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Original Article

The value and prognostic significance of neutrophil / lymphocyte ratio in predicting pancreatic fistula in patients undergoing pancreaticoduodenectomy for periampullary tumors

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Abstract

Aim: In this study, we aimed to determine the clinical value and prognostic significance of neutrophil / lymphocyte ratio in predicting pancreatic fistula in patients who underwent pancreatoduodenectomy due to periampullary tumor.

Material and Methods: Patients who underwent pancreatoduodenectomy for periampullary tumor between 2010-2019 were included in the study. Group 1 (LowNLR) and Group 2 (HighNLR) were formed. Demographic and clinical characteristics, intraoperative and postoperative outcomes, and mean survival were compared between the groups. The significance of NLR in predicting pancreatic fistula at the cut off value was examined.

Results: Patients were divided into two groups according to the 3.15 cut off value. Group 1 consisted of 61 patients and Group 2 consisted of 62 patients. In Group 2, albumin gr/dl value was lower (3.25 vs 3.70, p:000). in Group 2 pancreas tumors were more common (59.7% vs 42.6%, p: 0.041). The number of metastatic lymph nodes was higher in Group 1 (1.21 vs 0.63, p: 0.043), and the postoperative pancreatic fistula rate was similar (14.8% vs 21%, p: 0.254). Postoperative complications were higher in Group 2 (41.9% vs 14.8%, p: 0.032) NLR predicted pancreatic fistula with a sensitivity of 31.8% and specificity of 86.4%. In multivariate analysis, we found NLR to be a risk factor for survival (HR 1.760, 95% CI,1.179-2.627; p:0.006).

Conclusion: Patients with a preoperative high NLR have a worse prognosis than patients with low NLR. It cannot be used alone to predict pancreatic fistula. NLR has the potential to be used in the management of patients.

Keywords: Neutrophil/lymphocyte ratio; pancreatic fistula; periampullary tumor; prognosis

INTRODUCTION

Pancreatoduodenectomy is the gold standard surgery for the primary treatment of periampullary tumors (1). Even if the patient is managed successfully with surgical resection and subsequent chemotherapy, pancreatic cancer has a high recurrence rate or distant cancer metastasis, which can have fatal consequences. Pancreatic cancer is the fourth most common cause of cancer-related death and the overall survival rate is 10% to 20% (2,3).

Pancreatic fistula is a common complication after pancreaticoduodenectomy, and it is reported in the literature that the incidence of pancreatic fistula after pancreatoduodenectomy is approximately 11.4% - 64.3% (4,5). This complication causes additional morbidities such as delayed gastric emptying, intraabdominal abscess, wound infection, sepsis, and bleeding (6).

The possibility of combining a large number of clinically available host and tumor-related factors is of great interest as it can provide an excellent basis for clinical decision making, treatment planning, and follow-up plans (7).

Recently, an increasing amount of research has focused on the effects of systemic inflammatory response (SIR) on oncogenesis. They revealed a significant relationship between SIR and poor tumor-specific survival in numerous cancers (8,9). In particular, it has been suggested that neutrophil lymphocyte ratio (NLR), which is considered a biomarker of SIR, reflects the balance between pro-tumor inflammation and anti-tumor immune function, and its prognostic significance has been studied extensively in many solid tumors (10). In addition, it has been shown in previous studies that neutrophil-lymphocyte ratio does

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not play an important role in predicting postoperative complications after pancreaticoduodenectomy (2).

In this study, we aimed to determine the relationship between neutrophil / lymphocyte ratio and its clinical value in predicting postoperative pancreatic fistula in patients undergoing pancreaticoduodenectomy for periampullary tumor.

MATERIAL and METHODS

One Hundred and sixty patients, who underwent pancreaticoduodenectomy for periampullary tumors between January 2010 and January 2019, participated in our study. The patients were analyzed retrospectively. Patients under 18 years of age, with chronic inflammatory (Tuberculosis, Sarcoidosis) disease, with an autoimmune disease, with a hematologic disease, steroid users, patients without a pathological diagnosis of adenocarcinoma, with a choledochal tumor, and those whose records could not be reached were excluded from the study. A total of 123 patients were included in the study.

Cutoff value was determined by ROC curves and divided into two groups according to the cutoff value; Group 1 (Low NLR) and Group 2 (High NLR). Demographic characteristics of the patients, body, ASA score, Hgb and Albumin levels, tumor markers CEA and Ca 19.9, tumor localization, tumor grade, T, N, M of tumors, total and metastatic lymph nodes removed in both groups, lymph node positivity and the presence of pancreatic fistula was evaluated. Postoperative pancreatic fistula was defined, as proposed by the international study group of pancreatic fistula (ISGPF), as any measurable volume of fluid on or after POD 3 with amylase content greater than 3 times the serum amylase activity (11). Postoperative complications (wound infection, evisceration, intrabdominal abscess, intrabdominal hemorrhage, and anastomotic leakage were accepted as complications), postoperative hospital stay, 30-day mortality and survival time were compared. The value of NLR in predicting pancreatic fistula and survival was determined at the cutoff value.

Tumor-nod-metastasis (TNM) 2010 and 2016 systems were used for tumor staging.

The total blood count was measured by an automated hematology analyzer (Roche Hitachi ***Cobas® 8000*** Roche Diagnostics, Indianapolis, IN, USA). NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

Statistical Analysis

SPSS 23.0 (IBM Corp., Armonk, N.Y., USA) was used for the statistical analysis of the data. According to the survival of the patients, cutoff value was found by ROC analysis and groups were formed according to this cutoff value. Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean, standard deviation and minimum-maximum. Pearson's Chi-squared test was used to compare categorical variables. In the comparison of continuous measurements between groups, independent student t-test analysis was applied to binary variables by controlling distributions. In order to determine the neutrophil / lymphocyte ratio and the power to predict pancreatic fistula, ROC analysis was also performed. ROC analysis revealed cutoff, specificity, sensitivity, positive predictive and negative predictive values. Cox regression was used for multivariate evaluations. Kaplan-Meier analysis and Log Rank tests were used for survival analysis. Statistical significance was taken as 0.05 in all tests.

RESULTS

123 patients were included in our study. Groups were formed according to the 3.12 cut off value determined by the ROC curve. Group 1 (Low NLR) consisted of 61 patients and Group 2 (High NLR) consisted of 62 patients. Male sex was dominant in both groups (59% vs 66%, p: 0.265).

Table 1. Characteristics of patients

		Group 1 Low NLR (n:61)	Group2 High NLR (n:62)	p*
Age (min-max)		64.39±11.21 (25-91)	65.71±12.96 (22-93)	0.548
Sex	Male	36 (59.0)	41 (66.1)	0,265
	Female	25 (41.0)	21 (33.9)	
ASA score	1	25 (43.1)	24 (41.4)	0,470
	2	23 (39.7)	28 (48.3)	
	3	10 (17.2)	6 (10.3)	
Hemoglobin (min-max)		12.75±1.82 (8.8-17.7)	12.49±1.87 (7.4-16.7)	0.431
Albumin (min-max)		3.70±0.65 (2-4.9)	3.25±0.63 (1.8-4.6)	**0.000***
Preoperative Cea (min-max)		5.00±10.73 (0-81.6)	3.53±6.69 (0-52.2)	0.364
Preoperative ca19.9 (min-max)		570.17±1449.89 (1-9683)	673±1617.54 (1-9625)	0.711

ASA 1 (43%) was higher in Group 1, and ASA 2 (48.3%) was higher in Group 2. The distribution of ASA scores was similar between the groups (p: 0.470). Preoperative Hgb gr/dl values were similar between the groups (12.75 vs 12.49, p: 0.431). In Group 2, albumin gr/dl value was lower (3.25 vs 3.70, p: 000). Tumor markers were similar between the groups (CEA p:0.364; Ca19,9 p:0.711). It is shown in Table 1.

When we examined the tumor localizations, pancreas was seen more frequently in Group 2 with 59.7% and ampulla was more common in Group 1 with 57.4% (p:0.041). Moderately differentiated tumors were the most common in both groups (50.8% vs 54.8%, p: 0.789). T-stage (p: 0.146), N-stage (p: 0.470) and M-stage (p: 0.348) were similar in the groups. The number of dissected lymph nodes (12.41 vs 9.19, p: 0.005) and the number of metastatic lymph nodes (1.21 vs 0.63, p: 0.0043) were higher in Group 1. The rate of lymph node positivity was similar (42.6% vs 40.3%, p: 0.470). Characteristics of tumors are shown in Table 2.

Table 2. Characteristics of tumor

		GRUP 1	GRUP 2	
Localization	Ampulla	35 (57.4)	23 (37.1)	**0.041***
	Duodenum	0 (0.0)	2 (3.2)	
	Pancreas	26 (42.6)	37 (59.7)	
Differentiation	Well	16 (26.2)	13 (21.0)	0.789
	Moderate	31 (50.8)	34 (54.8)	
	Poor	14 (23.0)	15 (24.2)	
T	T1	2 (3.3)	4 (6.5)	0.146
	T2	33 (54.1)	21 (33.9)	
	T3	24 (39.3)	35(56.5)	
	T4	2 (3.3)	2 (3.2)	
N	N0	35 (57.4)	37 (59.7)	0.470
	N1	26 (42.6)	25 (40.3)	
M	M0	59 (96.7)	58 (93.5)	0.348
	M1	2 (3.3)	4 (6.5)	
Number of total dissected lymph nodes (min-max)		12.41±7.01 (3-42)	9.19±5.34 (1-27)	**0.005***
Metastatic lymph node number (min-max)		1.21±2.10 (0-11)	0.63±0.93 (0-4)	**0.043***
Lymph node positivity	Negative	35 (57.4)	37 (59.7)	0.470
	Positive	26 (42.6)	25 (40.3)	

Pancreatic fistula development rate in the postoperative period was similar between the groups (14.8% vs 21%, p: 0.254). Postoperative complications were higher in Group 2 (41.9% vs 24.6%, p: 0.032). Postoperative hospital stay was higher in Group 2 (19.63 vs 16.18 days, p:0.040). The development of local recurrence was higher in Group 2, but was not statistically significant (51.6% vs 39.3%, p: 0.118). Postoperative 30-day mortality was similar between the groups (9.8% vs 19.4%, p:0.107. Postoperative outcomes are shown in Table 3.

Table 3. Postoperative outcomes

Pancreatic fistula	Yes	9 (14.8)	13 (21.0)	0.254
	No	52 (85.2)	49 (79.0)	
Postoperative complication	Yes	15 (24.6)	26 (41.9)	**0.032***
	No	46 (75.4)	36 (58.1)	
Postoperative hospitalization duration (min-max)		16.18±8.0 (5-42)	19.63±10.21 (1-47)	**0.040***
Local recurrence	Yes	24 (39.3)	32 (51.6)	0.118
	No	37 (60.7)	30 (48.4)	
Postoperative 30-day mortality	Yes	6 (9.8)	12 (19.4)	0.107
	No	55 (90.2)	50 (80.6)	

To determine a cutoff value for the neutrophil / lymphocyte ratio to predict the pancreatic fistula ratio, ROC analysis and ROC curve were created. The area under the ROC curve of the ROC analysis was calculated as 54.7%. According to the cutoff value, the neutrophil / lymphocyte ratio and pancreatic fistula ratio were found to be 31.82% sensitive and 86.41% specific, if the NLR was above 5.18. It is shown in Figure 1 and Table 4.

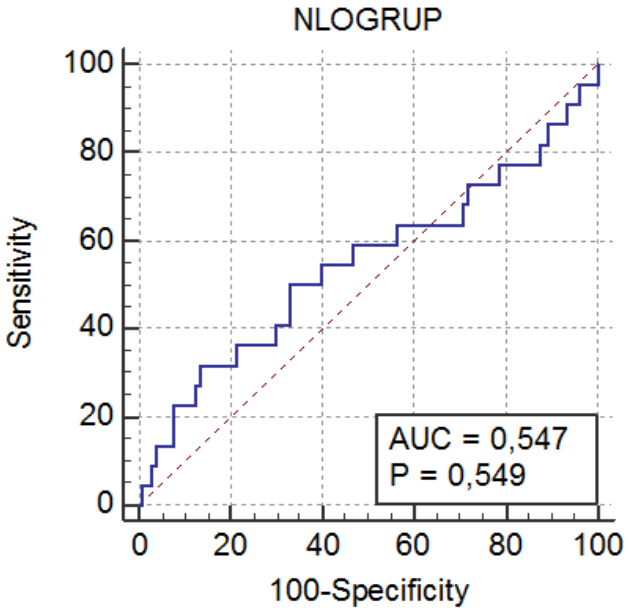

Figure 1. Receiver operating characteristic (ROC) curve analyses for pancreatic fistula

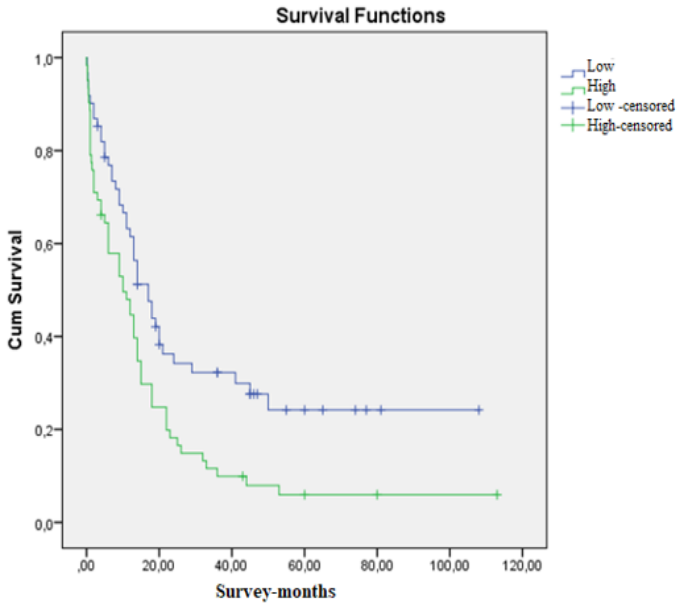

Figure 2. Total survival duration according to NLR groups

Table 4. Proposed cut-off values for significant parameters in pancreatic fistula

	NLR
AUC	0.547
Cutoff	> 5.18
Specificity	86.41
95%-CI (%)	78.2-92.4
Sensitivity (%)	31.82
95%-CI (%)	13.9-54.9
PPV	33.3
NPV	85.6
+LR	2.34
-LR	0.79
p	0.549

Neutrophil-to-lymphocyte ratio (NLR); AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio

When we look at survival curves and average survival, Group 2 had lower survival (17.91 vs 37.07 months, p:0.004). It is shown in and Table 5.

Table 5. Total survival time according to NLR groups

		Mean Mean+sd (Min-Max)	Median Mean+sd (Min-Max)	p
NLR Group	Low NLR	37.07±5.76 (25.76-48.37)	17.0±2.62 (11.85-22.14)	0.004*
	High NLR	17.91±3.45 (4.31-15.68)	10.0±2.89 (4.31-15.68)	

In the univariate and multivariate analysis for survival, being older than 65 years (p:0.007), grade of tumor differentiation (p:0.044), N stage (p:0.005), M stage (p:0.00), postoperative pancreatic fistula (p:0.006), postoperative complications (p:0.020), lymph node positivity (p: 0.005) and high NLR ratio (HR 1,760 95% - CI 1,179-2,627 p: 0.006) were found to be factors related to survival. It is shown in Table 6.

Table 6. Univariate and multivariate analysis of factors associated with overall survival in periampullary tumors

Measurements		Univariate	Multivariate	
		P	HR (95% - CI)	p
Age group	< 65	**0.006***	1.00	**0.007***
	> 65		1.743 (1.167-2.603)	
Sex	Male	0.662	1.00	0.663
	Female		0.912 (0.602-1.381)	
NLR	<3.15	**0.005***	1.00	**0.006***
	>3.15		1.760 (1.179-2.627)	
Localization	Ampulla	0.230	1.00	0.233
	Duodenum		1.366 (0.330-5.654)	0.667
	Pancreas		1.418 (0.947-2.123)	0.090
Differentiation	Poor	**0.044***	1.00	**0.041***
	Moderate		0.664 (0.417-1.057)	0.084
	Well		0.485 (0.273-0.860)	**0.013***
T	T1	0.061	1.00	**0.027***
	T2		0.592 (0.232-1.509)	0.272
	T3		0.814 (0.324-2.044)	0.661
	T4		2.761 (0.723-10.545)	0.137
N	N0	**0.006***	1.00	**0.005***
	N1		1.774 (1.189-2.647)	
M	M0	**0.003***	1.00	**0.000***
	M1		4.722 (1.991-11.200)	
Pancreatic fistula	No	**0.011***	1.00	**0.006***
	Yes		0.508 (0.313-0.825)	
Postoperative complication	Yes	**0.024***	1.00	**0.020***
	No		0.614 (0.407-0.927))	
Local recurrence	Yes	0.353	1.00	0.353
	No		0.826 (0.552-1.236)	
Lymph node positivity	Negative	**0.006***	1.00	**0.005***
	Positive		1.774 (1.189-2.647)	

DISCUSSION

The systemic inflammatory response from cancer cells promotes the infiltration of neutrophils, which increase the secretion of mediators such as interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10) and provide a negative tumor environment for cancer progression. The important role of lymphocytes in immune defense against cancer cells is well known. A decrease in the number of lymphocytes leads to an inadequate immunological reaction against cancer cells. In general, the relative proportion of high neutrophils and decreased lymphocytes can be a scientific marker to assess systemic inflammatory response and oncologic outcomes of individuals (12-16).

However, the reason NLR is related to postoperative complications may be related to quite different mechanisms. The mechanisms underlying the relationships between systemic inflammation and postoperative complications have not been fully elucidated. Previous studies have found that a high NLR may increase microvascular damage which is unsuitable for wound healing (17-19).

Watanbe et al, in their study on patients who underwent pancreaticoduodenectomy for pancreatic cancer, found that when the NLR cut off value was 2.5, the incidence of postoperative complications above grade 3 of the postoperative Clavien-Dindo classification was significantly higher in the group with NLR (≥2.5) (P = 0.041) (20). Kumamoto, Y et al., in their study on patients who underwent pancreaticoduodenectomy for periampullary region tumor, found in the multivariate analysis that NLR (> 2.0; OR: 6.77, 95.0% CI: 2.44-21.13; P <0.001) is an independent risk factor for postoperative complications (19). In our study, when we formed the groups according to the 3.15 cutoff values postoperative complication was seen more in the group with an NLR above 3.15 (41% vs 24%, p: 0.032). The length of hospitalization was prolonged in the group with high NLR due to postoperative complications. Our 30-day mortality is 14.6 that can be described with the high rate by litarature, the patients are advanced age (average 75 years) and the asa scores are high (average 2.5) (21,22).

The neutrophil lymphocyte ratio was not associated with our 30-day mortality rate. Many factors associated with mortality such as low albumin, postoperative complications, and postoperative pancreatic fistulas were found to be higher in the group with high NLR.

Postoperative pancreatic fistula and concomitant abdominal sepsis are among the potential causes of mortality after pancreatic surgery. Prediction or early diagnosis of pancreatic fistula is important to eliminate mortality in the treatment of this complication (23,24). Several biochemical parameters (PH, NLR at the end of the operation, platelet-to-lymphocyte ratio (PLR), preoperative bilirubin and red cell distribution width-to-platelet ratio (RPR) drain amylase) have been studied in the literature to predict pancreatic fistula (25). In our series, we did not find a statistically significant relationship between NLR rate and pancreatic fistula. The value of NLR at 5.18 cutoff values was limited in predicting pancreatic fistula. In our series, the specificity was found as high as 86%, while the sensitivity was as low as 31%.

Mowbray, N. G. et al. found no relationship between survival and NLR in only one study in their meta-analysis which included 8 studies, and NLR was a risk factor for survival in all other studies. In their meta-analysis, the pooled Hazard Ratio was 1.77 (95% CI [1.45–2.15]; p < 0.01). The NLR cut-off values ranged from 2 to 5. In their meta-analysis, heterogeneity between studies was low and moderate (I2 =31%; p = 0.17) (16). Similarly, Zhou et al., in their meta-analysis to evaluate NLR as an indicator of prognosis in patients with pancreatic cancer, found pooled HRs with high NLR versus low NLR for overall survival and disease-free survival, respectively, in pancreatic cancer as (95% CI) 1.81 (1.59- 2.05) and 1.66 (1.17-2.35) (23). In the study of Sierzega, M. et al, using the cutoff value of 5 for pancreatic cancer, NLR had a PPV of 47.1% and an NPV of 83.6% for death within 12 months of surgery (15).

Our series also supported the data in the literature, mean survival was significantly lower in the group with high NLR (17 vs 37 months, p:0.004). We found that NLR ratio higher than 3.15 (HR 1.760, 95% Cl, 1.179-2.627, p: 0.006) was associated with survival. As expected, the most important risk factor for survival was tumor stage.

Limitations of our study were the fact that it was single-centered and its retrospective nature. However, we believe that our study provides comprehensive data to the literature regarding the value of NLR for predicting pancreatic fistula and its relationship with prognosis for periampullary region tumors. Our study is one of the few studies on the value of NLR in predicting postoperative pancreatic fistula.

CONCLUSION

In conclusion, NLR rate is closely related to the localization and postoperative complications, duration of hospitalization and prognosis in periampullary region tumors. Although it has high specificity in predicting pancreatic fistula, it cannot be used alone due to its low sensitivity.

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