-2.2.796, P < 0.05; PFS: HR 1.285, 95% CI 1.014-1.630, P < 0.05) (Table 3 and 4).

# Discussion

In this study, we demonstrated that the prognostic significance of several preoperative inflammatory parameters, include NLR, dNLR, PLR, mGPS, PI and PNI, for predicting the prognosis in a cohort of 358 patients who suffered from AC and had received Whipple procedure as a curative resection. Significantly, NLR score was found to be an effective prognostic factor for both OS and PFS after surgical treatment. Beside, our study also showed that there was an correlation between dNLR and OS while PLR can prognosticate the PFS of whole patients. More innovative, when we combined NLR and PI, we have investigated a new inflammation-based score, NLR-PI, as a powerful prognostic factor which has superior discriminative capacity for predicting OS or PFS compared with other indicators. The cohort was divided into three groups according to the NLR-PI score and patients in higher NLR-PI score group were associated with poor prognosis.

It has been well proved that the inflammatory state of patients quantified and characterized by various inflammation factors is strongly associated with specific tumorigenesis and development[20]. Cancer-related inflammatory responses have extensive effects on the malignant biological properties of tumor tissue, include cellular proliferation and survival, angiogenesis, migration, invasion and metastasis and so on[21, 22]. More precisely, besides kinds of inflammatory factors are expected to be promising indicators for the early diagnosis of neoplasia which plays a key role in improving prognosis of patients, malignant cells have a tight cross-talk with tumor immune microenviroment regulated by relevant cytokines and signal transduction[23]. For example, inflammatory substance lipopolysaccharide (LPS) which activates toll-like receptors (TLRs) increased the invasive behavior and anti-apoptotic effects of cancer through the activation of the transcription factor nuclear factor κB (NF-κB) signaling pathway. Although the occurrence mechanisms of unique systemic inflammation in cancer patients remains disputed, necrosis and local tissue damage together with the production of inflammatory mediators released by the cancer itself or leukocytes maybe one of the prime reasons[24].

On the basis that systemic inflammation is responsible for cancer generate, invasion, metastasis and even the resistance to chemotherapy or radiotherapy, growing evidences have shown that the measurement of part of inflammatory markers have prognostic significance in cancer patients. Severe systemic inflammatory response is usually associated with poor prognosis in multiple types of carcinomas. And it is worth noting that kinds of inflammation-based assessment tools which is based on inflammatory indexes, such as GPS, NLR, PLR, PNI and so on, have been developed and put into use in

some institutions. With the emergence of immunotherapy, the immune system status of patients and the role of innate immunity-mediated inflammation in cancer biology have drawn great attention[25].

As a marker of systemic inflammation, several retrospective studies have been confirmed that NLR is a reliable predictor of postoperative prognosis for patients with multiple types of tumors. Various systemic inflammation-based scoring system, in which a certain preoperative NLR score act as an independent prognostic factor, are supposed to be used for speculating the OS or PFS of patients after curative resection. For instence, Han et al proved that pre-treatment NLR was a prognostic index for patients with glioblastoma (GBM) and Weng et al showed that NLR level was associated with the different grades of gliomas[20]. Wang et al suggested that the albumin-NLR was a superior independent prognostic factor of the OS for colorectal cancer patients who received radical resection in the multivariate survival analysis[26]. Moreover, these results also be verified in patients who suffering from hepatocellular carcinoma. Elegant theories which reveal the reason accounting for why elevated NLR is associated with poor prognosis remain unclear. However, several underlying mechanisms have been recognized. That elevated NLR was significantly related to high neutrophils infiltration and low cytolytic activities of lymphocytes. Elevated neutrophils will produce more pro-angiogenic factors, including vascular endothelial growth factors (VEGFs) and matrix metalloproteinases, to stimulate tumor development and progression through enhancing vascularization. On the other hand, adaptive immune cells, such as B-lymphocytes, T-lymphocytes, CD8+ cytotoxic and CD4+ helper T-lymphocytes take pivotal effects on the suppression of oncogenesis[27]. So that the decreased lymphocyte count which represented an insufficient immunologic reaction to the malignant tumor consequently enables tumor progression and metastasis[24, 28]. Consistent with others research results and the immune dysregulation state represented by morbid NLR score, in this study, we also discovered that higher NLR score predicted a shorter OS and PFS which means a worse clinical outcome in patients with AC after pancreaticoduodenectomy.

Postoperative PLR also has been extensively researched as evaluation tools for the inflammatory and immune responses and is reportedly a novel prognostic factor in various malignancie. At present, many studies focusing on the prognostic role of PLR were contradictive. Lim et al showed that a higher PLR was an independent predictor of shorter survival of stage IV non-small cell lung cancer (NsCLC) patients with cytologically proven malignant pleural efusion (MPE)[29]. However, different result was detected in Peng et al and Kabir et al study, which revealed PLR was not evidently associated with the OS or recurrence-free survival (RFS) of patients with Hepatocellular carcinomas (HCC)[30, 31]. In our study, although no signifcant difference between the PLR and OS was found in patients who received Whipple procedure as a curative resection for periampullary carcinoma, PLR is a strong and independent prognostic factor for PFS. And, specifically, an elevated PLR was associated with a shorter PFS. Theoretically, platelets can also release various growth factors, including VEGF and platelet derived growth factor (PDGF), to the tumor microenvironment and promote tumor growth, migration and the evasion of immune detection[11, 32]. PI was proposed by G. Kasymjanova et al and proved as a reliable index for evaluating the prognosis of multiple kinds of tumors by others[25]. It was defined by the inflammatory markers C-reactive protein (CRP) and white blood cells (WBCs) of patients. In our study, we

hypothesize that the combination of certain inflammation scores might improve their prognostic power. Surprisingly, when we established the NLR-PI index as mentioned above, our results demonstrated the combined score consistently exhibited a higher AUROC value at 1, 2 and 3 years OS and PFS compared to the NLR or PI alone and the Kaplan-Meier survival curves showed that the combined score divides patients into subgroups more accurately. The NLR-PI index is based on the level of neutrophile granulocyte, lymphocyte and CRP, which can be easily obtained. Among these indexes, CRP, which is synthesized that released by macrophages, is one of the most useful markers for systemic inflammation of the host and is tightly related to tumor progression[33, 34]. So we believe that the combining inflammation factor may contribute to a robust prognostic model for patients who were diagnosed as AC and underwent PD as a curative resection.

This study has several limitations. Firstly, this report had a retrospective study design, which may induce some selection bias and relied on a single institutional dataset. Secondly, some patients were administered routine adjuvant chemotherapy, but since the chemotherapy data were incomplete, thorough analysis of the relationship between treatment agents and inflammation factors is not available. Thirdly, there are still two subtypes of ACs: pancreaticobiliary and intestinal subtypes. Part of patients, especially, who underwent the surgery in the earlier years, cannot be specifically classified according to the pathology, so all patients were brought into our study as a whole cohort and analyzed. Finally, there might be other reasonable cutoff values for variables from other studies and NLR-PI is a novel inflammation score, therefore, a large-scale prospective validation study is needed to confirm these results and validate this factor's prognostic value and further applications.

# Conclusion

In conclusion, the predictive powers of several preoperative inflammation-based prognostic scores were assessed and compared in patients with AC who received PD as a curative resection. Among these indexes, NLR was found can predict both OS and PFS of patients while dNLR or PLR was only related to one of them. More significantly, we proposed a novel factor, NLR-PI, which was a more effective and independent predictive factor for the poor outcome of patients. Further prospective studies should be conducted to confirm these results and to provide evidences for individualized treatment.

# Abbreviations

AC: ampullary cancers; PD: pancreaticoduodenectomy; ROC: receiver operating characteristic; AUROCs: area under the time-dependent receiver operating characteristic curves; WBC: White blood cell count; HGB: hemoglobin; PLT: Platelets; NE: neutrophilic granulocyte; LY: lymphocyte; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: glutamyltranspeptidase; ALP: alkaline phosphatase; ALB: Albumin; TBIL: Total serum bilirubin; IBIL: Indirect serum bilirubin; CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; NLR: Neutrophil-lymphocyte ratio; dNLR: drive neutrophil-to-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; mGPS : modified Glasgow Prognostic Score; PNI: Prognostic Nutritional Index; PI: prognostic index; TNM: Tumor-node-metastasis; LN: lymph

node; LNMS: lymph node metastasus stage; PLNR: positive lymph node ratio; OS: overall survival; PFS: progression-free survival; RFS: recurrence-free survival; HCC: Hepatocellular carcinomas; SII: systemic immune inflammation index; CT: Computed Tomography; MR: Magnetic Resonance; EUS-FNA: Endoscopic ultrasonography-guided fine needle aspiration; HR:Hazard Ratio; LPS: lipopolysaccharide; TLRs: toll-like receptors; GBM: glioblastoma; VEGFs: vascular endothelial growth factors; PDGF: platelet derived growth factor; MPE:malignant pleural efusion; NsCLC: non-small cell lung cancer.

# Declarations


### Acknowledgments

We acknowledge the Medical Records Department of Sun Yat-sen University Cancer Center for collecting the survival data of patients. We thank the patients who were brought into this study.

### Funding

This work was supported by grants from the National Natural Science Foundation of China (No.81972299, No.81672390) and the National Key Research and Development Plan of China (No.2017YFC0910002). The funding bodies did not have any influence on the design of the study, collection, analysis, interpretation of data or in writing the manuscript.


### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

Shuxin Sun and Chaobin He performed the statistical analysis and drafted the manuscript. Shuxin Sun and Chaobin He contributed to this work equally. Shengping Li was responsible for conception, design and quality control of this study. Jun Wang and Xin Huang collected the clinical data. Jiali Wu revised the manuscript critically. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All procedures performed in the present study involving human participants were in accordance with the ethical standards of institutional and/or national research committees and the 1964 Helsinki Declaration and its later amendments or similar ethical standards. Written informed consent was obtained from all individual participants included in the study.

### Consent for publication

Not applicable

### Competing interests

The authors do not have any competing interests in the manuscript.

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# Figures

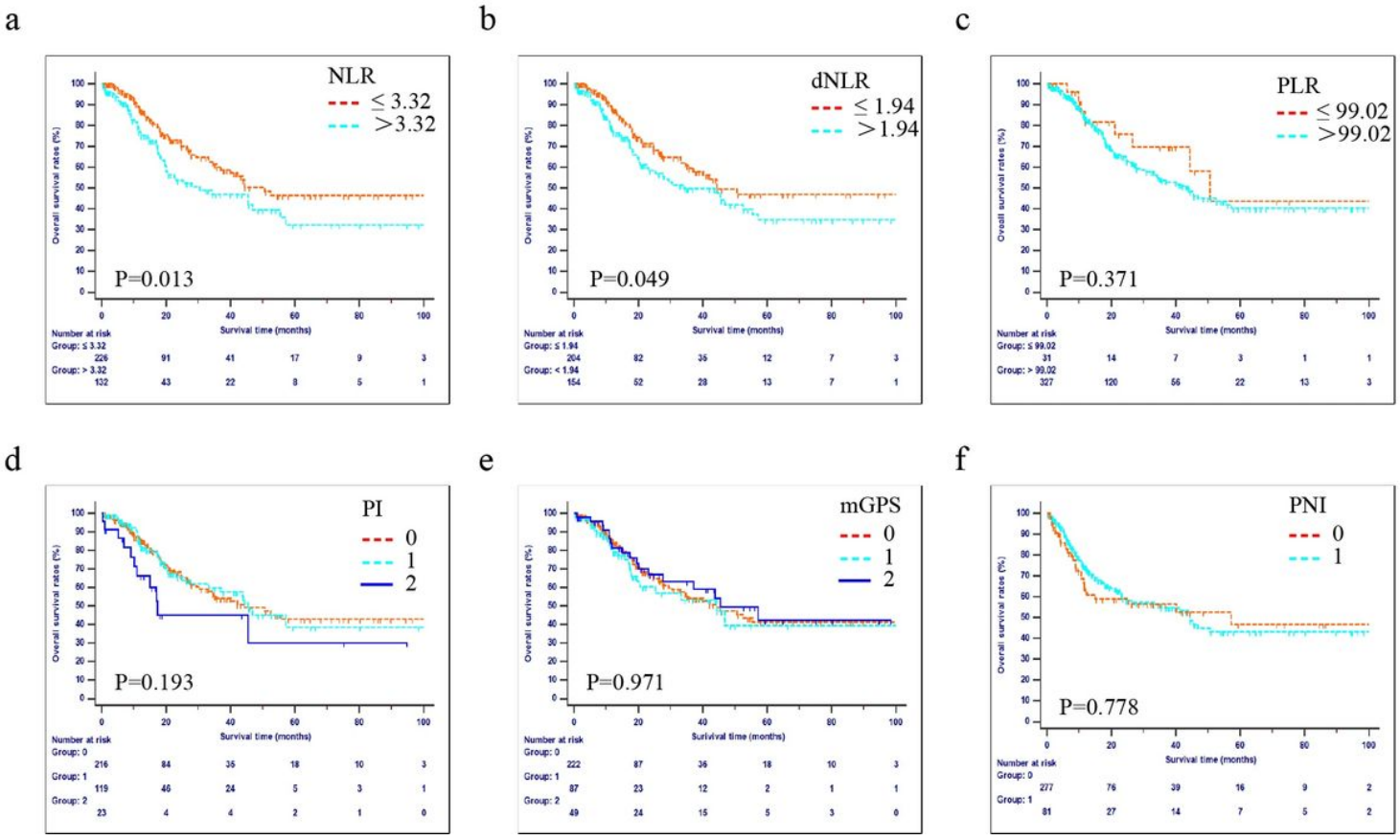
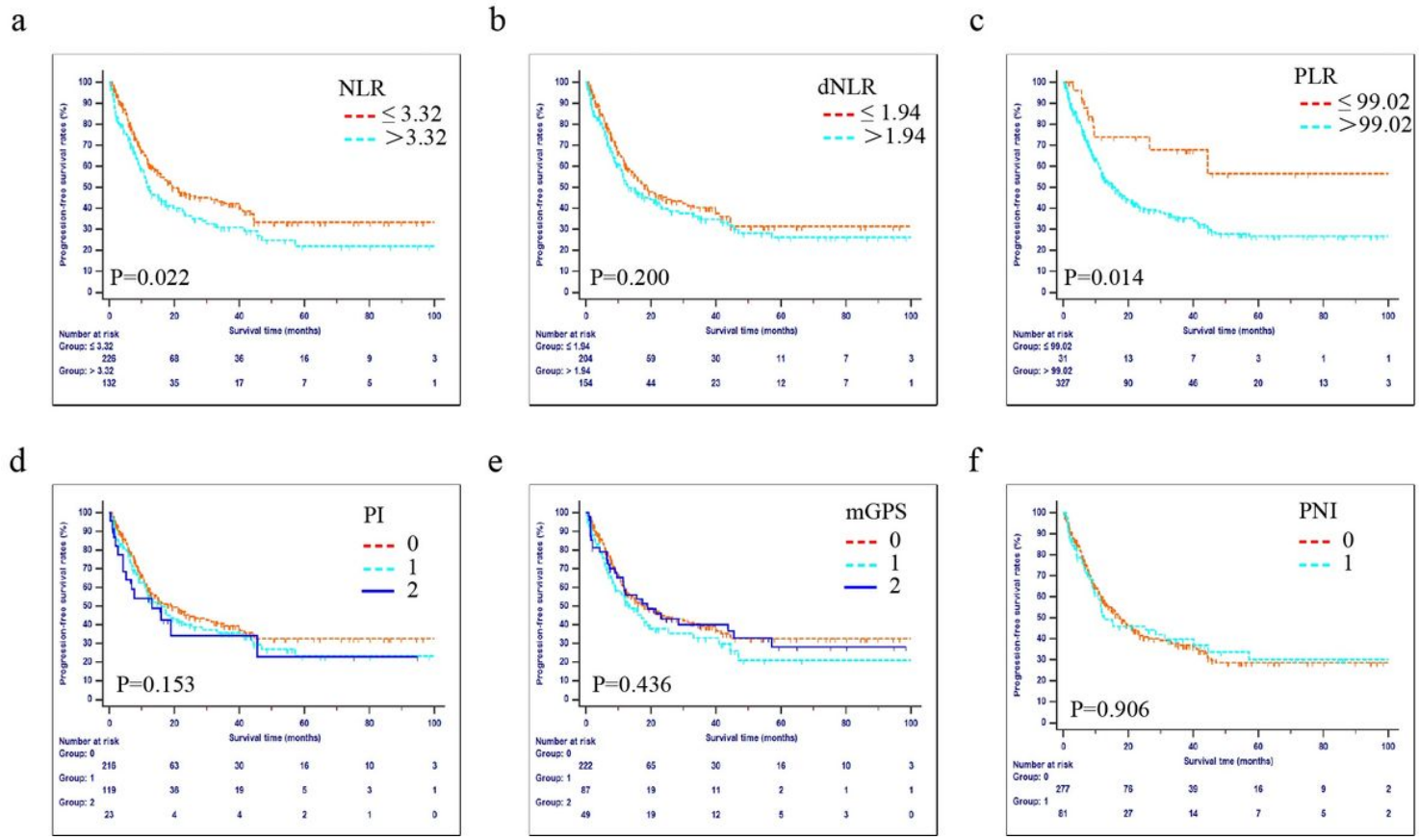


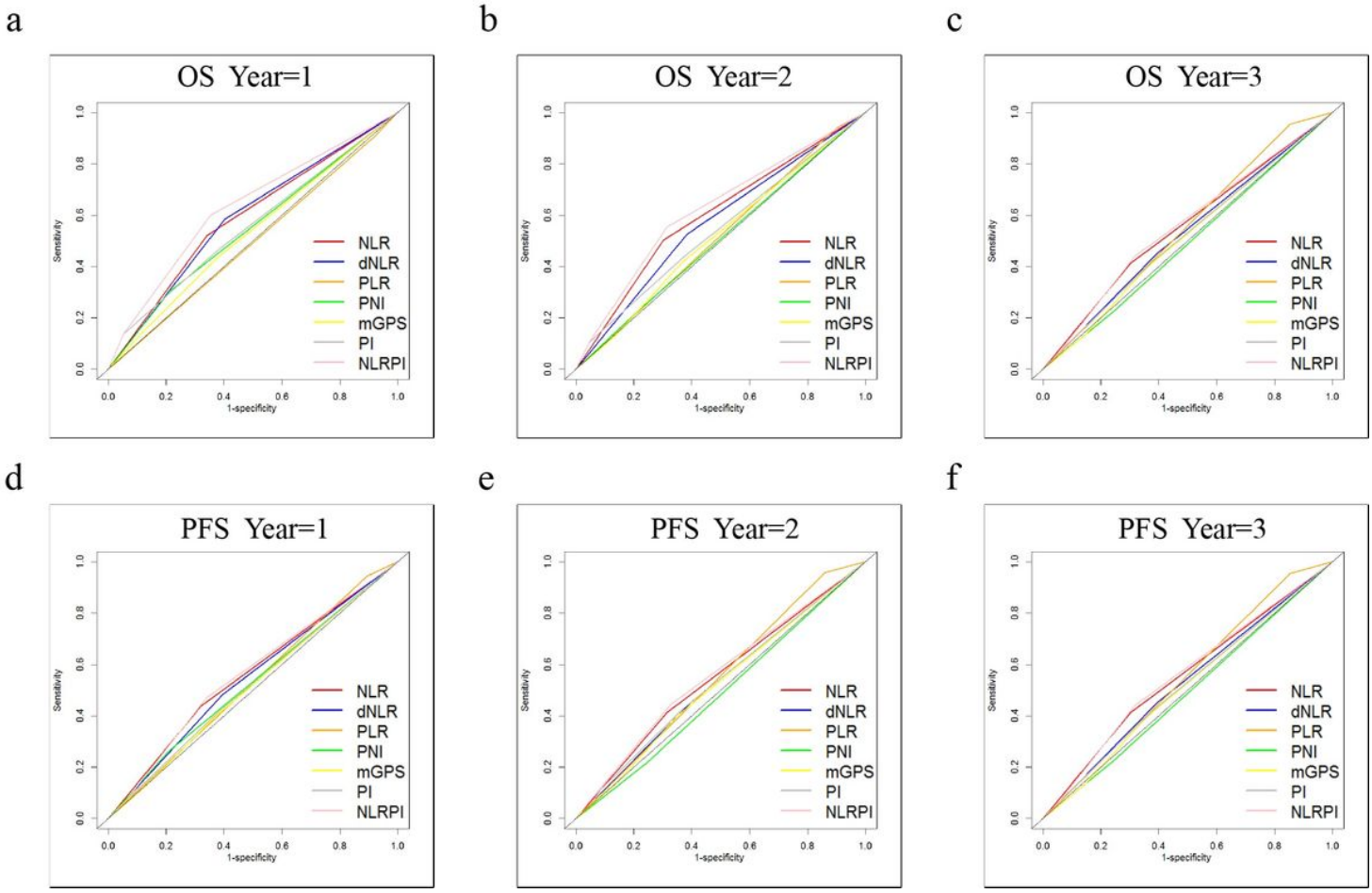

**Figure 1**

Kaplan-Meier curves of the OS in patients who were diagnosed with AC after PD. Patients were stratifed according to each inflammation-based index. (a) NLR, (b) dNLR, (c) PLR, (d) PI, (e) mGPS and (f) PNI.




## Figure 2

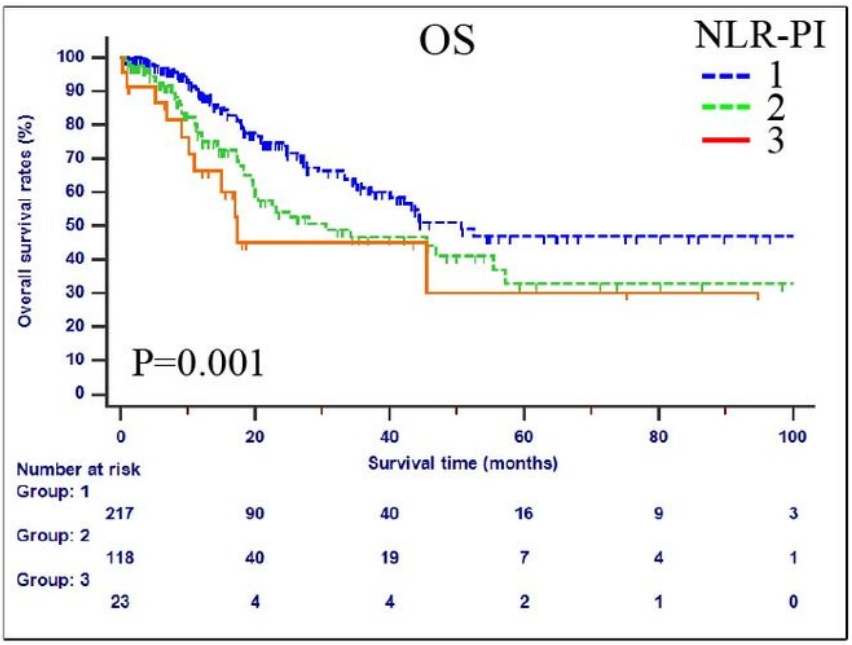
Kaplan-Meier curves of the PFS in patients who were diagnosed with AC after PD. Patients were stratifed according to each inflammation-based index. (a) NLR, (b) dNLR, (c) PLR, (d) PI, (e) mGPS and (f) PNI.




## Figure 3

AUROC for OS and PFS stratifed by each inflammation-based index at 1-year, 2-year and 3-year. (a) OS at 1-year, (b) OS at 2-year, (c) OS at 3-year, (d) PFS at 1-year, (e) PFS at 2-year and (f) PFS at 3-year.

a




b

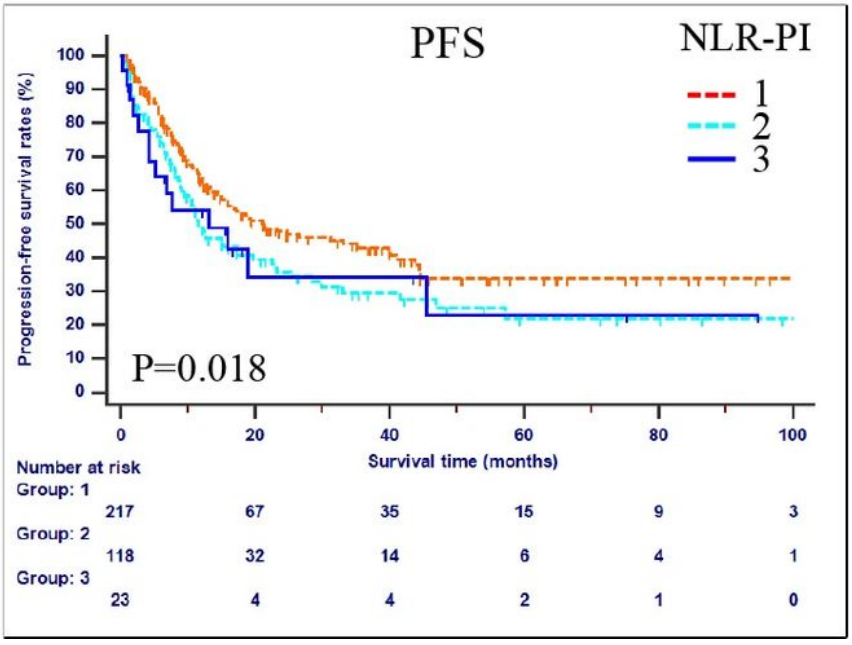



**Figure 4**

Kaplan-Meier curves of the OS and PFS according to NLR-PI score. (a) OS, (b) PFS.