Original Article

Iraqi National Journal of Medicine. Jan. 2022; Vol. 4, Issue 1

Perioperative Risk Factors & Outcome After Pancreatico-Duodenectomy (Whipple Procedure)

Mustafa M. Fakhir [1], Issam Mardan [2], Ali Dawood [3]

[1] M.B.Ch.B. Board Candidate.

[2] MBChB; FIBMS; CABS, Professor of Surgery, Department of Surgery, College of Medicine, University of Basrah.

[3] MD; FRCS; FACS, Consultant of General & Gastrointestinal & Hepatobiliary Surgery, Al-Sader Teaching Hospital/Basrah.

ABSTRACT

Background: Periampullary cancers have poor prognosis, mainly due to late diagnosis. Although pancreaticoduodenectomy is considered the only possible curative option for these cancers, it is associated with high morbidity and mortality.

Aim: To identify the risk factors associated with postoperative morbidity and mortality.

Patients and Methods: Data were prospectively collected from the 44 patients who underwent pancreaticoduodenectomy for periampullary cancers in Al-Sader Teaching Hospital, Basrah, Iraq, from June 2017 to June 2020. These variables were reviewed according to developing postoperative morbidity and mortality. The statistical analysis was done using SPSS version 23 and the chi-squared or Fisher's exact (FE) test. Any level of significance below 0.05 was considered statistically significant.

Results: Increased age and the presence of preoperative co-morbidities are independent predictors of developing postoperative morbidity and mortality. The most common postoperative complications leading to mortality are pulmonary embolisms and pancreatic leaks.

Conclusion: Improvement in the management of comorbidities and perioperative care are essential in decreasing postoperative morbidity and mortality.

Keywords: Pancreatico-Duodenectomy, Whipple Procedure, Periampullary cancers

Corresponding author: *Issam Mardan email issam.alnajjar@yahoo.com*

Disclaimer: *The authors have no conflict of interest.*

DOI: https://doi.org/10.37319/iqnjm.4.1.8

Received: 18 Jul 2021 ***Accepted: 16 Sep 2021*** ***Published online: 15 Jan 2021***

INTRODUCTION

Pancreatic cancer is the fourth cause of cancer death in both males and females;[1] it has the worst prognosis among all other malignancies, with a 5-year survival rate of approximately 6%.[2] This incidence increases with age, as approximately 80% of patients are over the age of 60.[3]

Other periampullary cancers (which include distal cholangiocarcinoma, duodenal carcinoma and ampullary cancer) have a slightly better prognosis than pancreatic head cancer. Although this maybe because they cause early bile duct obstruction and jaundice, leading to an earlier diagnosis.[4]

Pancreaticoduodenectomy (Whipple procedure) was and still the only possible curative option for patients with periampullary tumors.[5,6] Moreover, although the postoperative median survival rate is only about 22 months, it is considered the best possible palliative modality that offers some survival improvement.[7]

Other modalities of treatment such as radiotherapy and chemotherapy are associated with worse long-term prognosis and higher morbidity and mortality.[8-10]

Although recent advancements in surgical techniques and increased surgical knowledge have reduced mortality after pancreaticoduodenectomy,[11-13] it remains high compared to other GIT operations.[8] Also, despite the decrease in mortality in the last two decades, morbidity is still high.[14]

The mortality rate in high volume centers (where individual surgeons perform more than 15 cases yearly) is about 5%.[15]

Many important variables contribute to the outcome of this operation, based on patient's general health, experience of surgeons and the volume of complex operations done by the surgeon.[16,17]

Better patient's selection decreases postoperative morbidity and mortality,[18] while increased age and poor general health have a negative impact on postoperative outcome.[19,20] Since these tumors are mostly diagnosed in older people, who already have other comorbidities, this further contributes to the high morbidity and mortality.[21]

The current test of choice for diagnosis and staging of periampullary tumors is dynamic contrast enhanced computed tomography scanning, with a sensitivity of 90–95% for predicting unresectability. However, it is less accurate in predicting resectability unless combined with other tests like MRI, EUS and diagnostic laparoscopy.[22]

The first step of a pancreaticoduodenectomy is inspection and assessment for resectability, followed by resection and then reconstruction.[23]

The most common complication of this operation is pancreatic leakage and subsequent intra-abdominal abscess and sepsis that may require re-laparotomy;[24] but this is usually managed conservatively with prolonged drainage.[25,26]

Other possible complications include early hemorrhage[13,21] and delayed gastric emptying.[27]

The most common causes of postoperative mortality are sepsis, hemorrhage and cardiopulmonary events.[28]

AIM

The aim of this study is to identify the perioperative risk factors that affect morbidity and mortality after pancreaticoduodenectomy for malignant periampullary tumors.

MATERIALS & METHODS

This prospective study was conducted at Al-Sader Teaching Hospital, Department of General Surgery, in Basrah, Iraq. The study period was 3 years, from June 2017 to June 2020.

Patients included in this study are those who underwent Whipple procedure for malignant periampullary tumors (which include pancreatic head cancer, duodenal cancer, distal cholangiocarcinoma, and ampullary cancer) by the same surgical team.

Patients who were operated on for benign lesions as provided by histopathological report and patients who were found to have unresectable tumor intraoperatively were excluded from the study.

All data were collected from preoperative assessment and postoperative follow-up during hospitalization and after discharge for up to 6 months, through the patients' visit to the surgical ward, outpatient clinics or private clinics.

Preoperative characteristics were reviewed regarding age, sex, presence of co-morbidity and the reason for operation (tumor type). Co-morbidities were classified as cardiopulmonary diseases, hypertension, diabetes and smoking.

Preoperative workup for all patients includes a thorough history and physical examination. Laboratory tests include complete blood picture (CBP), renal function test (RFT), serum electrolytes, liver function test (LFT), bleeding profile and virology. All patients underwent an abdominal ultrasound and computed tomography scan, while endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP) and esophagogastroduodenoscopy (EGD) were used in select cases.

Informed consent was taken from all patients. All patients received perioperative prophylactic antibiotics (third generation cephalosporin one hour before incision) and antithrombotic prophylaxis.

All operations were done in the open method and under general anesthesia, with the patient in supine position. A Foley catheter and NG tube were inserted after induction of anesthesia. The operative approach was a midline incision. After confirming resectability, classic Whipple resection was performed (en bloc removal of the distal stomach, duodenum, proximal jejunum, pancreatic head, common bile duct and gall bladder and lymph nodes dissection).

Pancreaticoenteric reconstruction was performed by end-to-side, duct-to-mucosa anastomosis using 4/0 monofilament absorbable suture. Bilioenteric anastomosis was performed with an interrupted 3/0 or 4/0 polyfilament absorbable suture. Gastrojejunostomy was done either by conventional hand sewn method or stapled anastomosis. Right subhepatic and pelvic drains were inserted in all patients. The operative time ranged from 3.5 to 5 hours.

All resected specimens were sent for histopathological examination.

Most patients were discharged within 7 days postoperatively, when there was no or mild postoperative complications. The longest hospital stay was 35 days, and some patients required readmission.

Histopathological findings include tumor differentiation and the presence or absence of lymph nodes involvement.

Postoperative (surgical and non-surgical) complications were analyzed and causes of postoperative mortality were specified.

All data were analyzed using SPSS version 23. To test for the difference and/ or associations, the chi-squared or Fisher's exact (FE) test were used. Any level of significance below 0.05 was considered statistically significant.

RESULTS

The study included 44 patients (24 males and 20 females), with their ages ranging from 42 to 72 years (and a mean of 62 years), 16 patients had preoperative a co-morbidity, of which 4 had more than one co-morbidity. All patients underwent Whipple operation, which was performed by the same surgical team.

The indication for the operation was pancreatic head cancer in (13) patients, cholangiocarcinoma in (12) patients, cancer of the ampulla of Vater in (11) patients and duodenal cancer in (8) patients (Table 1).

Table 1: Demographic and other characteristics of the patients.

Variables		Total cases = 44
Sex	Male	24 (54.5%)
	Female	20 (45.5%)
Age	≤ 60 years	16 (36.4%)
	> 60 years	28 (63.6%)
Co-morbidity	Yes	16 (36.4%)
	No	28 (63.6%)
Reason for operation	Duodenal cancer	8 (18.2%)
	Distal cholangiocarcinoma	12 (27.3%)
	Ampullary cancer	11 (25.0%)
	Pancreatic head cancer	13 (29.5%)

The presenting symptoms were jaundice in (25) patients, weight loss in (6) patients, abdominal pain in (6) patients, upper gastrointestinal bleeding in (5) patients and poor appetite in (2) patients (Table 2).

Table 2: The presenting symptoms of the patients.

Presenting symptom	Percentage
Jaundice	25 (56.8%)
Weight loss	6 (13.6%)
Abdominal pain	6 (13.6%)
Upper gastrointestinal bleeding	5 (11.4%)
Poor appetite	2 (4.6%)

Histopathological reports showed that (13) patients had a poorly differentiated tumor, while (31) patients had a well-differentiated tumor. Additionally, (9) patients had positive lymph nodes, while (35) patients showed no lymph nodes involvement (Table 3).

Table 3: Histopathological findings of the tumors.

Variables		Total cases = 44
Tumor Grade	Poorly Differentiated	13 (29.5%)
	Well-Differentiated	31 (70.5%)
Lymph Nodes Involvement	Yes	9 (20.5%)
	No	35 (79.5%)

The most frequent postoperative complication was pancreatic leakage in (7) patients; 3 of them died due to sepsis, while the other 4 were improved by conservative management. The next most frequent complication was superficial surgical site infection in (6) patients. Other complications included pulmonary embolism in (5) patients (4 of whom died), heavy bleeding requiring transfusion in (4) patients, delayed gastric emptying in (4) patients, deep vein thrombosis in (3) patients, bile leakage in (2) patients (one died due to sepsis and the other one was managed conservatively), acute respiratory distress syndrome in (2) patients, intra-abdominal collection in (2) patients, myocardial infarction in (1) patient (died after 3 days) and wound disruption due to leakage from the gastrojejunal anastomosis in (1) patient, which required re-operation but resulted in the patient dying from sepsis (Table 4).

Table 4: The frequency of postoperative complications.

Postoperative Complication	Percentage
Pancreatic leak	7 (15.9%)
Superficial surgical site infection	6 (13.6%)
Pulmonary embolism	5 (11.3%)
Bleeding requiring transfusion	4 (9.0%)
Delayed gastric emptying	4 (9.0%)
Deep vein thrombosis	3 (6.8%)
Bile leak	2 (4.5%)
Acute respiratory distress syndrome	2 (4.5%)
Intra-abdominal collection	2 (4.5%)
Wound disruption	1 (2.2%)
Myocardial infarction	1 (2.2%)

The most frequent cause of 30 days mortality was sepsis, followed by pulmonary embolism (Table 5).

Table 5: The frequency of causes of postoperative 30 days mortality.

Cause of Death	Percentage
Sepsis	5 (50.0%)
Pulmonary embolism	4 (40.0%)
Myocardial infarction	1 (10.0%)

Table 6 shows that there is significant association between the occurrence of postoperative morbidity with increased age and the presence of co-morbidities.

Table 6: Comparison of various factors affecting postoperative morbidity.

Variables		Total cases = 44	Cases with no postoperative morbidity = 25	Cases with postoperative morbidity = 19	P-value
Sex	Male	24 (54.5%)	14 (56.0%)	10 (52.6%)	0.82
	Female	20 (45.5%)	11 (44.0%)	9 (47.4%)	
Age	≤ 60 years	16 (36.4%)	13 (52.0%)	3 (15.8%)	0.03
	> 60 years	28 (63.6%)	12 (48.0%)	16 (84.2%)	
Co-morbidity	Yes	16 (36.4%)	2 (8.0%)	14 (73.7%)	0.0001
	No	28 (63.6%)	23 (92.0%)	5 (26.3%)	
Reason for Operation	Duodenal cancer	8 (18.2%)	6 (24.0%)	2 (10.5%)	0.38
	Distal cholangiocarcinoma	12 (27.3%)	8 (32.0%)	4 (21.1%)	
	Ampullary cancer	11 (25.0%)	6 (24.0%)	5 (26.3%)	
	Pancreatic head cancer	13 (29.5%)	5 (20.0%)	8 (42.1%)	
Tumor Grade	Poorly Differentiated	13 (29.5%)	6 (24.0%)	7 (36.8%)	0.35
	Well-Differentiated	31 (70.5%)	19 (76.0%)	12 (63.2%)	

Presence of Lymph Nodes	Yes	9 (20.5%)	3 (12.0%)	6 (31.6%)	0.14
	No	35 (79.5%)	22 (88.0%)	13 (68.4%)	

From Table 7, it is clear that the presence of a co-morbidity is significantly associated with increased mortality.

Table 7: Effect of comorbidity on postoperative mortality.

Variables		Total Cases = 44	Cases with no co-morbidity = 16	Cases with co-morbidity = 28	P-value
Mortality	No	34 (77.3%)	27 (96.4%)	7 (43.7%)	0.001
	Yes	10 (22.7%)	1 (3.6%)	9 (56.3%)	

DISCUSSION

Risk stratification for pancreatic surgeries has gained popularity because of the growing numbers of patient with advanced age and many comorbidities who are requiring pancreatic resection surgeries.[29, 30]

Although the Whipple operation is considered one of the most challenging abdominal operations, it remains the only curative option for periampullary malignancy.[31]

In this study, developing postoperative morbidity was not statistically significant in association with sex distribution (P-value = 0.82), which is similar to a study done in India by Prasad et al.[32]

Regarding age, this study showed that there is significant association between increased age and developing postoperative morbidity (P-value = 0.03), which is similar to a study done by Haigh et al.[33]

The presence of preoperative co-morbidities, be it hypertension, diabetes, cardiac and pulmonary diseases or a history of smoking, were associated with significant morbidity in this study (P-value = 0.0001), which is similar to a study done in India by Madhav et al.[14]

The site of the tumor (pancreatic, duodenal, ampullary or distal common bile duct) had no significant association with developing postoperative morbidity (P-value = 0.38), which is similar to a study done by House et al.[34]

Tumor differentiation was not significantly associated with postoperative morbidity (P-value = 0.35), in contrast to a study done by Ajith Prasad et al., where there was a significant difference in postoperative morbidity with poorly differentiated tumors.[32]

Lymph nodes involvement by histopathological report was not associated with postoperative morbidity (P-value = 0.14), which is similar to a study done by Yeo et al.[35]

The most common postoperative complications in this study were pancreatic leakage (15.9%), superficial surgical site infection (13.6%) and pulmonary embolism (11.3%), which is similar to a study done by Greenblatt et al.,[36] whose frequencies of the above complications were 15.3%, 13.1% and 9.5%, respectively.

The study showed that postoperative mortality was significantly associated with the presence of comorbidity (P-

value = 0.001), which is similar to the study conducted by Greenblatt et al.[36]

When looking to the frequency of causes of postoperative mortality in our study, we found that sepsis is the main cause of death, with 50% of total mortality, which is similar to a study done by Grobmyer et al.[37] On the other hand, the percentage of patients who died due to pulmonary complications was 40%, which is similar to a study by Nagle et al.[38]

CONCLUSION

In this study, increased age and the presence of preoperative co-morbidities are strong independent predictors of developing postoperative morbidity and mortality after Whipple procedure.

Improvement in the management of comorbidities and perioperative complications are essential for improving the outcome of this operation.

Larger multi-centric study is recommended to achieve larger sample size.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics 2008. CA: Cancer J Clin. 2008;58:71-96.
2. Seigel R, Naishadham D, Jemal A. Cancer Statistics 2012. CA: Cancer J Clin. 2012;62:10-29.
3. Shaib YH, Davila JA, El-Serag HB. The Epidemiology of Pancreatic Cancer in the United States: Changes below the Surface. Aliment Pharmacol Ther. 2006;24(1):87-94.
4. Wilentz RE, Hruban RH. Pathology of Cancer of the Pancreas. Surg Oncol Clin N Am. 1998;7:43-65.
5. Aoki S, Miyata H, Konno H, et al. Risk Factor of Serious Postoperative Complications After Pancreaticoduodenectomy and Risk Calculators for Predicting Postoperative Complications: A National Study of 17,564 Patients in Japan. J Hepatobiliary Pancreat Sci. 2017 May;24(5):243-251.
6. Vin Y, Sima CS, Getrajdman GI. Management and Outcomes of Post-pancreatectomy Fistula, Leak and Abscess: Result of 908 Patients Resected at a Single Institution Between 2000 and 2005. J Am Coll Surg. 2008 Oct;207(4):490-8.
7. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative Neoadjuvant Therapy in Pancreatic Cancer: A Systematic Review and Meta-analysis of Response and Resection Percentages. PLoS Med. 2010 Apr 20;7(4):e1000267.
8. Glazer, E., Amini, A., Jie, T., et al. Recognition of Complications After Pancreaticoduodenectomy for Cancer Determines Inpatient Mortality. J Pancreas. 2013 Nov;14(6):626-631.
9. Winter JM, Cameron JL, Campbell KA, et al. 1423 Pancreaticoduodenectomies for Pancreatic Cancer: A Single Institution Experience. J Gastrointest Surg. 2006 Nov;10(9):1199-210.
10. M Squadroni, N Fazio. Chemotherapy in Pancreatic Adenocarcinoma. Eur Rev Med Pharmacol Sci. 2010 Apr;14(4):386-94.
11. Wiltberger G, Muhl B, Benzing C, et al. Preoperative Risk Stratification for Major Complications Following Pancreaticoduodenectomy: Identification of High Risk Patients. Int J Surg. 2016 Jul;31:33-9.
12. Wiltberger G, Krenzien F, Benzing C, et al. Prognostic Accuracy of the Seventh Edition of the TMN Classification Compared with the Fifth and Sixth Edition for Distal Cholangiocarcinoma. Ann Surg Oncol. 2016;23(4):1320-1326.
13. Schmidt CM, Turrini O, Parikh P, et al. Effect of Hospital Volume, Surgeon Experience, and Surgeon Volume on Patient Outcomes after Pancreaticoduodenectomy: A Single Institution Experience. Arch Surg. 2010;145(7):634-40.
14. Thumma VM, Gunturi SR, Kishore N, et al. Assessment of Risk Factor for Complications

after Pancreatic Surgery. Int J Surg Sci. 2019;3(4):92-99.
15. Birkmeyer JD, Finlayson SR, Tosteson AN, et al. Effect of Hospital Volume on In-hospital Mortality with Pancreaticoduodenectomy. Surgery. 1999;125:250.
16. de Wilde RF, Besselink MG, van der Tweel I, et al. Impact of Nationwide Centralization of Pancreaticoduodenectomy on Hospital Mortality. Br J Surg. 2010 Mar;99(3):404-10.
17. Pecorelli N, Balzano G, Capretti G, et al. Effect of Surgeon Volume on Outcome Following Pancreaticoduodenectomy in a High-volume Hospital. J Gastrointest Surg. 2012 Mar;16(3):518-23.
18. Potrc S, Ivanecz A, Pivec V, et al. Impact Factor for Preoperative Morbidity and Mortality and Repercussion of Perioperative Morbidity and Long term Survival in Pancreatic Head Resection. Radiol Oncol. 2018 Mar;52(1):54-64.
19. Ho CK, Kleeff J, Friess H, et al. Complications of Pancreatic Surgery. Hepatobiliary Journal. 2005 Feb;7(2):99-108.
20. Terhune K., Merchant N.B., Parikh A.A. (2008) Complications of Pancreaticoduodenectomy. In: Lowy A.M., Leach S.D., Philip P.A. (eds) Pancreatic Cancer. M. D. Anderson Solid Tumor Oncology Series. Springer, Boston, MA.
21. Venkat R, Puhan MA, Schulick RD, et al. Predicting the Risk of Perioperative Mortality in Patients Undergoing Pancreaticoduodenectomy. Arch Surg. 2011;146(11):1277-1284.
22. Squillaci E, Fanucco E, Scuito F. Vascular Involvement in Pancreatic Neoplasm: A Comparison between Spiral CT and DSA. Dig Dis Sci. 2003;48:449-458.
23. Bachellier P, Nakano H, Oussoultzoglou PD, et al. Is Pancreaticoduodenectomy with ZMesentericoportal Venous Resection Safe and Worthwhile? Am J Surg. 2001;182:120-129.
24. Aroori S, Puneet P, Bramhall SR, et al. Outcomes Comparing a Pancreaticogastrostomy (PG) and a Pancreaticojejunostomy (PJ) After a Pancreaticoduodenectomy (PD). HPB (Oxford). 2011 Oct;13(10):723-731.
25. Fisher WE, Hodges SE, Silbefein EJ, et al. Pancreatic Resection Without Routine Intraperitoneal Drainage. HPB (Oxford). 2011 July;13(7):503-510.
26. Kazanjian KK, Hines OJ, Eibl G, et al. Management of Pancreatic Fistulas After Pancreaticoduodenectomy: Results in 437 Consecutive Patients. Arch Surg. 2005;140:849-856.
27. Wente MN, Bassi C, Dervenis C, et al. Delayed Gastric Emptying (DGE) After Pancreatic Surgery: A Suggested Definition By the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007 Nov;142(5):761-8.
28. Gordon TA, Bowman HM, Tielsch JM, et al. Statewide Regionalization of Pancreaticoduodenectomy and its Effect on In-hospital Mortality. Ann Surg. 1998;228:71-78.
29. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. Biometrika. 1994;81(3):515-526.
30. de la Fuente SG, Bennett KM, Pappas TN, et al. Pre- and Intra-operative Variable Affecting Early Outcomes in Elderly Patients Undergoing Pancreaticoduodenectomy. HPB (Oxford). 2001;13(12):887-892.
31. Braga M, Capretti G, Picorelli N, et al. A Prognostic Score to Predict Major Complication After Pancreaticoduodenectomy. Ann Surg. 2011;254(5):702-708.
32. Prasad AJ, Kumar SV. Postoperative Morbidity Following Whipple Procedure for Periampullary Carcinoma: A Retrospective Study Spanning 5 Years. Int J Res Med Sci. 2019 Nov;7(11):4314-4319.
33. Haigh PI, Bilimoria KY, DiFronzo LA. Early Postoperative Outcomes After Pancreaticoduodenectomy in the Elderly. Arch Surg. 2011;146(6):715-723.
34. House MG, Fong Y, Arnaoutakis DJ, et al. Preoperative Predictors for Complications after Pancreaticoduodenectomy. J Gastrointest Surg. 2008;12(2):270-278.

35. Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy With or Without Extended Retroperitoneal Lymphadenectomy for Periampullary Adenocarcinoma. Ann Surg. 1999 May;229(5):613.
36. Greenblatt DY, Kelly KJ, Rajamanickam V, et al. Preoperative Factors Predict Perioperative Morbidity and Mortality After Pancreaticoduodenectomy. Ann Surg Oncol. 2011 Aug;18(8):2126-2135.
37. Grobmyer SR, Pieracci FM, Allen PJ, et al. Defining Morbidity After Pancreaticoduodenectomy: Use of A Prospective Complication Grading System. J Am Coll Surg. 2007 Mar 1;204(3):356-64.
38. Nagle RT, Leiby BE, Lavu H, et al. Pneumonia is Associated with a High Risk of Mortality After Pancreaticoduodenectomy. Surgery. 2017 Apr 1;161(4):959-67.