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Original Article

Evaluation of factors related to postoperative mortality in patients who underwent pancreatoduodenectomy due to periampullary region tumors

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Abstract

Aim: In this study, we aimed to investigate the factors related to postoperative mortality after pancreatoduodenectomy in our clinic.

Materials and Methods: Patients who underwent pancreatoduodenectomy due to a periampullary region tumor between 2010 and 2019 were included in the study. Mortality that occurred within 30 days after PD was defined as postoperative mortality and groups were formed according to this definition Group 1(Postoperative Mortality) and Group 2(No mortality). The demographic and clinical features, laboratory parameters, and tumor features of the patients were compared between the groups. Risk factors for mortality were analyzed by univariate analysis and multivariate logistic regression analysis.

Results: 155 patients participated in our study. We found our postoperative mortality rate as 11.6%. Accordingly, Group 1 consisted of 18 and Group 2 consisted of 137 patients. The sex was similar (p: 0.235). The average age was higher in Group 1 than 2 (71.2 vs 63.7, p:0.013). Tumor localizations were similar in groups (p:0.275). Lymph node positivity was similar in the groups (50% vs 41.6%, p:0.333). The pancreatic fistula was higher in Group 1, but not statistically significant (33% vs 18.2%, p:0.119). Preoperative white blood cell count (9490 mm^3 vs 8050 mm^3) and neutrophil count (6898 mm^3 vs5442 mm^3) were higher in Group 1. In multivariate analysis, no parameters were single-handedly risk factors.

Conclusion: No factor was found to be effective alone in the development of mortality after pancreaticoduodenectomy. We think that postoperative mortality may decrease by revealing the factors in the preoperative, intraoperative and postoperative periods.

Keywords: Pancreaticoduodenectomy; postoperative mortality; prognosis

INTRODUCTION

Pancreatic cancer is the 11th most common cancer in the world and the fourth leading cause of cancer-related deaths (1,2).

Periampullary region tumors include tumors originating from the pancreatic head, the lower end of the ductus choledochus the ampulla vateri, and the duodenum adjacent to the ampulla. Pancreaticoduodenectomy (PD) is the preferred treatment for patients with a periampullary tumor and resectable disease. Despite improvements in surgical technique, patient selection, and advances in perioperative care, PD is still associated with high morbidity and mortality (3). Population-based studies in recent years have shown that the morbidity of PD varies from 20% to 40% and mortality rates from 2.8% to 10.2% (4-9).

In recent years, studies using large, national databases have shown that many factors contribute to perioperative mortality in patients undergoing pancreatic resection. Important morbidity markers include old age, male sex, being overweight and obese, daily life activities within 30 days before surgery, chronic obstructive pulmonary disease (COPD), steroid use, bleeding disorders, leukocytosis, high serum creatinine and hypoalbuminemia. Important determinants of 30-day mortality are male sex, bleeding disorders, COPD, hypertension, neoadjuvant radiation therapy, more than 10% weight loss, an ASA score over 3, over 400 Brinkman index, a body mass index over 25, over 11,000 white blood cell count, less than 120,000 platelet count, increased serum creatinine level and hypoalbuminemia. Also, low hospital volume is strongly related to worsening results after resection (4,10,11).

Understanding the risk factors for potential morbidity and mortality following pancreatic cancer surgery, determining the changeable ones among these factors, and taking necessary measures are important for the prevention of postoperative mortality. Although, the factors that are

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expected to be associated with mortality, they are not effective alone. It can come together to increase mortality rates. For this reason, considering the patient as a whole while performing the patient assessment may prevent mortality.

In this study, we aimed to investigate the factors related to mortality associated with pancreatoduodenectomy in our clinic over a 10-year period and discuss our findings in the light of the literature.

MATERIALS and METHODS

In our study, 172 patients who underwent pancreatoduodenectomy due to a periampullary region tumor (ampulla, distal choledoch, pancreas head, duodenum) between 2010-2019 were included. Seventeen patients under the age of 18, whose records could not be reached and those with a pathological diagnosis other than adenocarcinoma were excluded. A total of 155 patients were included. The clinical records, pathology and surgery reports of the patients were retrospectively analyzed from the patient files and the hospital automation system database.

Mortality that occurred within 30 days after PD was defined as postoperative mortality and groups were formed according to this definition: Group 1 (Mortality present) and Group 2 (No mortality). Demographic and clinical data such as sex, age, presence of comorbid disease, American Society of Anesthesiologists (ASA) score, and tumor localization; laboratory parameters such as complete blood count, albumin, bilirubin and tumor markers (CEA, CA19.9); pathological features such as tumor differentiation, stage, diameter, number of dissected and metastatic lymph nodes, presence of positive lymph node; postoperative follow-up data such as the presence of non-pancreatic fistula complications, duration of postoperative hospital stay, 30-day postoperative survival, local recurrence status, current clinical status, cause of exitus, and total survival time were analyzed. In addition, independent risk factors were evaluated in univariate and multivariate analysis.

In terms of postoperative complications, patients with pancreatic fistula, wound infection, evisceration, intraabdominal abscess, intraabdominal hemorrhage, anastomosis leakage were considered to have complications. Intraabdominal abscess was defined as a collection that appears on computed tomography (CT) and needs drainage. Wound infection was considered purulent drainage from the incision. As the definition of pancreatic fistula, the drain fluid amylase value observed on the 3rd day after PD being 3 times higher than the serum amylase value or the amylase value determined as the upper limit by the hospital laboratory (12). Postoperative bleeding was determined according to the data of the International Pancreatic Surgery Working Group (13).

Patients were staged according to the American Joint Committee on Cancer (AJCC) TNM staging system. TNM 2010 and 2016 systems were used.

All patients underwent respiratory physiotherapy (triballs spirometry) 24 hours before the operation and 1gr of Cefazolin within 60 minutes before the operation. Low molecular weight heparinized venous thromboembolism (VTE) prophylaxis was performed. The patients were given post-hospital VTE prophylaxis.

All patients were evaluated at the hepatobiliary tumor council before the operation.

Statistical analysis

SPSS 23.0 (IBM Corp., Armonk, N.Y., USA) package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean, deviation, and minimum-maximum. Pearson's Chi-squared test was used to compare categorical variables. In comparing the continuous measurements between the groups, the distributions were checked and independent student t-test analysis was applied to the binary variables. Cox regression was used for multivariate evaluations. Statistical significance level was taken as 0.05 in all tests.

RESULTS

155 patients participated in our study. We found our postoperative mortality rate as 11.6%. Accordingly, Group 1 consisted of 18 and Group 2 consisted of 137 patients. In the groups, male sex was dominant (55.6% and 67.2%, respectively) and the groups were similar (p: 0.235). The average age was higher in Group 1 than 2 (71.2 vs 63.7, p: 0.013). Presence of comorbid disease was similar (44 vs 46%, p:0.390). The most common ASA score was ASA 2 in Group 1 (55.6%) and ASA 1 in Group 2 (46%) (p:0.425).

Table 1. Characteristics of patients

	Group 1 (n:18) n(%)	Group 2 (n:137) n(%)	p
Sex			
Male	10 (55.6)	92 (67.2)	0.236
Female	8 (44.4)	45 (32.8)	
Age	71.27±16.25 (22-93)	63.79±11.18 (22-91)	**0.013**
Additional disease			
Absent	10 (55.6)	67 (48.9)	0.390
Present	8 (44.4)	63 (46.0)	
ASA Score			
1	6 (33.3)	63 (46.0)	0.425
2	10 (55.6)	54 (39.4)	
3	2 (11.1)	20 (14.6)	
Tumor localization			
Ampulla	9 (50.0)	55 (40.1)	0.275
Duodenum	1 (5.6)	1 (0.7)	
Ductus choledochus	2 (11.1)	23 (16.8)	
Pancreas	6 (33.3)	58 (42.3)	

ASA American Society of Anesthesiologists

Tumor placement was most commonly in the ampulla in Group 1 (50%), and pancreas in Group 2 (42.3%), and localizations were similar in groups (p: 0.275). The demographic and clinical characteristics of the patients are shown in Table 1.

Preoperative white blood cell count (9490 mm^3 vs 8050 mm^3) and neutrophil count (6898 mm^3 vs 5442 mm^3) were higher in Group 1. Lymphocyte count (p:0.702), platelet count (p:0.106), hemoglobin level (p:0.238), albumin level (p:0.754), total bilirubin (p:0.363), CEA level (p:0.790), and Ca 19.9 level (p:0.673) were similar between the groups. Laboratory parameters are shown in Table 2.

Table 2. Laboratory parameters

	Group 1 (n:18) Mean±sd (min-max)	Group 2 (n:137) Mean±sd (min-max)	p
WBC mm^3	9499.44±3937.32 (5000-18390)	8050.43±2650.35 (1430-18000)	**0.042**
Neutrophil mm^3	6898.88±3605.57 (3130-15000)	5442.71±2318.17 (840-12650)	**0.021**
Lymphocyte mm^3	1646.11±576.22 (710-2700)	1716.27±746.92 (460-4630)	0.702
Platelet mm^3	334.72±158.28 (159-690)	292.75±938.57 (92-608)	0.106
Hemoglobin gr/dl	13.05±2.03 (9.8-17.7)	12.50±1.79 (7.4-16.7)	0.238
Albumin gr/dl	3.47±0.66 (2.3-4.6)	3.53±0.71 (1.4-4.9)	0.754
Total bilirubin mg / dL	4.42±5.57 (0.2-20)	5.99±7.01 (0.1-34)	0.363
Preoperative CEA ng/ml.	5.26±11.87 (0.01-52.2)	4.52±11.02 (0-87.4)	0.790
Preoperative Ca 19.9 U/ml	735.5±1042.96 (2-3166)	585.23±1455.75 (1-9683)	0.673

WBC-White Blood Cell

Both groups mostly had poorly differentiated tumors (38.9% vs 53.3%, p: 0.208). T2 stage (50%) was more common in Group 1, and T3 stage (50.4%) was more common in Group 2 (p: 0.657). Lymph node positivity was similar in the groups (50% vs 41.6%, p: 0.333). The number of dissected and metastatic lymph nodes were similar in the groups (9.1 vs 10.64, p: 0.330) and (1.27 vs 0.99, p: 0.528), respectively. Tumor diameters were similar (2.41 cm vs 2.26 cm, p: 0.600). Postoperative complication rates were similar (33% vs 28.5%, p: 0.428). The presence of pancreatic fistula was higher in Group 1, but not statistically significant (33% vs 18.2%, p: 0.119). Tumor characteristics and postoperative follow-up results are shown in Table 3.

Table 3. Characteristics of tumor and postoperative outcomes

	Group 1 (n:18) n (%)	Group 2 (n:137) n (%)	p
Differentiation			
Well	7 (38.9)	28 (20.4)	0.208
Moderate	4 (22.2)	36 (26.3)	
Poor	7 (38.9)	73 (53.3)	
T			
T1	2 (11.1)	12 (8.8)	0.657
T2	9 (50.0)	56 (40.9)	
T3	7 (38.9)	69 (50.4)	
N			
N0	9 (50.0)	80 (58.4)	0.333
N1	9 (50.0)	57 (41.6)	
Number of total dissected lymph nodes (min-max)	9.1±5.18 (2-26)	10.64±6.35 (1-42)	0.330
Metastatic lymph node number (min-max)	1.27±2.21 (0.0-8.0)	0.99±1.73 (0-11)	0.528
Lymph node positivity			
Negative	9 (50.0)	80 (58.4)	0.333
Positive	9 (50.0)	57 (41.6)	
Tumor diameter	2.41±1.30 (0.7-5.0)	2.26±1.15 (0.4-6.5)	0.600
Postoperative complication			
Present	6 (33.3)	39 (28.5)	0.428
Absent	12 (66.7)	98 (71.5)	
Pancreatic Fistula			
Present	6 (33.3)	25 (18.2)	0.119
Absent	12 (66.7)	112 (81.8)	

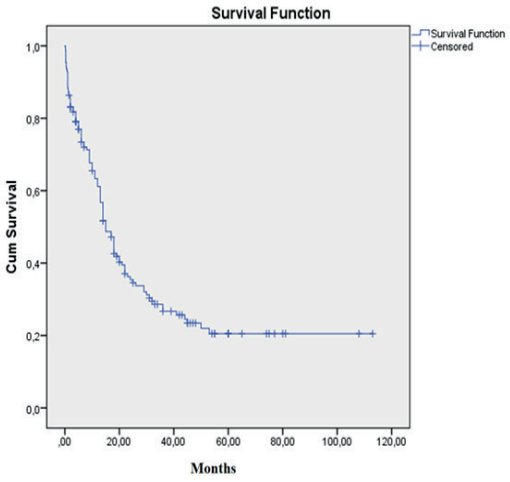

Figure 1. Overall survey graphics

The mean survival was 34.97±3.73 (27.65-42.30) months it is shown in Table 4 and Figure 1.

Table 4. Overall survival time (monhts)

Average Mean ± sd (min-max)	Median Mean ± sd (min-max)
34.97±3.73 (27.65-42.30)	15.0±1.48 (12.08-17.91)

None of the parameters evaluated in univariate and multivariate analyzes were independent risk factors for mortality. It is shown in Table 5.

Table 5. Univariate and multivariate analysis of factors associated with postoperative 30-day mortality in periampullary tumors

Measurements	Univariate	Multivariate	
	P	HR (95% - CI)	p
Age Group			
< 65	0.068	1.00	0.084
> 65		2.482 (0.885-6.964)	
Sex			
Male	0.382	1.00	0.377
Female		1.520 (0.600-3.852)	
Localization			
Ampulla	0.503	1.00	0.405
Duodenum		3.321 (0.421-26.213)	0.255
Ductus choledochus		0.561 (0.121-2.594)	0.459
Pancreas		0.641 (0.228-1.800)	0.398
Differentiation			
Poor	0.462	1.00	0.233
Moderate		1.236 (0.978-1.625)	0.355
Well		1.345 (0.811-1.435)	0.442
T			
T1	0.663	1.00	0.669
T2		0.918 (0.198-4.248)	0.913
T3		0.606 (0.126-2.918)	0.532
N			
N0	0.549	1.00	0.549
N1		1.327 (0.527-3.343)	
Postoperative complication			
Yes	0.709	1.00	0.706
No		0.828 (0.311-2.207)	
ASA score			
1	0.397	1.00	0.399
2		1.924 (0.699-5.293)	0.205
3		1.049 (0.212-5.196)	0.954
Tumor diameter			
Below 2	0.888	1.00	0.887
2 and over		0.934 (0.362-2.409)	
WBC			
Below 10	0.267	1.00	0.243
10 and over		1.849 (0.659-5.186)	
Neutrophil			
Below 7	0.197	1.00	0.177
7 and over		1.963 (0.737-5.231)	
Hemoglobin			
Below 12	0.133	1.00	0.159
12 and over		2.221 (0.731-6.748)	
Albumin			
Below 3.5	0.626	1.00	0.626
3.5 and over		0.795 (0.315-2.002)	
Bilirubin			
Below 5	0.389	1.00	0.398
5 and over		0.655 (0.246-1.747)	
Pancreatic fistula			
No	0.190	1.00	0.170
Yes		1.986 (0.745-5.291)	
Ca19.9			
Below 100	0.657	1.00	0.658
100 and over		1.234 (0.487-3.126)	

None of the parameters evaluated in univariate and multivariate analyzes were independent risk factors for mortality. It is shown in Table 5.

DISCUSSION

PD is the only valid curative treatment of periampullary region tumors (14). The biggest problems in PD surgery are the complexity of the surgical procedure and the high morbidity and mortality rates due to the operation. In the 1970s, postoperative hospital mortality was reported to be over 25% in many series (15,16). Today, this rate has decreased dramatically in postoperative hospital mortality and is reported between 2.8% and 8.1% (4-8). We found this rate as 11.6% in our series.

In the modern era, significant advances in diagnostic methods, patient selection, post-operative care, and many aspects of experience gained in pancreatic surgery have contributed significantly to the dramatic increase in the reliability of this surgery.

Early postoperative mortality, which is the evaluation of the first 30 days reported by ACS-NSQIP, is an important parameter in determining the quality of pancreatic surgery (17).

In the studies in the literature, they are united in the opinion that an increase in the hospital volume decreases mortality and morbidity (7,18,19). However, in contrast to these views, in a study by Nathan et al. in 2009, they concluded that the effect of the surgeon's patient volume was not significant (20). The effect of hospital volume on surgical outcomes has attracted the attention of surgeons, and in a study by Sosa et al., hospitals were divided into 3 groups based on the number of pancreatic resections performed each year, these were low scale (<5 procedures / year), medium scale (5-19 procedures / year) and high scale (> 20 procedures / year). In this study, hospital mortality was reported as 18.8% for low-scale hospitals, 6.9% for medium-scale hospitals and 0.9% for high-scale hospitals (20). According to NCCN 2016, a high-volume center is described as a center where PD was performed over 20 cases per year (22). In their analysis, Macedo, F. I. B et al. found that the surgeon's annual number of

cases would also affect the results, and showed that the results of the surgeon with more than 6 cases per year were better (23). According to this definition, our hospital is in the middle-scale class with an annual number of 17.2 PD performed. Although our mortality rate seems to be high for a medium-scale hospital, we have seen that our mortality rates have decreased in our cohort in recent years. In a complex surgery such as PD, experienced selection, preoperative patient evaluation, technical skills and postoperative patient care are also important in the performing center. In the literature, one reason for the reduction of mortality and morbidity in high-volume hospitals is that complication management is performed more effectively in these centers (24).

Understanding the relationship between age and complications is important for counseling patients. However, it remained unclear whether there was an age value at which the risk of complications increased significantly. In the series of Yuan, F et al, pancreaticoduodenectomy after age 72 was found to be associated with longer hospital stay and higher costs related to more postoperative complications and deaths (25). McMillan M. T et al. found an age of 85 and over to be a strong independent risk factor for postoperative mortality (OR (95% CI) 7.0 (1.2–42.5), p: 0.033) (26). In the group developing mortality in the Greenblatt, D. Y. et al series, the average age was 5 years higher (68.7 vs 63.9, p: 0.001) and an age above 80 was independent risk factor in their studies (26). In our series, the mean age was higher in patients with mortality, similar to the literature (71.27 vs 63.79, p: 0.013). When we formed groups based on the age 65, being over 65 was not an independent risk factor.

Pancreatic cancers are the most common among periampullary tumors. In a study of 207 patients by Pomianowska et al., the frequency of pancreatic carcinoma was 33%, of ampulla vateri carcinoma was 25%, of distal choledochal carcinoma was 28% and of duodenum carcinoma was 14% (28). In our series, it was most frequently seen with pancreas and ampulla. Tumor localization was not associated with postoperative mortality in our series.

Routine preoperative laboratory tests can assist surgeons in identifying patients at high risk of morbidity and mortality after pancreaticoduodenectomy. The importance of preoperative albumin, bilirubin, hemoglobin and white blood cells have been proven in many studies (8,23,29,30). Although serum albumin level may also be affected by acute factors such as trauma and surgical stress, it is associated with postoperative bad results as a marker of disease and malnutrition (31). In their cohort, Gleeson, E. M et al. found an albumin value below 3.5 g / dl [OR (95% CI) 1.80 (1.36–2.37) p <.001] as an independent risk factor for post-PD mortality (29). Kimura W et al found in their 8575-case series that serum albumin levels <2.5 g / dL were associated with postoperative 30-day mortality and in-hospital mortality (4).

Leukocytosis is a nonspecific marker for the systemic inflammatory condition. While systemic inflammation is a protective response in the body, it is associated with humoral and cellular components that result in vascular injury and ultimate organ dysfunction. Surgical trauma inflammation worsens the situation in patients with pre-existing systemic inflammatory conditions associated with adverse outcomes (32,33). Kimura W et al. found that white blood cell counts above 11,000 / μL were associated with postoperative 30-day mortality and in-hospital mortality (4). While albumin levels were similar in our series, the number of white cells and neutrophils were higher in the group with mortality. When we analyzed these parameters in multivariate analysis, they were not independent risk factors.

Our study has some limitations. Deficiencies during follow-up and observation and it being a retrospective analysis are important limitations. With prospective randomized studies to be conducted with larger series, it will be possible to obtain more clear and definitive results and make guiding suggestions for the future.

LIMITATIONS

Our study has some limitations. Deficiencies during follow-up and observation and it being a retrospective analysis are important limitations. With prospective randomized studies to be conducted with larger series, it will be possible to obtain more clear and definitive results and make guiding suggestions for the future.

CONCLUSION

In conclusion, an increase in the number of white blood cells before the operation and age was associated with mortality in our study. Knowing the preventable factors before or after the operation will help us prevent a possible mortality.

Conflict of interest: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the ethics committee of Erciyes University with protocol number 2020/575.

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