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Pankreatikoduodenektomi Ameliyatı Öncesi Kan Biyokimyasal, İnflamatuvar ve Beslenme Biyobelirteçleri ile Postoperatif Mortalite ve Morbiditeyi Öngörebilir Miyiz?

Can We Predict Postoperative Mortality and Morbidity with Blood Biochemical, Inflammatory and Nutritional Biomarkers Before Pancreaticoduodenectomy Procedure?

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ÖZ

Giriş: Whipple operasyonundan sonra morbidite oranı oldukça yüksektir (%40-50). Bu prosedüre giren hastalarda morbidite ve mortaliteyi öngörmek için kullanılan preoperatif biyokimyasal, inflamatuar ve beslenme biyobelirteçlerinin etkinliğini ve perioperatif biliyer drenaj ve anastomoz tekniğinin postoperatif dönem üzerindeki etkisini değerlendirmeyi amaçladık.

Yöntem: Bu retrospektif klinik araştırma 23/07/2010 ile 22/12/2021 tarihleri arasında pankreatikoduodenektomi uygulanan hastaların verileri hastane bilgisayar veri tabanından veya arşiv dosyalarından çıkarılarak yapılmıştır.Whipple operasyonu geçiren ve R0 cerrahi rezeksiyon elde eden tüm hastalar çalışmaya dahil edildi. Demografik veriler (yaş ve cinsiyet), stent varlığı, preoperatif hemoglobin, trombosit, nötrofil, lenfosit, toplam bilirubin, direkt bilirubin, albümin kan testi değerleri retrospektif olarak kaydedildi. Tüm hastalar için preoperatif nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve prognostik beslenme indeksi (PNI) hesaplandı.

Bulgular: Çalışmaya toplam 153 hasta dahil edildi. Toplam bilirubin ve direkt bilirubin ortalama değerleri kanama ve komplikasyonları olan ve olmayan vakalar arasında önemli ölçüde farklıydı. Cinsiyet, stent varlığı, anastomotik teknik, albumin, PLR ve PNI mortaliteyi önemli ölçüde etkilemedi. Yaş, hemoglobin, NLR, toplam bilirubin ve direkt bilirubin mortaliteyi etkiledi. Ancak daha ileri analizler, yaşın mortalite için tek risk faktörü olduğunu ortaya koydu.

Sonuç: Analizlerde yüksek bilirubin seviyeleri perioperatif kanama ile ilişkilendirildi. Yaş, hemoglobin, bilirubin ve NLR mortaliteyi tahmin etmede belirginken, daha ileri analizler sadece yaşın erken postoperatif mortalite ile güçlü bir şekilde ilişkili olduğunu ortaya koydu.

Anahtar Kelimeler: pankreatikoduodenektomi prosedürü, biyokimyasal enflamtuar ve nütrisyonel biyobelirteçleri, prediktivite, morbidite ve mortalite

ABSTRACT

Objective: The morbidity rate after Whipple operation is quite high (40-50%). We aimed to evaluate the efficacy of preoperative biochemical, inflammatory and nutritional biomarkers used as predictors for morbidity and mortality in patients undergoing this procedure, as well as the effect of perioperative biliary drainage and anastomosis technique on the postoperative period.

Method: This retrospective clinical study was conducted by extracting data from hospital computer databases or archive files of patients who underwent pancreaticoduodenectomy between 23.07.2010 and 22.12.2021.All patients who underwent Whipple procedure and achieved R0 surgical resection were included in the study. Demographic data (age and gender), presence of stent, preoperative hemoglobin, platelet, neutrophil, lymphocyte, total bilirubin, direct bilirubin, albumin blood test values were recorded retrospectively. Preoperative neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and prognostic nutritional index (PNI) were calculated for all patients.

Results: A total of 153 patients were included in the study. The mean values of total bilirubin and direct bilirubin were significantly different between cases with and without bleeding and complications. Gender, presence of stent, anastomotic technique, albumin, PLR and PNI did not significantly affect mortality. Age, hemoglobin, NLR, total bilirubin and direct bilirubin affected mortality. However, further analysis revealed that age was the only risk factor for mortality

Conclusion: High bilirubin levels were associated with perioperative bleeding in the analyses. While age, hemoglobin, bilirubin and NLR were prominent in predicting mortality, further analysis revealed that only age was strongly associated with early postoperative mortality.

Keywords: pancreaticoduodenectomy procedure, biochemical inflammatory and nutritional biomarkers, predictivity, morbidity and mortality

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INTRODUCTION

Although the medical care, treatment modalities, and research methods have improved significantly, pancreatic cancer remains as the fourth most frequently encountered cancer-related deaths with the 12% 5-year survival rate. (1, 2) Whipple procedure, also called Pancreaticoduodenectomy (PD), is the primary choice of surgery to resect and limit the resectable pancreatic ductal adenocarcinomas. (3) Whipple procedure was initially proposed by Whipple et al. in 1935 for periampullary carcinoma. (4) The primary studies that the Whipple procedure was performed indicated significant mortality rate (5, 6), however with the advancements in the diagnosis, surgical techniques, anesthesia and increased experience of surgeon, the mortality rate dropped significantly. (1) Nevertheless, perioperative morbidity after Whipple surgery is still high as 40-50%. (7, 8, 9)

Pancreatic adenocarcinomas are the most common form of pancreatic cancer. (10) Whipple procedure has been performed for resection both benign lesions and malignant neoplasms of pancreas. (11, 12) The main complications of Whipple surgery comprise intraabdominal abscesses, pancreatic fistula/leak, bile leak, delayed gastric emptying, hemorrhages, infection of surgical sites, pulmonary complications and organ failure. (13, 14, 15) Although many surgical anastomosis techniques have been described for pancreaticojejunal anastomosis, none of them has been clearly proven to be superior. (16, 17) Demographic, biochemical, nutritional and immunological features have been investigated in many studies to identify high risk patients and many factors were associated with post-operative death and adverse events.Previous studies have shown that; obesity, some preoperative biochemical and immunological markers, hyperbilirubinemia requiring biliary drainage were associated with serious postoperative adverse events.(18, 19, 20) Albumin, C reactive protein (CRP), transaminase enzymes have been highlighted as preoperative predictors for post operative morbidity. (19, 21) Recent studies focused on nutritional and inflammatory status of patients and numerous formulas created from biomarkers such as prognostic nutritional index, neutrophil-lymphocyte ratio and platelet-CRP ratio have been reported to predict the postoperative events. (22, 23, 24, 25) In consequence, preoperative evaluation of these markers will be meaningful when they are used to establish feasible interventions to improve operative results.

In this study, we aimed to investigate the effectiveness of preoperative biochemical, inflammatory and nutritional biomarkers which have been used as a predictor for early clinical outcomes (morbidity and mortality) in patients underwent Whipple procedure for pancreatic cancer. We also aimed to consider effect of perioperative biliary drainage and anastomosis technique on post operative period.

MATERIALS AND METHODS

In this retrospective study, the data of patients who underwent pancreaticoduodenectomy between 23.07.2010 and 22.12.2021 were reviewed. All patients with final diagnosis of malignity underwent R0 surgical resection and reported with clean surgical margin were included, while patients without malignity did not undergo R0 resection were excluded. Besides the demographic data (age and gender) of the patient, presence of stent, blood test values of hemoglobin (Hb), platelet (PLT), neutrophil, lymphocyte, total bilirubin, direct bilirubin and albumin preceding surgery were recorded.

Length of stay in intensive care unit (ICU), length of hospitalization in ward, anastomosis technique Pancreaticojejunostomy (PJ) or Wirsungojejunostomy (WJ), presence of morbidity and mortality were recorded. Biochemical leak, grade 2-3 pancreatic fistula, bleeding, deep surgical site infection and severe respiratory problem requiring mechanical ventilation support were considered as morbidity. Biochemical leak or grade 2-3 fistulas were defined according to the 2016 revised postoperative pancreatic fistula classification of the International Study Group of Pancreatic Surgery. (26) Visible surgical site hemorrhage that required transfusion during the intraoperative and postoperative period was defined as bleeding. Complications requiring intensive care and ventilator support were included in respiratory complications. Patients who died within 30 days after were considered as perioperative mortality.

Preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and prognostic nutritional index (PNI) were calculated for all patients. NLR was calculated using neutrophil count / lymphocyte count and PLR was calculated using platelet count / lymphocyte count× 100 formulas. The PNI is scoring system to assess nutritional and immunological status was calculated using 10 × serum albumin, g/dL + 0.005 × lymphocyte count, $10^3/\mu L$ formula.

Surgical Procedure

Standard Whipple procedure was applied to all patients. PJ was performed in all patients whose pancreatic duct could not be cannulated in the procedure and WJ was performed in all patients whose pancreatic duct could be cannulated. Then, sequentially, hepaticojejunostomy, gastrojejunostomy and Braun jejunojejunostomy were performed.

Statistical Analysis

Morbidity, subtype of morbidity and mortality were accepted as dependent variables. Distribution of the continuous variables was investigated by histogram graphs and/or Shapiro-Wilk normality test. Descriptive statistics were presented as mean and standard deviation (Mean(±SD)) for normal distribution, median and 25%-75% percentile (Median (Q1, Q3)) for non-normal distribution, frequency and ratio (n(%)) for categorical data. Continuous variables with normal distribution were analyzed by using Student's t-test,variables with non-normal distribution were analyzed by Mann-Whitney U test. Categorical variables were compared by Chi-square test or Fisher's exact test. Three or more categorical variables were analyzed with One-Way Anova or Kruskal-Wallis test depending on the distribution of variable. Binary logistic regression analyzes were performed to investigate the level of effect. A p-value less than 0.05 was considered to be statistically significant for the differences between groups. Statistical analyses were conducted by using Statistical Package for the Social Sciences (SPSS, version 24.0, IBM) software.

RESULTS

A total of 153 patients were included in the study. Mean age of the patients was 65.39 (±12.39) years. Eighty-eight of the patients were

female (57.5%). Preoperative biliary drainage stents were applied to 42 (27.5%) patients. PJ anastomosis was performed with the PJ technique in 87/153 (57%) patients and the WJ technique in 56/153 (43%) patients. Postoperative morbidity developed in 77/153(50%) patients. Type of complications are summerized in Table 1. Twenty-six of 153 (17%) patients died within two months postoperatively.

Table 1. Complication, Complication Type and Mortality Rates.

Complication situation	n	%
None	**76**	**49%**
Yes	**77**	**51%**
Biochemical leak	20	13%
Respiratory	18	12%
Grade 2 or 3 pancreatic fistula	18	12%
Wound infection	12	8%
Bleeding	9	6%
Mortality	**26**	**17%**

Gender, anastomosis technique, presence of stent, age, levels of hemoglobin, albumin, NLR, PLR and PNI, total bilirubin and direct bilirubin levels were not detected as the factors affecting morbidity in univariate analyzes (Table 2). One-way ANOVA test was performed to examine the relationship between with normally distributed variables and subgroups of complication. No difference observed between any type of complication for hemoglobin, albumin, PLR and PNI, but revealed that significant difference in mean age between at least two of complication ($F(5,147) = 2.701$, $p=0,023$). Kruskal-Wallis analysis was performed to examine non-normal distributed variables andsubgroups of complication determined significantly difference for total bilirubin ($H(5) = 17.642$, $p=0.003$) and direct bilirubin ($H(5) = 17.642$, $p=0.001$) between at least two type of complications (Table 3). Post hoc analysis; Bonferroni test for multiple comparisons found that the mean value of age was significantly different between biochemical leak and respiratory complication ($p=0.040$, 95% C.I. =0.28, 23.85). Also, Games Howell test found that the mean value of total bilirubin and direct bilirubin were significantly different between bleeding and none complication respectively ($p=0.047$,95% C.I.=0.10, 14.98) and ($p=0.014$, 95% C.I.=0.88, 8.16). Univariate analyzes revealed that gender, presence of stent, anastomosis technique, albumin, PLR and PNI were not detected as the factors significantly affecting mortality. Age, hemoglobin, NLR, total bilirubin, direct bilirubin affecting the mortality as single factors (Table 4). On the other hand, further analyses with binary logistic regression analysis revealed that age is only risk factor for mortality ($p=0.043$, OR:1.050, 95% CI: 1.001,1.101) (Table 4).

Table 2. Relationship Between Preoperative Values, Anastomosis Technique and Morbidity.

	Morbidity (-) (n=76)	Morbidity (+) (n=77)	Univariate Analysis P value
Age (years)	64.5 ± 11.5	66.1 ± 13.2	0.433[a]
Gender Female Male	 29 (38.2%) 47 (61.8%)	 36 (46.8%) 41 (53.2%)	0.181[b]
Anastomosis technique PJ WJ	 39 (51.3%) 37 (48.7%)	 48 (62.3%) 29 (37.7%)	0.112[b]
Presence of stent None ERCP PTD	 52 (68.4%) 23 (30.3%) 1 (1.3%)	 59 (76.6%) 16 (20.8%) 2 (2.6%)	0.363[b]
Hb	11.4 ± 1.8	11.2 ± 2.1	0.542[a]
Albumin	3.49 ± 0.40	3.45 ± 0.47	0.572[a]
PLR	1.8 ± 1.1	1.8 ± 0.9	0.915[a]
PNI	34.9 ± 4.0	34.5 ± 4.7	0.572[a]
NLR	2.86 (1.99,4.31)	3.17 (2.10,4.68)	0.775[c]
Total Bilirubin	3.70 (1.20,8.55)	5.90 (1.50,12.90)	0.094[c]
Direct Bilirubin	1.65 (0.36,4.70)	2.98 (0.56,7.72)	0.089[c]

ERCP: Endoscopic retrograde cholangiopancreatography; Hb: Hemoglobin; NLR: neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PNI: Prognostic nutritional index; PTD: Percutaneous transhepatic drain. [a] Student's t-test, [b] Chi-square test or Fisher's exact test, [c] Mann Whitney U test.

Table 3. Comparison of Complication Types According to Preoperative Values and Mortality Results.

	None (n:76)	Biochemical leak (n:20)	Respiratory complication (n:18)	Grade2-3 leak (n:18)	Wound infection (n:12)	Bleeding (n:9)	Statistical result
Age	64.59 (±11.59)	58.05 (±15.79)	70.11 (±13.96)	69.33 (±9.13)	69.33 (±10.39)	65.89 (±11.06)	F(5,147)=2.701,p=0.023[a]
Hemoglobin	11.42 (±1.84)	11.63 (±1.76)	11.98 (±1.76)	11.10 (±1.77)	11.66 (± 2.04)	11.62 (±1,36)	p=0.825[a]
Albumin	3.50 ± 0.40	3.48 ± 0.50	3.52 ± 0.52	3.34 ± 0.40	3.44 ± 0.49	3.51 ± 0.47	P=0.834[a]
PLR	1.82 (±1.12)	1.59 (± 0.88)	2.18 (±1.26)	1.91 (±0.70)	1.58 (±0.80)	1.92 (±1.12)	p=0.569[a]
PNI	34.98 (4.03)	34.86 (±4.95)	35.23 (±5.26)	33.45 (±4.04)	34.42 (4.86)	35.12 (±4.70)	p=0.834[a]
NLR	2.86 (2.02,4.29)	2.38 (1.48,3.79)	3.98 (2.36,5.00)	3.55 (2.95,4.36)	2.75 (1.92,3.76)	3.36 (2.12,5.47)	p=0.248[b]
Total bilirubin	3.70 (1.20,8.50)	1.30 (0.65,6.60)	7.65 (2.40,17.00)	6.35 (3.10,15.40)	3.30 (1.60,6.75)	**11.10 (10.20,15.60)**	H(5)=17.642, p=0.003[b]
Direct bilirubin	1.65 (0.37,4.70)	0.35 (0.10,3.28)	4.51 (1.30,7.96)	3.30 (1.68,8.41)	1.48 (0.86,3.03)	**8.02 (5.79,8.41)**	H(5)=17.642, p=0.001[b]
Mortality (n)	3	0	**16**	5	0	2	P=0.003[c]

[a] One-way ANOVA test ; [b] Kruskal Wallis test; [c] Chi-square test

Table 4. Relationship Between Preoperative Values, Anastomosis Technique and Mortality.

	Mortality (-) (n=127)	Mortality (+) (n=26)	Univariate Analysis (P value)	Logistic regression (P value)
Age	63.91 ± 12.13	73.62 ± 11.90	0.001	0.043 (OR:1.050, 95%CI:1.001,1.101)
Gender Female Male	 55 (43.3%) 72 (56.7%)	 10 (38.5%) 16 (61.5%)	0.409	-
Anastomosis technique PJ WJ	 68 (53.5%) 59 (46.5%)	 19 (73.1%) 7 (26.9%)	0.067	0.052
Presence of stent None ERCP PTD	 92 (72.4%) 34 (26.8%) 1 (0.83%)	 19(73.1%) 5 (19.2%) 2 (7.7%)	0.947	-
Hemoglobin	11.56 ± 1.77	10.58 ± 1.70	0.011	0.053
Albumin	3.50 ± 0.42	3.36 ± 0.49	0.169	
PLR	1.82 ± 1.01	1.87 ± 1.23	0.830	-
PNI	35.0 ± 4.25	33.70 ± 4.09	0.169	-
NLR	2.82 (1.96,4.31)	4.07 (2.89,6.38)	0.027	0.654
Total Bilirubin	3.70 (1.20,9.40)	8.25 (2.70,16.25)	0.017	0.758
Direct Bilirubin	1.75 (0.36,5.24)	5.22 (1.58,8.65)	0.008	0.341

ERCP: Endoscopic retrograde cholangiopancreatography; Hb: Hemoglobin; NLR: neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet number; PNI: Prognostic nutritional index; PTD: Percutaneous transhepatic drain.

DISCUSSION

The aim of this study is to investigate preoperative and perioperative predictive factors of morbidity and mortality in patients who underwent pancreaticoduodenectomy. There was not any remarkable factor that predicts development of complication, but high bilirubin level was associated with postoperative hemorrhage. While age, hemoglobin, bilirubin and NLR came forward to predict mortality, further analysis revealed just age is strongly associated with early postoperative mortality. Anastomosis technique of pancreaticojejunostomy and preoperative biliary drainage were not associated postoperative results.Ansari et al. stated that there was no difference in 30-day complication and mortality rates in their study of 556 patients, comparing pancreatic cancer in patients over and under the age of 75years. (27) Andreu et al. in their study including 346 patients, reported more complications and deaths in the group of patients aged 80 and over. (28) Bozkurt et al. reported more complication rate in over age 75 years group but no difference in 90 days mortality rate. (29) Hancker et al. reported in their study including 213 patients, that similar perioperative morbidity and mortality rate, but lower overall survival in older 70 years old group was seen. (30) Panagiotakis at al. pointed out that preoperative hemoglobin levels influenced survival after pancreaticoduodenectomy. (31) Perocelli et al. reported that preoperative anemia was an independent risk factor for increased complications in patients undergoing proximal pancreas resections. (32) Also Sert et al. reported that low hemoglobin values were related with postoperative pancreatic fistula. (33) Many studies dealt with relationship between hypoalbuminemia and pancreatic surgery outcomes. Winter et al. reported that albumin level <3.5 g/dl was associated with post-operative morbidity and mortality. (19) Rungsakulkij et al. reported that albumin level was correlated with serious postoperative complications. (34) Ahmetasevic et al. reported that preoperative albumin level <3.2 g/dl group was associated with severe postoperative complications. (35) Recent studies interested in the relationship between immunologic status and cancer outcomes. (36) Coppola et al. reported that lower values of NLR were associated with a lower risk of pancreatic fistula and abdominal collection. (24) Wang et al. defined NLR as a reliable predictor of postoperative complication after pancreaticoduodenectomy. (37) Prognostic nutritional index (PNI) was found as an independent prognostic factor for various malignancies. (38, 39, 40, 41) Recently, PNI was found to be a significant prognostic factor to predict the survival of patient with pancreatic cancer (20) ,however did not predict serious postoperative complications. (22) Preoperative biliary decompression is still a controversial issue in patients with mechanical jaundice due to periampullary cancer. Das et al. reported high bilirubin level and stenting was associated with postoperative hemorrhage. (42) Scheufele et al. reported that preoperative bilirubin level had no predictive value of postoperative outcome, however postoperative complications increased after preoperative biliary drainage. (43) Mosquera et al. stated that there was no significant difference in postoperative complications between those who underwent biliary decompression and those who did not, in patients with bilirubin levels between 10 and 15 mg/dl. They also reported that biliary decompression in patients with bilirubin levels > 15 mg/dl was associated with less severe complications. (44) Santos et al. reported that 90-day mortality was not related with preoperative bilirubin levels, biliary drainage, but solely with age. (45) Chen et al. reported in their retrospective study including 803 pancreaticoduodenectomy patients that higher than 13 mg/dl total bilirubin levels was associated with increased 90-day mortality and recommended reducing bilirubin levels before surgery. (46) Also Gao et al. reported that a preoperative TB level > 162 µmol/L predicted postoperative complications and hemorrhage was lower in biliary drainage group. (47) Failure of a pancreaticoduodenectomy anastomosis may be one of the most common of all abdominal anastomoses leading to serious complications. Moreover, there is no gold standard anastomotic technique to be performed following pancreatic ductal adenocarcinomas. Until the last decade, the PJ anastomosis technique was a highly debated issue and opposing results were suggested. (48, 49, 50) However, meta-analyzes published recent years showed no significant difference between various pancreaticojejunal anastomosis techniques for post-operative complications. (51, 52, 53)

Major limitations of our study were its retrospective design and small sample size. Also, conditions such as comorbidities and body mass index were not included in the analysis due to lack of data. Moreover, we did not include the surgeon factor and intraoperative events while analyzing the outcomes.

CONCLUSION

The fact that there is still so much research being done shows that Whipple surgery continues to be a challenging process for surgeons. . Despite all the research, no definitive indicator has been found to predict the process. Available reports point that age is the only independent predictor for postoperative risk assesment in patients who are candidates for pancreaticoduodenectomy. However, it seems that the interest in the patient's nutritional and immunological status, which will affect the convalescent period, will continue. Patient-based assessment still seems to be the most appropriate approach because of the influence of many complex factors.

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