Clinical Research

Validation of simplified predictive score for postoperative mortality after pancreaticoduodenectomy

Adianto Nugroho, Toar J.M. Lalisang

Department of Surgery, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Abstrak

Latar belakang: *Pankreatikoduodenektomi sejak lama dihubungkan dengan angka morbiditas dan mortalitas yang tinggi. Kunci keberhasilan pasca operasi adalah pemilihan pasien yang baik. Tujuan penelitian ini adalah menyusun sistem skoring preoperatif untuk memprediksi mortalitas pasca pankreatikoduodenektomi.*

Metode: *Dilakukan identifikasi pasien yang menjalani pankreatikoduodenektomi elektif antara tahun 1995 - 2012 dari database Divisi Bedah Digestif. Analisis bivariat dan multivariat regresi logistik dilakukan untuk prediksi morbiditas dan mortalitas. Estimasi kurva ROC digunakan untuk menentukan nilai potong skor prediktif.*

Hasil: *Dari 138 pasien yang menjalani pankreatikoduodenektomi, 27 pasien (19,6%) meninggal. Faktor prediktor mortalitas adalah bilirubin total serum ≥ 10 mg/dL, kreatinin serum ≥ 1,3 mg/dL, hematokrit ≤ 30%, albumin serum ≤ 3,0 g/dL dan status ASA ≥ 3, masing-masing dengan skor 1, 1, 2, 1, 1. Nilai potong adalah 4 dengan sensitivitas 96% dan spesifisitas 91%. Area di bawah kurva ROC adalah 0,974 (SE 0,011; p < 0,001), yang menunjukkan nilai prediksi yang baik untuk penskoran.*

Kesimpulan: *Skor total 4 atau lebih berhubungan dengan meningkatnya mortalitas pasca pankreatikoduodenektomi.*

Abstract

Background: Pancreaticoduodenectomy has long been associated with high rates of morbidity and mortality. The key to a better postoperative outcome is a good patient selection. The aim of this study was to develop a simplified preoperative predictive score for postoperative mortality after pancreaticoduodenectomy.

Methods: Patients who underwent elective pancreaticoduodenectomy from 1995 to 2012 were identified from the Division of Digestive Surgery database. Bivariate analysis and multivariate logistic regression analysis identified prediction of morbidity and mortality. ROC curve estimation is use to determined the cut-off value of the predictive score.

Results: Of 138 patients who underwent pancreaticoduodenectomy, 27 patients (19.6%) died. The predictor of mortality are serum total bilirubin ≥ 10 mg/dL, serum creatinin ≥ 1.3 mg/dL, hematocrit ≤ 30%, serum albumin ≤ 3.0 g/dL and ASA status ≥ 3, with assign score 1, 1, 2, 1, 1, respectively. The cut-off value was 4 with 96% sensitivity and 91% specificity. The area under the receiver operator characteristic curve was 0.974 (SE 0.011; p < 0.001), which demonstrated a reasonable predictive value for the score.

Conclusion: A total score of 4 or more is associated with increased postoperative mortality in patients underwent pancreaticoduodenectomy.

Keywords: mortality, pancreaticoduodenectomy, predictive score

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Correspondence author: Adianto Nugroho, adiyusuf97@gmail.com

Surgical resection offers the only curative therapy for pancreatic cancer, only if the disease is limited and no vascular encasement or metastases are presence. A recent study by Hoem, et al in 2012 reported a 2 years and 5 years survival after R0 resection of 34.6% and 11.8%, respectively.[1]

However, the morbidity of pancreatic surgery remains high, and the mortality may be significantly increased in high risk patients. Impaired liver functions as a consequence of severe obstructive jaundice found in periampullary malignancies,[2] together with the complexity of Whipple's operations (including its modification, pyloric preserving pancreatico duodenectomy (PPPD)) increase the perioperative risk of mortality and morbidity.[3]

Several risk prediction score have been developed and widely used around the world.[3-5] Multiple factors have been found to influence survival after pancreaticoduodenectomy, including both patient-specific and hospital-level factors, from which the scoring systems were constructed. But each scoring system often adheres to the local condition where it was developed and was not suitable to be directly implemented in other centers.

Using our own database of pancreaticoduodenectomy for periampullary malignancies, we sought to develop and validate a simplified risk prediction score that could be applied for patients under consideration of pancreaticoduodenectomy in centers with minimal resources.

METHODS

We did a prognostic study of patients underwent pancreaticoduodenectomy for periampullary malignancies from 1995 to 2012 in Cipto Mangunkusumo Hospital, Universitas Indonesia. Data were collected from medical records. Database management ensured patient anonymity and confidentiality.

All data were entered into an SPSS for Mac spreadsheet (Version 20.0). Bivariate analysis was then performed on all potential variables in order to select predictors of postoperative mortality at 30 days. The variables considered were based upon factors highlighted as significant in previously published research. The included variables were: age, sex, tumor locations, malignancy status, American Society of Anesthesiologists (ASA) status, serum hemoglobin, hematocrit, white blood cell (WBC) counts, serum total bilirubin, serum albumin, serum alkaline phosphatase (ALP), serum alanine transaminase (ALT), and serum creatinine.

A multivariate logistic regression analysis was then applied to the data to construct the score. Variables identified from the bivariate analysis as potential predictors were included in the multivariate analysis. The p-value for entry into the model was less than 0.25. Postoperative mortality at 30 days after pancreaticoduodenectomy was entered as the dependent variable and the independent predictor variables were entered as covariates. The final coefficients produced were then altered by rounding to integer values to create a more easily applicable, and clinically usable, scoring system.

The performance of the score was assessed using the data within the validation set. Goodness of fit of the score to the data was assessed using the Hosmer - Lemeshow statistic. A lack of difference between the predicted and the observed deaths indicates good concordance of the score. Sensitivity analysis was performed using standard receiver operating characteristic (ROC) curves. Cut-off value was then defined using the sensitivity-specificity table and graphics.

RESULTS

Of 138 patients who underwent pancreaticoduodenectomy between 1995 to 2012, 35 (25.4%) suffered a serious complication and 27 (19.6%) died. The characteristics of risk factors for perioperative mortality are shown in table 1.

The variables analyzed as predictors of perioperative mortality on bivariate analysis are shown in table 2. Those variables which were significant predictors ($p < 0.25$) were then included in the multivariate analysis.

The following variables were found to be independent predictors of perioperative mortality on multivariate logistic regression analysis with backward method: total serum bilirubin $\geq$ 10 mg/dL, serum creatinin $\geq$ 1.3 mg/dL, hematocrit $\leq$ 30%, serum albumin $\leq$ 3.0 g/dL and ASA status $\geq$ 3. (Table 3).

The predictive score was produced by dividing the value of B with S.E., followed by dividing the coefficients (B/S.E.) with the smallest integer value (B = 1.99). The score are shown in table 4, with total score ranging from 0 to 6 points.

Table 1. Characteristics of risk factors for perioperative mortality after pancreaticoduodenectomy (n = 138)

Risk factors	n	%	Risk factors	n	%
Sex			Hematocrit		
Male	73	52.9	≤ 30 %	40	29.0
Female	65	47.1	> 30%	98	71.0
Tumor Location			WBC		
Pancreas	65	47.1	< 10,000/uL	43	31.2
Duodenum, Papila of Vater	73	52.9	≥ 10,000 /uL	95	68.8
Malignancy			Albumin		
Yes	127	92.0	< 3 g/dL	43	31.2
No	11	8.0	≥ 3 g/dL	95	68.8
Age			Total Bilirubin		
< 60 years	115	83.3	< 10 mg/dL	71	51.4
≥ 60 years	23	16.7	≥ 10 mg/dL	67	48.6
ASA			ALP		
1	11	8.0	< 200 IU	13	9.4
2	40	29.0	≥ 200 IU	125	90.6
3	77	55.8	Creatinine		
4	10	7.2	< 1.3 mg/dL	122	88.4
Hemoglobin			≥ 1.3 mg/dL	16	11.6
≤ 11 g/dL	73	52.9	ALT		
> 11 g/dL	65	47.1	< 35 IU	112	81.2
			≥ 35 IU	26	18.8

ASA: American Society of Anesthesiologists, WBC: White blood cell, ALP: Alkaline phosphatase, ALT: Alanine transaminase

Table 2. Bivariate analysis of risk factors for perioperative mortality after pancreaticoduodenectomy (n = 138)

		Perioperative mortality	RR	95% CI	p
Sex	Male	16 (21.9%)	1.30	0.65-2.58	0.460
Tumor location	Pancreas	14 (21.5%)	1.21	0.61-2.38	0.581
Malignancy	Yes	25 (19.7%)	1.08	0.29-3.98	1.000
Age	≥ 60 years	7 (30.4%)	1.75	0.84-3.65	0.158
ASA	3-4	24 (27.6%)	4.69	1.49-14.80	0.002*
Hemoglobin	≤ 11 g/dL	17 (23.3%)	1.51	0.75-3.07	0.243
Hematocrit	≤ 30 %	26 (65.0%)	63.70	8.94-453.67	< 0.001*
WBC	≥ 10,000 /uL	26 (27.4%)	11.7	1.65-83.93	< 0.001
Albumin	≤ 3 g/dL	18 (41.9%)	4.42	2.16-9.03	< 0.001*
Total bilirubin	≥ 10 mg/dL	23 (34.3%)	6.09	2.22-16.70	< 0.001*
ALP	≥ 200 IU	26 (20.8%)	2.70	0.40-18.33	0.463
Creatinine	≥ 1.3 mg/dL	13 (81.2%)	7.08	4.10-12.23	< 0.001†
ALT	≥ 35 IU	7 (26.9%)	1.51	0.71-3.18	0.294

p < 0.05 is considered significant, *Chi-Square test, †Fisher's exact test, ASA: American Society of Anesthesiologists, WBC: White blood cell, ALP: Alkaline phosphatase, ALT: Alanine transaminase

The ROC curve is shown in figure 1. A perfect test would produce a right angle with an AUC of 1. The AUC for the predictive score for perioperative mortality after pancreaticoduodenectomy is 0.974 (SE 0.011; p < 0.001). The cut-off value of 4 produces a sensitivity of 96% and a specificity of 91% to predict perioperative mortality after pancreaticoduodenectomy (Figure 2 and Table 5). Pitt's score with cut-off value of 5 produces a sensitivity of 96% and specificity of 83%, with AUC 0.949 (SE 0.018; p < 0.001).

Table 3. Multivariate logistic regression analysis of risk factors for perioperative mortality after pancreaticoduodenectomy (n = 138)

	B	S.E.	Wald	df	p
Total bilirubin ≥ 10 mg/dL	3.48	1.594	4.77	1	0.029
Hematocrit ≤ 30%	4.672	1.277	13.393	1	< 0.001
Albumin ≤ 3.0 g/dL	2.291	1.152	3.957	1	0.047
ASA ≥ 3	3.37	1.379	5.97	1	0.015
Creatinin ≥ 1.3 mg/dL	4.066	1.535	7.021	1	0.008
Constant	-11.234	3.278	11.744	1	0.001

ASA: American Society of Anesthesiologists

Table 4. Assignment of score

	B/S.E.	Score	
Total bilirubin ≥10 mg/dL	2.18	1.10	1
Hematocrit ≤ 30%	3.66	1.84	2
Albumin ≤ 3.0 g/dL	1.99	1.00	1
ASA ≥ 3	2.44	1.23	1
Creatinin ≥1.3 mg/dL	2.65	1.33	1
Constant	-3.43	-1.72	

ASA: American Society of Anesthesiologists

Table 5. Sensitivity and specificity of the predictive score for perioperative mortality after pancreaticoduodenectomy

No	Score	Sensitivity	Specificity
1	-1	1.00	0.00
2	0.5	1.00	0.24
3	1.5	1.00	0.54
4	2.5	1.00	0.85
5	**3.5**	**0.96**	**0.91**
6	4.5	0.56	0.99
7	5.5	0.30	1.00
8	7	0.00	1.00

The Hosmer-Lemeshow goodness of fit statistic for each decile of risk showed that there was good concordance between observed and predicted perioperative mortality (X^2 test, p = 0.987), compare to the original Pitt's score Hosmer-Lemeshow goodness of fit statistics (X^2 test, p = 0.833).

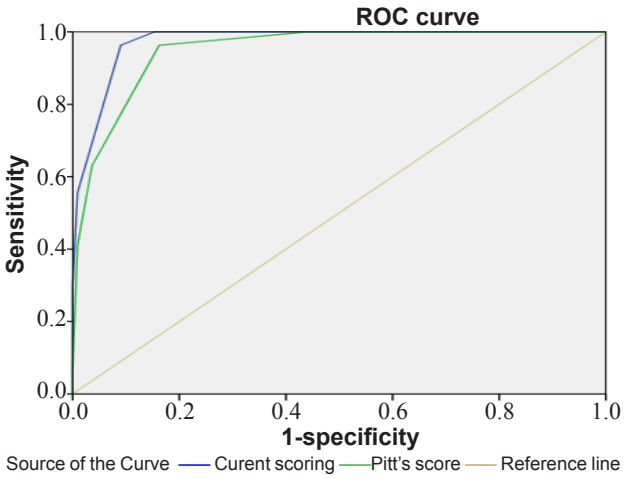

Figure 1. Receiver operating characteristic curve for perioperative mortality after pancreaticoduodenectomy (AUC 0.974; SE 0.011; p < 0.001) as compared to Pitt's Score (AUC 0.949; SE 0.018; p < 0.001)

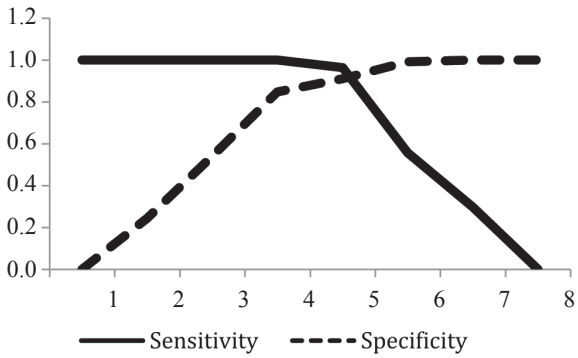

Figure 2. Cut-off value produce by sensitivity and specificity graphs, showing point 5, correspond to sum score of more than 3.5 (see Table 5)

DISCUSSION

Periampullary cancer are malignant tumor arise within 2 cm of the ampulla in the duodenum and include pancreatic head cancer, lower common bile duct cancer, ampullary cancer, and periampullary duodenal cancer.[6] It is the third most frequent gastrointestinal tumors following gastric and colorectal cancers.[7] These tumors exhibit similar symptoms, with obstructive jaundice being the most common presentation.

Surgical resection offers the only survival benefit for periampullary cancers, but is generally limited to a localized disease.[1,8] Presence of vascular encasement and extra-pancreatic spreads of disease are generally contraindicated for resection.[9] In such cases, either endoscopic palliation or double bypass surgery is indicated for a better quality of life.[10,11]

Impairment of liver functions in obstructive jaundice patients often leads to a catastrophic coagulation disorders, hepato-renal syndrome and severe biliary infections which endanger a major surgical procedures.[2,5] A preoperative biliary drainage has been used to relieve the jaundice and is beneficial to reduced postoperative morbidity and mortality when performed selectively in patients with signs of infection and possible delayed definitive surgery.[2,12,13]

Although obstructive jaundice contributes to the increase of perioperative mortality, we cannot rely solely to the degree of obstructive jaundice alone, because other factors are involved, such as age and sex of the patients, extent and complexity of surgery, and the biology of the tumor itself.

Accurate assessment of risk may affect how we as surgeons manage their patients. It allows surgeons to have informed discussions with patients and relatives about the likely outcome, and enables rational decisions before the conduct of such complex procedures like pancreaticoduodenectomy. It serves as part of a personalized patient assessment and clinical judgment.

Pitt, et al has pioneered the study of risk factors for perioperative mortality in obstructive jaundice patients in early 1980s.[5] Pitt's score is the sum of 8 variables, each scored 1 when positive, including Age ≥ 60 years old, malignancy, Total Serum Bilirubin ≥ 10 mg/dL, White blood cell count ≥ 10,000/uL, Hematocrit ≤ 30%, Albumin ≤ 3 g/dL, Alkaline Phosphatase (ALP) ≥ 200 IU, and Creatinin ≥ 1.3 mg/dL. Total score of 5, 6, > 7 are associated with mortality rate 44%, 67% and 100%, respectively.

Since then, many authors have also published their works in this field, including the development of risk prediction score.[3,4,14,15] But the available scoring systems are often failed to answer the local problems because it was tightly adhered to the conditions where it was developed. Many variables included in the scoring were not readily available in centers with limited resources.

Using retrospectively gathered data, we have developed a simplified risk scoring system to predict postoperative mortality after pancreaticoduodenectomy. For a scoring system to be clinically useful, it should accommodates readily available and verifiable clinical information. In this study, risk predictive scoring system was developed using our own database of patients underwent pancreaticoduodenectomy for periampullary tumors. This ensures that every variable included in this scoring system is similar to what we encounter in every day practices, which will give an added value to the scoring system.

Bivariate analysis revealed that ASA status of 3 or more, hematocrit ≤ 30%, WBC count ≥ 10,000 /uL, serum creatinine ≥ 1.3 mg/dL, total bilirubin ≥ 10 mg/dL, serum albumin ≤ 3.0 g/dL are significantly associated with increased perioperative mortality ($p < 0.05$). This 6 variables, together with age ≥ 60 years and ALT ≥ 35 IU ($p < 0.25$) were included in the multivariate regression analysis.

This finding are consistent with the study by Pitt, et al except for the exclusion of serum ALP level and malignant origin of disease which was appear to be a positive predictive variables in Pitt's score.[5] The small number of total samples and also discrepancy between benign and malignant cases in our study seems to be the reason behind the difference.

From multivariate analysis we learned that only five out of eight variables are significantly associated with postoperative mortality. ASA status, hematocrit, total bilirubin, serum albumin and serum creatinin were all have significant level below 0.05 and were further analyzed for the creation of the scoring system. After dividing the coefficient with the smallest integer, we assign scores for serum total bilirubin ≥ 10 mg/dL, serum creatinin ≥ 1.5 mg/dL, hematocrit ≤ 30%, serum albumin < 3.0 g/dL and ASA status ≥ 3, as follow 1, 1, 2, 1, 1, respectively. The total score varies from 0 to 6 points, with cut-off value 4. Using this cut-off value, we can expect a 96% sensitivity and 91% specificity. The perfect test cut-off would have perfect sensitivity (ruling out all of those who will survive) and perfect specificity (ruling in only those who are to die). The area under the receiver operator characteristic curve was 0.974 ($p < 0.001$), which demonstrated a reasonable predictive value for the score.

Our study addressed the high mortality rate as a clinical problem in our center, which already improved with a careful patient selection and a good perioperative management. Since the data was retrospectively gathered from our own database, we are confidence that it was similar to our daily clinical practice and the outcome should be able to be well implemented. Moreover, the scoring system includes modifiable risk factors as variables (bilirubin,

creatinin, hematocrit, albumin and ASA status), allowing perioperative support for a better outcome. The limitations of this study were its retrospective nature and a relatively small sample size for a prognostic modeling.

In conclusion, we have developed and validated a simplified multi-factorial scoring system to predict postoperative mortality risk after pancreaticoduodenectomy, with the cut-off value of 4 from a total score of 6. We plan to implement this scoring system to our daily services. We believe that this scoring system will be of use for surgeons in the field of HPB surgery as part of a personalized patient assessment and clinical judgment.

Conflict of interest

The authors hereby affirm that there is no conflict of interest in this study.

REFERENCES

1. Hoem D, Viste A. Improving survival following surgery for pancreatic ductal adenocarcinoma: A ten-year experience. Eur J Surg Oncol. 2012;38(3):245-51.
2. Lalisang T, Suryaatmadja M. Serum bile acid: an alternative liver function marker in the obstructive jaundice patient. Acta Med Indones. 2012;44(3):233-8.
3. Parikh P, Shiloach M, Cohen ME, Bilimoria KY, Ko CY, Hall BL, et al. Pancreatectomy risk calculator: an ACS-NSQIP resource. HPB (Oxford). 2010;12(7):488-97.
4. Ragulin-Coyne E, Carroll JE, Smith JK, Witkowski ER, Ng SC, Shah SA, et al. Perioperative mortality after pancreatectomy: A risk score to aid decision-making. Surgery. 2012;152(3 Suppl 1):S120-7.
5. Pitt HA, Cameron JL, Postier RG, Gadacz TR. Factors affecting mortality in biliary tract surgery. Am J Surg. 1981;141(1):66-72.
6. Sugita R, Furuta A, Ito K, Fujita N, Ichinohasama R, Takahashi S. Periampullary tumors: high spatial resolution imaging and histopathologic findings in ampullary region specimens. Radiology. 2004;231(3):767-74.
7. Coppola R, Riccioni ME, Ciletti S, Cosentino L, Ripetti V, Magistrelli P, et al. Periampullary tumors: analysis of 319 consecutive cases submitted to preoperative endoscopic biliary drainage. Surg Endosc. 2001;15(10):1135-9.
8. Hatzaras I, George N, Muscarella P, Melvin WS, Ellison EC, Bloomston M. Predictors of survival in periampullary cancers following pancreaticoduodenectomy. Ann Surg Oncol. 2010;17(4):991-7.
9. Kennedy E, Yeo C. Pancreatic cancer: clinical aspects, assessment, and management. In: Jarnagin W, Belghiti J, Buchler M, Chapman W, D'Angelica M, DeMatteo R, et al., editors. Blumgart's Surgery of the liver biliary tract and pancreas. Philadelphia: Elsevier; 2012. p. 919-25.
10. Nieveen van Dijkum EJ, Kuhlmann KF, Terwee CB, Obertop H, de Haes JC, Gouma DJ. Quality of life after curative or palliative surgical treatment of pancreatic and periampullary carcinoma. Br J Surg. 2005;92(4):471-7.
11. Gillen S, Schuster T, Friess H, Kleef J. Palliative resections versus palliative bypass procedures in pancreatic cancer--a systematic review. Am J Surg. 2012;203(4):496-502.
12. Korontzi MI, Kontovounisios Ch, Karaliotas CC, Armoutithes V, Lanitis S, Sgourakis G, et al. Preoperative biliary drainage: a routine or selective strategy in jaundiced patients with pancreatic cancer? Hellenic Journal of Surgery. 2012;84(2):120-7.
13. Lalisang T, Sjamsuhidajat R, Siregar NC, Taher A. Profile of hepatocyte apoptosis and bile lakes before and after bile duct decompression in severe obstructive jaundice patients. Hepatobiliary Pancreat Dis Int. 2010;9(5):520-3.
14. Venkat R, Puhan MA, Schulick RD, Cameron JL, Eckhauser FE, Choti MA, et al. Predicting the risk of perioperative mortality in patients undergoing pancreaticoduodenectomy. Arch Surg. 2011;146(11):1277-84.
15. JS Hill, Z Zhoi, JP Simons, SC Ng, TP McDade, GF Whalen, et al. A simple risk score to predict in-hospital mortality after pancreatic resection for cancer. Ann Surg Oncol. 2010;17:1802-7.