

Preoperative neutrophil-to-C-reactive protein ratio as a predictor of post-operative complications of pancreas cancer

Relación preoperatoria de neutrófilos a proteína C reactiva como predictor de complicaciones posoperatorias del cáncer de páncreas

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Abstract

Objective: We would like to investigate the prognostic utility of the previously described factors and offer a new parameter called neutrophil-to-C-reactive protein ratio (NCR) as a predictor of post-operative complications of pancreas cancer. **Methods:** 92 patients underwent pancreaticoduodenectomy for the pancreatic head tumor were enrolled in this study. Receiver operating curve analysis was performed to detect the cutoff values, and logistic regression analyses were performed to identify the independent risk factors of complications. **Results:** In univariate analysis, complications were observed in lymphocyte-to-C-reactive protein ratio levels below 0.06 (Odds Ratio [OR]: 3.92, 95% confidence interval [CI] = 1.08-14.21, $p = 0.037$). In multivariate analysis, albumin < 3.6 (OR: 3.25, 95% CI: 1.16-9.06, $p = 0.024$) and NCR < 0.28 (OR: 2.81, 95% CI: 1.07-7.63, $p = 0.042$) were the independent and significant predictors of the overall survival. **Discussion:** Quantification of preoperative NCR and albumin may help surgeons to settle an effective perioperative management, take extra caution, and be aware of post-operative complications of pancreatic cancer patients.

Keywords: Pancreas cancer. Postoperative complication. Neutrophil-to-C-reactive protein ratio.

Resumen

Objetivo: Se investigó la proporción de neutrófilos a proteína C reactiva (NCR) como predictor de complicaciones posoperatorias del cáncer de páncreas. **Material y Métodos:** 92 pacientes fueron sometidos a pancreaticoduodenectomía (PD) por el tumor de la cabeza del páncreas incluidos en este estudio. Se realizaron análisis de curva operativa del receptor (ROC) y análisis de regresión logística para detectar los valores de corte y los factores de riesgo independientes de complicaciones. **Resultados:** En análisis univariado; se observaron complicaciones en niveles de LCR por debajo de 0,06 (OR: 3.92, IC 95%: 1.08-14.21, $p = 0.037$). En análisis multivariado; albúmina < 3.6 (OR: 3.25, IC 95 %: 1.16-9.06, $p = 0.024$), NCR < 0.28 (OR: 2.81, IC 95 %: 1.07-7.63, $p = 0.042$) fueron los predictores independientes y significativos de la supervivencia. **Conclusión:** La cuantificación de la NCR y la albúmina preoperatorias puede ayudar a los cirujanos a establecer un manejo perioperatorio efectivo, tomar precauciones adicionales y estar atentos a las complicaciones posoperatorias.

Palabras clave: Cáncer de páncreas. Complicación posoperatoria. Proporción de neutrófilos a proteína C reactiva.

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Introduction

Pancreatic cancer is one of the most lethal cancers, and the 5-year survival rate is about 10%. Because of anatomical localization of the pancreas, cancer is mostly diagnosed at an advanced stage. The standard treatment is pancreaticoduodenectomy (PD) followed by complex reconstruction which may lead to early postoperative complications¹⁻³. Because to the challenging status of surgery and post-operative care difficulties, researchers try describing some parameters that predict post-operative complications before surgery and attempted to identify critical patients who need extra care. In some papers, patient-related inflammatory and immunonutritional markers, such as the prognostic C-reactive protein (CRP), albumin, prognostic nutritional index (PNI), modified Glasgow prognostic score, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-C-reactive protein ratio (LCR) are reported to be prognostic factors for the early postoperative complications, the survival of patients who have gastrointestinal cancer⁴⁻⁶.

In this study, we would like to reveal the prognostic utility of the previously described factors and offer a new parameter called neutrophil to C-reactive protein ratio (NCR) for patients who underwent resection for pancreatic head tumors.

Methods

Sample

From January 2016 to December 2021, 92 patients underwent PD for the pancreatic head tumors in the department of general surgery of a tertiary hospital. All patients were admitted to surgery, and no one received neoadjuvant chemotherapy. Patients who underwent additional hepatic resection for metastases which is not detected previously and the ones who had cholangitis were excluded from the study. Patient data including age, sex, underlying disease, blood levels of hemogram parameters such as hemoglobin, neutrophil, lymphocyte and platelet levels, serum levels of albumin, bilirubin (total and direct), CRP and additional organ resection, post-operative complications according to Clavien Dindo classification, post-operative hospital stay, intensive care requirements, mortality, and pathology results were collected retrospectively. PNI, NLR, LCR, and NCR were also calculated. PNI was calculated as $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$.

After initial analysis, patients were divided into two groups whether there were complications or not. Group one who had complications and group two who had discharged without any significant complications. The post-operative complications were classified according to the Clavien-Dindo⁷. Some demographic data and laboratory parameters were checked for difference if it existed between the groups. The receiver operating curve (ROC) analysis was performed between groups and detects the cutoff levels of PNI, NLR, CRP, albumin, LCR, and NCR. Univariate and multivariate logistic regression analyses were performed to identify the independent risk factors of complications. The study was approved by the local ethical committee of the University of Health Sciences, Antalya Education and Research Hospital.

Statistical analysis

All statistical analysis was carried out using JMP version 15.1 (SAS Institute Inc., Cary, NC, 1989-2019). Normality analysis of the data was tested using Shapiro-Wilk test. As the continuous variables were normally distributed, descriptive statistics are shown mean \pm standard deviation standard error of mean and for variables that were not normally distributed are shown as median interquartile range. Categorical variables were displayed using numbers (n) and percentages (%). A Chi-square test was performed for sex, additional comorbidity, complication status, pathology, whether it is malign or benign, and mortality status. Independent samples tests were performed for parametric and normally distributed variables such as albumin and PNI, Mann-Whitney U-test was used for non-parametric variables or were not normally distributed; such as age, length of hospital stay (days), neutrophil count, lymphocyte count, CRP, NLR, NCR, and LCR. ROC analysis was performed to determine the cutoff value of the PNI, NLR, NCR, and albumin between groups. The area under the curve and 95% confidence intervals (CI) were calculated. The Youden index is used for determining the best cutoff points in the ROC analysis. Univariate and multivariate logistic regression analyses were performed to determine independent factors affecting post-operative complications. A $p < 0.05$ was set as statistically significant.

Results

The detailed demographic data of the patients are given in table 1. The study was composed of

Table 1. Demographic data of patients (n = 92)

Age, median (IQR) year	67 (60.25-75)
Sex, Male/Female, n (%)	56 (61) / 36 (39)
Co-morbidity, n (%)	69 (75)
PNI, mean \pm SD (SEM)	42.3 \pm 8.27 (0.86)
Albumin, mean \pm SD (SEM)	3.33 \pm 0.57 (0.05)
LCR, median (IQR)	0.13 (0.01-0.39)
NCR, median (IQR)	0.32 (0.15-0.86)
Lymphocytes/CRP, median (IQR)	0.12 (0.32-0.38)
Complications, n	57
Clavien Dindo	
I-II	25 (43.9)
III-IV-V	32 (56.1)
Hospital stay, median (IQR), days	13.5 (8-21.75)
Pathology, n (%),	
Benign	11 (12)
Malignant	81 (88)
Mortality, n (%)	16 (17)

IQR: interquartile range; CRP: c-reactive protein; LCR: lymphocyte-to-c-reactive protein ratio; NCR: neutrophil-to-c-reactive protein ratio; PNI: prognostic nutritional index; IQR: interquartile range; SEM: standard error of mean; SD: standard deviation.

92 patients with a median age of 67 years, and 56 (61%) patients were male. Up to 75% of patients had comorbidities such as diabetes, coronary artery disease, hypertension, and chronic obstructive pulmonary disease. Post-operative complications were observed in 57 patients according to Clavien Dindo. 25 of them were Grade I-II and 32 of them were Grade III-IV and V. Median hospital stay was 13.5 days. Post-operative pathology results revealed 88% malignancy.

A comparison of demographic characteristics and laboratory parameters of the groups is presented in table 2. Age, albumin, CRP levels, and NCR were statistically significant between the groups. The median age was 69 in the Group 1, the mean albumin level was 3.21 and the median CRP level was detected at 17 in the complication group. The median NCR was 0.25 and 0.46, respectively, in Groups 1 and 2.

ROC analysis confirmed the cutoff values of the patient-related inflammatory and immunonutritional parameters between the groups which are given in table 3. Cutoff values for NCR and albumin were 0.28 and 3.6, respectively. High-sensitivity levels were observed in albumin and LCR, and high specificity was observed in NCR with a $p < 0.05$.

With the help of ROC analysis, patients were divided into two groups based on the cutoff levels of

NCR (0.28) and data are given in table 4. Mortality and complications were found to be statistically significant below the cutoff value of 0.28. ($p = 0.007$, $p = 0.02$ respectively)

Univariate and multivariate logistic regression analyses were performed to determine independent factors affecting complications. In univariate analysis, complications were observed at LCR levels below 0.06 (Odds Ratio [OR]: 3.92, 95% CI: 1.08-14.21, $p = 0.037$). In multivariate analysis, albumin < 3.6 (OR: 3.25, 95 % CI: 1.16-9.06, $p = 0.024$) and NCR < 0.28 (OR: 2.81, 95% CI: 1.07-7.63, $p = 0.042$) were the independent and significant predictors of the overall survival (Table 5).

Discussion

The nutritional status of patients with cancer is important that cannot be ignored as there is a correlation between nutritional status and post-operative complications and outcomes. Plenty of studies published for predicting the post-operative early and long-term results for gastrointestinal malignancies^{8,9}. Serum albumin and CRP levels are well-known parameters that provide valuable data about post-operative morbidity and long-term mortality. Albumin is synthesized in the liver and is known as a negative acute phase reactant. Malnutrition, underlying liver disease, malignancy, acute trauma, and surgery may alter the levels of serum albumin levels. Low levels of albumin were correlated with the worse post-operative outcome¹⁰.

CRP is also synthesized in liver as a positive acute phase reactant induced by pro-inflammatory cytokines, especially IL-6. In pancreatic cancer, peripheral blood mononuclear cells may also produce IL-6, which may lead increase in CRP levels¹¹. In our recent study, mean albumin level was 3.21 ($p = 0.01$) and CRP level was 17 ($p = 0.02$) in the complication group.

PNI is a widely investigated predictor of gastrointestinal and pancreatic cancer to predict post-operative outcomes that was initially identified in 1980 by Buzby et al.¹² Albumin and lymphocyte levels are important to calculate the PNI level, and PNI can give us a fast and sufficient information for the postoperative course. A PNI level of around 45 is mostly set as a cutoff value and values > 45 are better for convincing outcomes following surgery^{13,14}. The cutoff value for PNI was 44 in our study. Although there was a difference between the groups, there was no significance in logistic regression analysis.

Table 2. Comparison of demographic characteristics and laboratory parameters of groups (n = 92)

Variables	Group 1-complication (n = 57)	Group 2- no complication (n = 35)	p-value
Age, median (IQR range) year	69 (62.5-76.5)	63 (55-73)	0.01
Sex, Male/Female, n (%)	38 / 19 (66.7 / 33.3)	18/17 (51.4/48.6)	0.14
Co-morbidities, n (%)	45 (65.2)	24 (34.8)	0.26
Albumin, mean ± SD (SEM)	3.21 ± 0.55 (0.07)	3.53 ± 0.55 (0.09)	< 0,01
CRP median (IQR)	17 (7-43)	10 (3-21)	0.02
Bilirubin, median (IQR)	3.1 (0.75-10.6)	1.9 (0.7-10.5)	0.5
PNI, mean ± SD (SEM)	41.18 ± 8.48 (1.12)	44.2 ± 7.67 (1.29)	0.08
NCR, median (IQR)	0.25 (0.12-0.64)	0.46 (0.27-1.61)	0.03
NLR, median (IQR) (×10 ³ /mm ³)	3.06 (1.79-4.81)	2.68 (1.95-3.89)	0.57
LCR median (IQR)	0.1 (0.03-0.34)	0.18 (0.07-0.62)	0.1

CRP: c-reactive protein; LCR: lymphocyte-to-c-reactive protein ratio; NCR: neutrophil-to-c-reactive protein ratio; AUC: area under curve; CI: confidence interval; PNI: prognostic nutritional index; IQR: interquartile range; SEM: standard error of mean; SD: standard deviation.

Table 3. Receiver operating characteristics analysis of parameters for complication cases

Variables	Value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	p-value
PNI	44	0.60 (0.48-0.72)	57.1	65	0.08
NLR (×10 ³ /mm ³)	2.88	0.52 (0.4-0.64)	62.8	54.4	0.65
CRP (mg/dL)	16	0.64 (0.52-0.75)	54,2	71.5	0,03
Albumin (mg/dL)	3,6	0.65 (0.53-0.76)	82.4	45.8	0.02
LCR (×10 ³ /mm ³)	0.06	0.62 (0.5-0.74)	82.8	45.7	0.048
NCR (×10 ³ /mm ³)	0.28	0.65 (0.53-0.76)	52,54	77.2	0.02

CRP: c-reactive protein; LCR: lymphocyte to c-reactive protein ratio; NCR: neutrophil-to-c-reactive protein ratio; AUC: area under curve; CI: confidence interval; PNI: prognostic nutritional index; IQR: interquartile range; SEM: standard error of mean; SD: standard deviation.

NLR reflects online dynamic relationship between innate (neutrophils) and adaptive cellular immune response (lymphocytes) during illness and various pathological states¹⁵. NLR is also a well-known parameter correlated with many other gastrointestinal cancer outcomes. In a meta-analysis conducted by Yang et al. including eleven studies with 1804 patients, NLR was found to be a poor prognostic factor for pancreatic cancer patients' overall survival¹⁶. In another study, NLR and blood loss volume were associated with postoperative complications¹⁷. We could not find strong correlation between NLR and post-operative complications.

Recently, LCR is another marker shown to be a predictive factor for some various cancer types. In patients with colorectal, gastric, and hepatocellular cancer, LCR levels were found to be a prognostic factor for short-term and long-term outcomes^{5,8,18}. To our

knowledge, this study could be the early ones of the study that LCR was found to be an independent prognostic factor in the univariate analysis of early post-operative complications in patients with pancreatic cancer (p = 0.037).

Neutrophils occupy 50-70% of all leukocytes, which are the most abundant immune cell population. Patients with various cancer types, not limited to breast, lung, and colorectal cancer, often express increased numbers of circulating neutrophils¹⁹. In a recent study, we also evaluated the correlation between NCR and postoperative complications. NCR was described as a prognostic factor of bowel resection in incarcerated inguinal hernia. A level of 0.45 was the cutoff value for prediction resection of bowel²⁰. In another study, NCR and LCR used for prediction the severity of acute appendicitis²¹. In both univariate and multivariate

Table 4. Clinicopathological data of patients according to cutoff values of neutrophil to CRP ratio (n = 92)

Variables	NCR < 0.28	NCR > 0.28	p-value
Age, median (IQR) year	68.5 (64.25-75.75)	65 (57.25-74.75)	0.04
Sex, Male/Female, n (%)	31 (55.4) / 25 (44.6)	9 (25) / 27 (75)	0.004
Comorbidity, n (%)	32 (46.4)	37 (53.6)	0,3
Complications, n (%)	31 (54.4)	26 (45.6)	0.007
Clavien dindo, n (%)			0,4
I-II	12 (38.7)	19 (61.3)	
III-IV-V	13 (50)	13 (50)	
Hospital stay, median (IQR), days	15.5 (8.25-22.75)	12.5 (8-20)	0.4
Pathology, n (%),			0.6
Benign	4 (36.4)	7 (63.6)	
Malignant	36 (44.4)	45 (55.6)	
Mortality, n (%)	11 (68.8)	5 (31.2)	0.02

IQR: inter quartile range.

Table 5. Logistic regression analysis of the independent predictors of complications in periampullary tumor surgery

Variable	Univariate analysis		Multivariate analysis	
	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Age	0.218 (0.4-1.19)	0.079		
PNI	1.95 (0.83-4.61)	0.124		
NLR (x10 ³ /mm ³)	0.55 (0.23-1.31)	0.182		
CRP (mg/dL)	0.4 (0.11-1.32)	0.132		
Albumin (mg/dL)	3.96 (1.52-10.26)	0.005	3.25 (1.16-9.06)	0.024
LCR (x10 ³ /mm ³)	3.92 (1.08-14.21)	0.037	1.56 (0.37-6.66)	0.545
NCR (x10 ³ /mm ³)	3.44 (1.37-8.64)	0.008	2.81 (1.07-7.63)	0.042

CRP: c-reactive protein; LCR: lymphocyte-to-c-reactive protein ratio; NCR: neutrophil-to-c-reactive protein ratio; CI: confidence interval; PNI: prognostic nutritional index; OR: odds ratio.

logistic regression analyses, an NCR level of 0.28 was found to be an independent parameter of post-operative complications. To the best of our knowledge, this is the only study that has evaluated the effect of NCR on post-operative complications of PD.

Learning points

Complications after PD are a challenging issue. Several biomarkers such as PNI, NLR, and CRP have been studied to predict the better postoperative outcome.

The LCR and NCR could be valuable parameters in predicting the postoperative course.

To the best of our knowledge, there is no report on the use of NCR in the prediction of post-operative complications of PD.

Limitations of the study

Since this is a retrospectively designed study, we have some limitations. Data were collected from the database of our hospital and there may be some missing values due to coding errors. Even though the study was conducted in a tertiary hospital, it is a single-centered study.

Conclusion

Pancreatic cancer is one of the most lethal cancers in the world and post-operative complications are important issues to deal with. According to both univariate and multivariate logistic regression analyses, our results confirm that albumin and NCR can be used to predict post-operative complications of pancreatic cancer. Quantification of pre-operative NCR and albumin may help surgeons design more effective perioperative management, take extra caution, and be aware of post-operative complications of pancreatic cancer patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the ethics committee for analysis and publication of routinely acquired clinical data, and informed consent was not required for this retrospective observational study.

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