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Impact of Preoperative Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios on Long-Term Survival in Patients with Operable Pancreatic Ductal Adenocarcinoma

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Highlights of the Study

- The overall survival and disease-free survival of patients with pancreatic ductal carcinoma are determined not only by tumor-related factors but also by the systemic inflammatory response.
- The preoperative neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were correlated with better pathological features, but they do not influence overall and disease-free survival.

Keywords
Neutrophil-to-lymphocyte ratio · Platelet-to-lymphocyte ratio · Pancreatic ductal adenocarcinoma

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) has an extremely poor prognosis. The outcomes of patients with cancer are determined not only by tumor-related factors but also by systemic inflammatory response. The objective of the study was to identify whether the preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with the prognosis of PDAC of the pancreas head after curative pancreatoduodenectomy. ***Materials and Methods:*** Seventy-six patients were enrolled in this prospective, observational clinical study. The optimal NLR and PLR cut-off values were calculated using a receiver operating characteristic (ROC) curve analysis. ROC curve analysis revealed an optimal NLR and PLR cut-off point of 5.41 and 205.56, respectively. Consequently, the NLR and PRL scores were classified as NLR <5.41 or ≥5.41 and PLR <205.56 or ≥205.56. The clinical outcomes of overall survival (OS) and disease-free survival (DFS) were calculated by Kaplan-Meier survival curves. Univariate and multivariate analyses were performed to analyze the prognostic value of NLR and PLR. ***Results:*** Low preoperative NLR and PLR levels both correlated with better pathological features, including decreased depth of invasion ($p < 0.001$), less lymph node metastasis ($p < 0.001$), earlier stage ($p < 0.001$), and lymphovascular invasion ($p = 0.004$). Kaplan-Meier plots illustrated that higher preoperative NLR and PLR had does not influence OS and DFS. Univariate analysis revealed that depth of invasion, lymph node metastasis, stage, PLR, and NLR are risk factors affecting OS and DFS. Multivariate analysis revealed that

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only stage was independently associated with OS and DFS. ***Conclusions:*** NLR and PLR measurements cannot provide important prognostic results in patients with resectable PDAC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a tumor with a generally poor prognosis, with the 5-year overall survival (OS) rate less than 6% [1]. This is because more than 80% of these patients are diagnosed late when the disease is already advanced and unresectable. Only 10–20% of cases are diagnosed as resectable or borderline tumors. In these patients, curative resection followed by adjuvant chemotherapy is well-accepted as standard treatment. Despite this, the 5-year OS rate for patients after radical surgery is only around 25%, with 34.3% in patients with localized disease and 11.5% in patients with disease that has spread to regional lymph nodes [2].

Therefore, the overall prognosis associated with pancreatic cancer has not improved over the last 20 years, despite the emergence of new diagnostic and therapeutic strategies. Investigations on predictive factors in pancreatic cancer are needed because these factors should have predictive value in relation to survival. In addition to some well-known prognostic factors such as tumor stage, surgical margins, lymphovascular invasion, perineural invasion, performance status, treatment effect, and CA19-9, recently new prognostic indicators with impact on survival of patients with pancreatic cancer have been reported.

The prognostic value of the systemic inflammatory response has been shown [3, 4]. Neutrophil count, monocyte count, platelet count, lymphocyte count, mean platelet volume, and the ratios of various hematologic cells (neutrophils, monocytes, platelets, and lymphocytes) have been shown to be valuable prognostic factor in various malignancies, such as renal, gynecological, and colorectal cancers [5–7].

The index neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) combines two cells (inflammatory and immune) and reflect the complex interplay between inflammatory and immune cells in the tumor microenvironment. Recently, some studies investigated the possibilities of using NLR and PLR as a prognostic biomarker of pancreatic cancer, but with controversial results [8–10]. Thus, the objective of this study was to ascertain whether the preoperative NLR and PLR are associated with the prognosis of PDAC of the pancreas head after curative pancreatoduodenectomy.

Patients and Methods

Patients and Selection Criteria

From December 2014 to April 2018, 84 patients (47 men, 37 women: mean age 69.2 years) were enrolled consecutively in this prospective observational clinical study. All patients had histologically confirmed adenocarcinoma of the head of the pancreas and had undergone potentially curative open pancreatoduodenectomy, with neither gross nor microscopic evidence of residual disease.

We defined as positive a margin containing at least one cancer cell within 1 mm of any 1 of 7 resection margins on microscopic examination (transection, posterior, medial [superior mesenteric vein], anterior capsula, distal duodenal, proximal duodenal [or gastric], and bile duct) [11].

Patients with neoplasm other than adenocarcinoma, with invasion of portal or superior mesenteric vessels, with a known immune dysfunction (advanced liver disease, human immunodeficiency virus infection, and hepatitis C virus infection) and cardiac or pulmonary insufficiency were excluded from the study. Patients were also excluded if they had evidence of intraperitoneal sepsis or peritoneal contamination if they received antibiotics within 2 weeks before surgery and death within the 3 months after surgery. During hospitalization, patients were not given antispastic drugs, steroids, nonsteroidal anti-inflammatory drugs. The patients were classified as Grade I or II according to the American Society of Anesthesiologists (ASA) grading system. None of the patients underwent neoadjuvant chemotherapy. Moreover, in this study, we included only patients with at least 3-year follow-up data available (April 2018-April 2021). Nutritional status was assessed by means of Nutrition Risk Screening 2002 (NRS) or Kondrup score based on age, recent weight loss, BMI, severity of disease, and planned surgical intervention [12]. The study protocol was approved by the Ethical Committee of Faculty of Medicine of the University of L'Aquila. Informed consent was obtained from all subjects.

Data Collection

The database, used to collect information, included the following details: gender, age at the time of surgery, tumor size, depth invasion, lymph node status, TNM stage, tumor differentiation, lymphovascular invasion, perineural invasion, gastrointestinal carcino antigen (GICA), chemotherapy, and two inflammation scores, including NLR and PLR.

Definition of Inflammation Scores

Venous blood samples were collected from all subjects on the day before the operation and processed in a blood analyzer (Sysmex; TOA Medical Electronics, Kobe, Japan) for the determination of the complete blood cell counts and differential counts of leukocytes. We recorded counts of neutrophils, platelets, and lymphocytes and calculated the NLR and PLR by dividing the absolute neutrophil and platelet count by the absolute lymphocyte count. The optimal NLR and PLR cut-off values were calculated using a receiver operating characteristic (ROC) curve analysis. The Youden Index (sensitivity + specificity − 1) was used to select a

Table 1. The relationship between preoperative NLR-PLR (low and high) and demographic-pathological-hematologic findings

Parameters (*N* = 76)	NLR				PLR			
	low (*N* = 35)	high (*N* = 41)	χ^2	*p* value	low (*N* = 37)	high (*N* = 39)	χ^2	*p* value
Gender								
Men (*n* = 42)	19	23	0.059	0.808	22	20	2.370	0.124
Women (*n* = 34)	16	18			15	19		
Age								
<65 years (*n* = 43)	22	21	0.906	0.341	20	23	0.868	0.364
≥65 years (*n* = 33)	13	20			19	14		
Tumor size								
<5 cm (*n* = 48)	22	26	2.192	0.138	23	25	1.326	0.250
≥5 cm (*n* = 28)	13	15			14	14		
Depth invasion								
T1, T2 (*n* = 15)	10	5	33.475	<0.001	11	4	33.475	<0.001
T3 (*n* = 61)	25	36			26	35		
Lymph node metastasis								
– (*n* = 10)	8	2	25.49	<0.001	9	1	25.49	<0.001
+ (*n* = 66)	27	39						
Stage								
I (*n* = 10)	8	2	26.454	<0.001	8	3	26.454	<0.001
II (*n* = 66)	28	38			19	46		
Degree of differentiation								
High (*n* = 15)	7	8	0.263	<0.608	7	8	0.263	<0.608
Moderate/poor (*n* = 61)	28	33			31	30		
Lymphovascular invasion								
– (*n* = 45)	25	20	23.18	0.004	16	19	23.92	0.004
+ (*n* = 31)	10	21			11	20		
Perineural invasion								
– (*n* = 52)	24	28	1.820	0.215	23	29	1.106	0.318
+ (*n* = 24)	24	28			14	10		
GICA								
≤37 IU/mL (*n* = 48)	23	25	0.898	0.344	22	26	0.786	0.412
>37 IU/mL (*n* = 28)	12	16			15	13		
Chemotherapy								
No (*n* = 15)	5	10	0.364	0.728	8	7	0.410	0.615
Yes (*n* = 61)	30	31			29	32		

threshold to estimate sensitivity and specificity. The results of the ROC curve analysis revealed an optimal NLR and PLR cut-off point of 5.41 and 205.56, respectively. Consequently, the NLR and PRL scores were classified as NLR <5.41 or NLR ≥5.41 and PLR <205.56 or PLR ≥205.56 for all subsequent analyses.

Anesthesia and Operative Technique

Prophylactic antibiotic (Cefotaxime 2 g i.v.) was administered 1 h before surgery, followed postoperatively by two more doses. Prophylactic subcutaneous heparin was given daily until discharge from hospital. Pre-anesthesia was accomplished using atropine (0.01 mg/kg) plus promethazine (0.5 mg/kg), induction using sodium thiopental (5 mg/kg) and atracurium (0.5 mg/kg), and tracheal intubation and assisted ventilation using nitrogen dioxide (NO_2)/oxygen (O) in the ratio 2:1. After intubation anesthesia was maintained with oxygen in air, sevoflurane, and remifentanil (0.25 mg/kg/min).

The abdomen was opened through a bilateral subcostal incision, and spread of disease was excluded by careful exploration. None of the patients were found to have metastases in the liver, peritoneum, or retroperitoneum or invasion of the aorta or portal or superior mesenteric vessels. The pancreatic head, the duodenum, the gallbladder, the common bile duct, and the distal third of stomach were excised en bloc together with all retroperitoneal fat tissue extending to the left of the superior mesenteric artery. Twenty-nine patients (38.1%) had a pylorus-preserving resection. The jejunum was brought behind the superior mesenteric vessels, and the reconstruction consisted of an end-to-end pancreatojejunostomy, an end-to-side hepaticojejunostomy, and a retrocolic end-to-side gastrojejunostomy with a short afferent loop. A T-tube extending through the hepaticojejunostomy was inserted for decompression of the anastomoses, and a peritoneal drain was placed behind the hepato-duodenal ligament.

Follow-Up

All patients included in the study were followed up, as inpatients and outpatients, every 3 months for the first 3 years, every 6 months for the next 2 years, and once annually thereafter until death. Follow-up assessment included physical examination, laboratory tests, multislice computed tomography, and some other examination as it fits. The last follow-up date was April 30, 2018. Patients who died within 3 months of surgery (3 of 84 underwent pancreatoduodenectomy) were excluded from analyses. The overall follow-up rate was 93.8% (76/81). The prognostic analyses were performed to estimate disease-free survival (DFS) and OS. DFS was defined as the date of surgery to the date of identification of disease recurrence, either radiological and/or histological. OS was calculated from the date of surgery to the date of the death from pancreatic cancer. Patients who died of causes unrelated to the disease were excluded.

Statistical Analysis

The optimal cut-off values of NLR and PLR were determined by ROC curve analysis. The correlation between NLR and PLR levels and demographic-pathological features was analyzed by the χ^2 test. Cumulative event rates were calculated using the method of Kaplan and Meier, pairwise differences between survival and recurrence functions were evaluated using the log-rank test. Cox regression methodology was used for univariate analysis. Parameters with statistical significance in univariate analysis were further analyzed in multivariate Cox proportional hazard regression model. All tests were two-sided, and p values <0.05 were considered statistically significant. Data were analyzed using SPSS-software release 25 (SPSS, and IBM company, Armonk, NY, US), and R-software, version 3.6.3 (Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org).

Results

Demographic and Pathologic-Hematologic Characteristics of Patients

The demographic and pathologic-hematologic characteristics of the 76 enrolled patients are shown in Table 1. Forty-two patients (55.2%) were men, and the median patient age was 69.1 years (range 44–81). All patients had adenocarcinoma, largely well-differentiated tumors in 15 cases (19.7%). Only 15 patients (19.7%) had T1 or T2 lesions and 10 patients (13.1%) were lymph node-negative. The postoperative stages were I and II in 10 (13.1%) and 66 (86.8%) patients, respectively. All patients underwent surgical resection, 31 (40.7%) had lymphovascular invasion, and 24 (31.5%) had perineural invasion. The median number of harvested lymph nodes after surgical resection was 24 (range 16–55). A normal level of preoperative serum GICA was observed in 48 (63.1%) patients. 61 patients (80.2%) received 5-fluorouracil-based postoperative adjuvant chemotherapy or chemoradiation.

Correlations between NLR and PLR and Demographic, Pathologic-Hematologic Parameters

The median value of neutrophils was 4.88×10^6/μL (range 3.24–8.10), platelets were 386×10^6/μL (range 142-610), and lymphocytes was 1.64×10^6/μL (range 0.68–2.84). Patients were separated into two groups according to median preoperative NLR or PLR values (NLR low: <5.41 or NLR high: ≥5.41 and PLR low: <205.56 or PLR high: ≥205.56, respectively). There were 35 (46.0%) and 37 (48.6%) patients in the low NLR and PLR group, respectively. Moreover, there were 41 (53.9%) and 39 (51.3%) patients in the high NLR and PLR group, respectively (Table 1). Low pre-operative NLR and PLR levels were both correlated with better pathological features, including decreased depth of invasion ($p < 0.001$), less lymph node metastasis ($p < 0.001$), earlier stage ($p < 0.001$), and lymphovascular invasion ($p = 0.004$) (Table 1).

OS, DFS, and Evaluation of the Prognostic Significance of NLR and PLR

Median OS for all patients was 47 months (range 35–60 months) with median DFS of 27 months (range 16–38 months) (Fig. 1a, b). The influence of preoperative NLR and PLR status on OS and DFS are shown in Figure 1c–f. In the patients with NLR <5.41 versus those with NLR ≥5.41, no significant differences were found between OS rate ($p = 0.451$) and DFS rate ($p = 0.729$) (Fig. 1c, d). Also, no significant differences were found between OS rate ($p = 0.395$) and DFS rate ($p = 0.780$) in patients with PLR <205.56 versus those PLR ≥205.56 (Fig. 1e, f).

Univariate and multivariate analyses were performed to identify the risk factors related to OS (Table 2) and DFS (Table 3). Univariate analysis revealed that depth of invasion, lymph node metastasis, stage, PLR, and NLR are risk factors affecting OS (Table 2). A low PLR was associated with prolonged OS (OR 2.34; 95% CI: 1.18–3.64; $p = 0.004$). Also, a low NLR was associated with prolonged OS (OR 2.86; 95% CI: 1.64–4.84; $p = 0.004$) (Table 2). Moreover, univariate analysis indicated that depth of invasion, lymph node metastasis, lymphovascular invasion, stage, PLR, and NLR all had a statistically significant association with DFS. A low PLR was associated with prolonged DFS (OR 2.36; 95% CI: 1.36–3.98; $p = 0.003$). Also, a low NLR was associated with prolonged DFS (OR 2.62; 95% CI: 1.78–4.92; $p = 0.003$) (Table 3). In the multivariate analysis, we found that only stage, after adjustment for other variables, was independently associated with OS (OR 2.12; 95% CI: 1.22–3.68; $p < 0.001$) (Table 2), and DFS (OR 2.44; 95% CI: 1.36–4.01; $p < 0.001$) (Table 3).

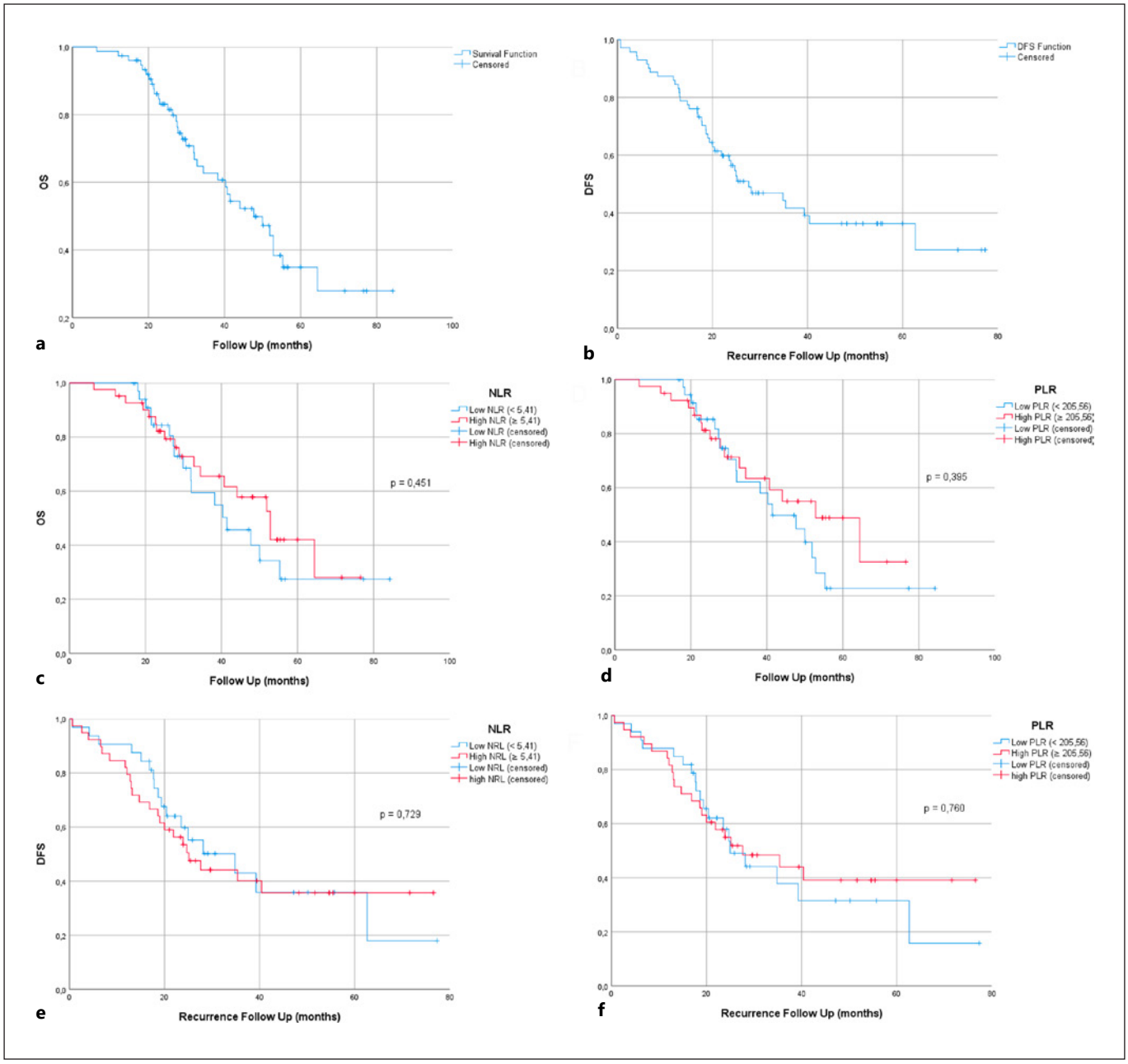

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Fig. 1. OS and DFS of patients with PDAC. **a** Kaplan-Meier analysis of OS of all patients with PDAC. **b** Kaplan-Meier analysis of DFS of all patients with PDAC. **c** Kaplan-Meier analysis of OS for the NLR of all patients with PDAC. **d** Kaplan-Meier analysis of DFS for the NLR of all patients with PDAC. **e** Kaplan-Meier analysis of OS for the PLR of all patients with PDAC. **f** Kaplan-Meier analysis of DFS for the PLR of all patients with PDAC. OS, overall survival; DFS, disease-free survival; PDAC, pancreatic ductal adenocarcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Discussion

The outcomes of patients with cancer are mainly determined by tumor-related factors such as stage, lymphovascular and perineural invasion, and resection margins. Also, host-related factors such as systemic inflammatory responses play important roles [13]. The inflammatory reaction is in fact a critical factor in the development of the tumor cell microenvironment and in the progression of malignancies. Studies have shown that neutrophils can

Table 2. Univariate and multivariate analysis of risk factors for the OS

Risk factors	OS					
	univariate analysis			multivariate analysis		
	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
Gender (men or women)	0.38	(0.22–1.36)	0.536	–	–	
Age (<65 years or ≥65 years)	1.11	(0.64–1.38)	0.622	–	–	
Tumor size <5 cm or ≥5 cm)	1.28	(0.681.98)	0.182	–	–	
Depth of invasion (T1, T2, or T3)	2.36	(1.18–2.68)	0.036			
Degree of differentiation (high/moderate/poor)	1.14	(0.36.1.54)	0.712	–	–	
Lymph node metastasis (yes or no)	3.10	(2.12–4.68)	0.032	–	–	
Lymphovascular invasion (yes or no)	0.64	(0.36–1.24)	0.412	–	–	
Perineural invasion (yes or no)	0.72	(0.48–1.78)	0.328	–	–	
Stage (I or II)	3.88	(2.18–6.74)	<0.001	2.12	(1.22–3.68)	<0.001
GICA (≤37 IU/mL or >37 IU/mL)	0.68	(0.76–1.24)	0.684	–	–	
Chemotherapy (yes or no)	1.20	(0.64–1.88)	0.326	–	–	
PLR (low or high)	2.34	(1.18–3.64)	0.004	–	–	
NLR (low or high)	2.86	(1.64–4.84)	0.004	–	–	

Table 3. Univariate and multivariate analysis of risk factors for the DFS

Risk factors	DFS					
	univariate analysis			multivariate analysis		
	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
Gender (men or women)	0.36	(0.28–1.64)	0.714	–	–	
Age (<65 years or ≥65 years)	1.28	(0.58–1.76)	0.824	–	–	
Tumor size	1.14	(0.58–2.16)	0.215	–	–	
Depth of invasion (T1, T2, or T3)	1.44	(1.18–2.96)	0.042	–	–	
Degree of differentiation (highly/moderate/poor)	1.26	(0.80–2.16)	0.688	–	–	
Lymph node metastasis (yes or no)	2.83	(1.84–4.98)	0.021	–	–	
Lymphovascular invasion (yes or no)	2.16	(1.64–3.08)	0.042	–	–	
Perineural invasion (yes or no)	1.18	(0.36–1.72)	0.815	–	–	
Stage (I or II)	3.15	(2.53–7.08)	<0.001	2.44	(1.36–4.01)	<0.001
GICA (≤37 IU/mL or >37 IU/mL)	0.42	(0.71–1.64)	0.384	–	–	
Chemotherapy (yes or no)	0.92	(0.84–1.72)	0.722	–	–	
PLR (low or high)	2.36	(1.36–3.98)	0.003	–	–	
NLR (low or high)	2.62	(1.78–4.92)	0.003	–	–	

promote the development and progression of cancer by providing an adequate tumor microenvironment via secretion of cytokines like interleukin (IL)-1, IL-3, and IL-6 that have pro-inflammatory effects cytokines like IL-10 and transforming growth factor-β (TGF-β) that have immune-suppressive effects, as well as chemokines [13–16].

Lymphocytes are crucial a component of the immune system, serving as the main defense against cancer cells. They control tumor progression by releasing cytokines such as interferon-γ and tumor necrosis factor-α [17]. Systemic inflammation is associated with the release of a number of inhibitory immunologic mediators, most notably IL-10 and TGF-β (secreted mainly by neutrophils), which can result in a significant immunosuppressive effect with consequent impaired lymphocyte function [17]. Pancreatic cancer cells directly secrete these two inhibitory cytokines [17] and decreased serum level of TGF-β2 has been shown to be associated with a more favorable survival outcome in PDAC [17].

The significance of tumor-platelet interactions is incompletely understood. A number of pro-inflammatory mediators (notably IL-1, IL-3, and IL-6) (secreted mainly by neutrophils) are known to stimulate the proliferation of megakaryocytes resulting in the gradual establishment of thrombocytosis [18]. In ovarian cancer elevated levels of IL-6 in ascites and cyst fluids have been associated with thrombocytosis. Furthermore, administration of recombinant IL-6 has been associated with an increased platelet count. Thus, the evaluation of platelet-count and functional status is consistent with the progression of malignancies [18]. The presence of thrombocytosis and its reported association with poor prognosis in pancreatic cancer could be explained by the observation that the platelet count is an index of systemic inflammation elicited by the tumor.

Therefore, it has been suggested that neutrophils, platelets, and lymphocytes play prominent roles in tumor-related inflammation and immune reactivity [19]. Based on this, several inflammatory markers in blood have been studied in various malignant tumors [20].

A similar but small number of studies have investigated the potential utility of the preoperative inflammation-based score as a prognostic marker in resected pancreatic cancer [21–28]. Schwarz et al. [23] and Zhang et al. [24] demonstrated that preoperative platelet count predicts survival after resection of pancreatic adenocarcinoma. On the other hand, in a study comprising 205 patients, there was no evidence to support preoperative platelet count as either an adverse or favorable prognostic factor in PDAC [25]. Also, the prognostic value of preoperative PLR and NLR in patients with pancreatic cancer has been evaluated in a few studies. PLR was shown to be a superior prognostic marker when compared with either individual parameter (lymphocyte, neutrophil, and platelet) or the NLR [26]. Aliustaoglu et al. [27] showed that there was no statistically significant difference between case with PLR values ≤160 and >160. However, they analyzed NLR in the same patients with pancreatic cancer. Patients with an NLR value of <5 had a significantly higher median OS time compared to those with a NLR value ≥5 ($p = 0.015$). Stotz et al. [28] evaluated NLR in 371 patients with primary operable and inoperable pancreatic cancer. They reported that multivariate analysis identified increased NLR as an independent prognostic factor for inoperable pancreatic cancer patients (HR = 2.53, $p < 0.001$) and surgically resected pancreatic cancer patients (HR = 1.61, $p = 0.039$).

In our study, we observed that both low preoperative NLR and PLR levels correlated with better pathological features, included decreased depth of invasion, less lymph node metastasis, and earlier stage. However, we observed that NLR and PLR are not significant prognostic indicators for postoperative OS and DFS in PDAC patients after radical surgery. Univariate analysis revealed that depth of invasion, lymph node metastasis, stage, a low NLR, and PLR were associated with prolonged OS and DFS, but in multivariate analysis, only stage was independently associated with OS and DFS. Contrary to the hypothesis that preoperative NLR and PLR are associated with the prognosis of PDAC of the pancreas head, our study demonstrates that preoperative low versus high NLR and PLR exhibited no significant differences between OS and DFS. A meta-analysis on the prognostic role of NLR and PLR for PDAC has shown a positive correlation of higher NLR and PLR with poor outcomes [29]. It is worth noting that previous authors acknowledged the limitations of their meta-analyses due to intrinsic heterogeneity, variation in demographic patient population, difference in interventions, and large spectrum of clinical stage included [7, 15, 29]. In our study the population is relatively homogeneous: it includes a single diagnosis (adenocarcinoma of the head of the pancreas), one type of operation (elective open pancreatoduodenectomy), and one type of surgical wound (bilateral subcostal incision). Moreover, it is uniform in terms of age, sex, BMI, ASA, grade (I–II), and tumor stage (I–II). An important bias is the inclusion of studies with positive results and possible exclusion of unpublished negative results [30]. Therefore, the role of NLR and PLR in patients with PDAC is still unresolved.

This study has a few limitations. First, the small sample size restricts the statistical power of our analysis; it may also influence the evaluation of the calibration of the biomarkers. Second, the peripheral blood findings were not compared to the findings of peritumoral and intratumoral inflammation in the primary tumor tissue. Finally, there was some heterogeneity in the treatment used for patients after surgical resection that led to different clinical prognoses.

Conclusion

We suggest that risk prediction for cancer-related endpoints NLR and PLR do not add independent prognostic information to other well-established prognostic factors in patients with pancreatic cancer.

Statement of Ethics

The study protocol was approved by the Ethical Committee of Faculty of Medicine of the University of L'Aquila (prot. N. 1488). Informed consent was obtained from all subjects.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest related to this publication.

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None.

Author Contributions

Romano Lucia and Giuliani Antonio: writing the article; Tomarelli Chiara, Nervini Andrea, and Lazzarin Gianni: data collection; Pessia Beatrice and Vicentini Vincenzo: data interpretation and analysis; Carlei Francesco and Schietroma Mario: conception and critical revision.

Data Availability Statement

All data from this study are included in this article. Further inquiries can be directed to the corresponding author.

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