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A novel preoperative scoring system to predict postoperative mortality after pancreaticoduodenectomy in pancreatic cancer patients at Dr. Soetomo General Hospital: a retrospective cohort study

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ABSTRACT

Introduction: Knowing the risk of surgery before performing one is essential for informed consent and decisions making for the doctors, patients, and their families. Complexities of surgery and pancreatic cancer aggressiveness are two factors that contribute to high mortality rate in pancreaticoduodenectomy. There has been a few scoring systems developed to predict mortality after pancreaticoduodenectomy. However, external validation of these scoring systems failed to achieve good predictive value consistently. This could happen due to differences in patient demographics, variables and their cut-off, patient samples, and hospital or health care standard where these scoring systems were constructed. This study aims to develop a novel scoring system to predict postoperative mortality and to compare its performance with the existing scoring systems.

Methods: Data were collected retrospectively from all patients who underwent pancreaticoduodenectomy in Dr. Soetomo General Hospital, starting from January 2012 to October 2022. 75 patients were included based on the inclusion criteria. Multivariate logistic regression analysis was performed to select multiple risk factors correlated with in-house mortality. A novel scoring system was formed using these risk factors. We also assessed and compared the predictive value of the existing scores (Parikh, Nugroho, and WHipple-ABACUS) using the ROC curve. Chi square test with odds ratio calculation and logistic regression were used in this study.

Results: Post pancreaticoduodenectomy mortality rate was 28% (21 out of 75 patients) with 4 statistically significant risk factors. Those factors are age > 52 years. (OR 7.435; 95% CI 1.113-49.677, $p = 0.038$), comorbidities (OR 5.793; 95% CI 1.116-30.067, $p = 0.037$), American Society of Anaesthesiology (ASA) 3 (OR 8.932; 95% CI 1.329-60.022, $p = 0.024$), and total bilirubin > 16.6 mg/dL (OR 8.329; 95% CI 1.577-43.983, p = 0,013). These factors were used to form a novel scoring system. The predictive performance of the newly created scoring system was 0.911 (95% CI 0.823-0.965). While external validation of the existing scoring systems was as follows: Parikh 0.684 (95% CI 0.567-9.787), Nugroho 0.829 (95% CI 0.724-0.906), and WHipple-ABACUS 0.736 (95% CI 0.62-0.832).

Conclusion: The newly created scoring system uses 4 relatively easy and accessible preoperative variables to predict post-pancreaticoduodenectomy mortality. However, it still requires external validation in multicenter hospitals with large numbers of patients.

Keywords: Pancreatic cancer, pancreaticoduodenectomy, in-house mortality, mortality predictive factors.
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INTRODUCTION

Pancreatic cancer is now the fourth cause of all cancer-related death in the United States and seventh in the world.[1] Surgical resection is the only curative treatment for non-metastatic resectable pancreatic cancer. As one of the surgical procedures, pancreaticoduodenectomy still carries high morbidity and mortality, especially if it's performed in low volume center hospital with total procedure less than 9 a year.[2] Mortality rate after pancreaticoduodenectomy is estimated around 1-5% in high-volume center hospitals.[3] In high-risk patients, mortality rate is significantly increased.[1,2] Therefore, preoperative risk assessment is mandatory since it helps predict surgery's outcome.

Several preoperative scoring systems have been developed to help predict postoperative mortality following pancreaticoduodenectomy, such as Parikh score, Nugroho score, and WHipple-

ABACUS score.[4–6] However, these scores consistently failed to achieve good predictive value. This could happen due to differences in patient demographics, variables and their cut-off, patient samples, and hospital or health care standard where these scoring systems were constructed.

Using our own set data on patients with pancreatic cancer undergoing pancreaticoduodenectomy, we sought to construct a novel preoperative scoring system that can help predict the outcome of surgery and applicable in low-volume center hospitals.

METHODS

This was an analytic observational study with retrospective cohort design. Data were collected retrospectively from medical records of all patients who underwent pancreaticoduodenectomy in Dr. Soetomo General Hospital, starting from January 2012 to October 2022. Inclusion criteria were patient undergo pancreatoduodenectomy, with mortality or survive outcome during the study period.

All data were entered into SPSS v23.0 for Windows. Dichotomies of independent variables with no clear cut-off value such as age, hematocrit, total bilirubin, creatinine, albumin, and aspartate aminotransferase were performed using ROC curve analysis to earn new cut-off values that significantly affect in-house mortality.

Bivariate analysis with chi square test and odds ratio calculation was performed to identify all variables that contribute to in-house mortality. From bivariate analysis, eight variables were statistically significant. Those variables were age, comorbidities, hematocrit, total bilirubin, creatinine serum, albumin, American Society of Anesthesiologists (ASA) status, and preoperative systemic inflammatory response syndrome (SIRS).

Multivariate logistic regression analysis using Backward Stepwise (Wald) method was performed to all statistically significant variables from the bivariate analysis (p-value<0.25) with in-house mortality as the dependent variable. Four variables were acquired and will be used to construct a new novel scoring system. The goodness of fit Hosmer-Lemeshow test was performed to this model. The probability score was counted by adding Constanta to each variable based on the difference in regression coefficient. Each variable was assigned with a score earned from the calculation based on Exp score from the multivariate analysis. Cut-off value from the new scoring system was performed using ROC curve analysis.

Table 1. ROC curve analysis to earn new cut-off value to all independent variables with no clear cut-off value.

Variables	Cut-off value	AUC	95% CI
Age	> 52 th	0.695	0.579-0.796
Hematocrit	≤ 30.1%	0.703	0.587-0.803
Total bilirubin	> 16.6 mg/dL	0.715	0.599-0.813
Creatinine serum	> 0.9 mg/dL	0.555	0.435-0.670
Albumin	≤ 2.64g/dL	0.738	0.623-0.833
AST	>135 U/L	0.502	0.384-0.619

Table 2. Characteristics of risk factors for in-house mortality following pancreaticoduodenectomy (n=75).

Variables	n	%
Sex		
- Male	35	46.7
- Female	40	53.3
Age		
- ≤52 years	33	44
- >52 years	42	56
Body mass index (BMI)		
- <18.5 kg/m^2	7	9.3
- 18.5-24.9 kg/m^2	66	88
- 25-29.9 kg/m^2	2	2.7
Comorbidities		
- No	56	74.7
- Yes	19	25.3
Hematocrit		
- ≤30.1%	24	32
- > 30.1%	51	68
Total bilirubin		
- > 16.6 mg/dL	23	30.7
- ≤16.6 mg/dL	52	69.3
Creatinine serum		
- > 0.9 mg/dL	15	20
- ≤ 0.9 mg/dL	60	80
Albumin		
- ≤ 2.64 g/dL	18	24
- > 2.64 g/dL	57	76
AST		
- > 135 U/L	10	13.3
- ≤ 135 U/L	65	86.7
ASA status		
- 2	15	20
- 3	60	80
Bleeding disorder (International Normalized Ratio / INR)		
- < 1.5	68	90.7
- ≥ 1.5	7	9.3
Disseminated cancer		
- No	70	93.3
- Yes	5	6.7
Preoperative SIRS		
- No	61	81.3
- Yes	14	18.7

Table 3. Bivariate chi square analysis of risk factors for in-house mortality following pancreaticoduodenectomy.

Variables	N	Outcome		OR (95% CI)	*p*
		Survive 54 (72%)	In-house mortality 21 (28%)		
Sex					
- Female	40	27 (67.5%)	13 (32.5%)	1	0.503
- Male	35	27 (77.1%)	8 (22.9%)	0.62 (0.220-1.723)	
Age					
- ≤ 52 years	33	30 (90.9%)	3 (9.1%)	1	0.003*
- > 52 years	42	24 (57.1%)	18 (42.9%)	7.50 (1.974-28.498)	
BMI					
- <18,5 kg/m^2	7	5 (71.4%)	2 (28.6%)	-	0.779
- 18,5-24,9 kg/m^2	66	48 (72.7%)	18 (27.3%)	-	
- 25-29.9 kg/m^2	2	1 (50%)	1 (50%)	-	
Comorbidites					
- No	56	48 (85.7%)	8 (14.3%)	1	<0.001*
- Yes	19	6 (31.6%)	13 (68.4%)	13.00 (3.826-44,17)	
Hematocrit					
- > 30,1%	51	43 (84.3%)	8 (15.7%)	1	0.001*
- ≤ 30,1%	24	11 (45.8%)	13 (54.2%)	6,35 (2.11-19.12)	
Total bilirubin					
- ≤ 16.6 mg/dL	52	45 (86.5%)	7 (13.5%)	1	<0.001*
- > 16,6 mg/dL	23	9 (39.1%)	14 (60.9%)	10 (3.149-31.759)	
Creatinine serum					
- ≤ 0,9 mg/dL	58	47 (81%)	11 (19%)	1	0.004*
- > 0,9 mg/dL	17	7 (41,2%)	10 (58.8%)	6.1 (1.899-19.625)	
Albumin					
- > 2,64 g/dL	57	47 (82.5%)	10 (17.5%)	1	0.001*
- ≤ 2,64 g/dL	18	7 (38.9%)	11 (61.1%)	7.39 (2.297-23.746)	
AST					
- ≤135 U/L	65	45 (69.2%)	20 (30.8%)	1	0.266
- > 135 U/L	10	9 (90%)	1 (10%)	0.25 (0.03-2.108)	
ASA status					
- 2	60	52 (86.7%)	8 (13.3%)	1	<0.001*
- 3	15	2 (13.3%)	13 (86.7%)	42,25 (7.99-223.19)	
Bleeding disorder (INR)					
- < 1,5	68	50 (73.5%)	18 (26.5%)	1	0.392
- ≥ 1,5	7	4 (57.1%)	3 (42.9%)	2.08 (0.424-10.226)	
Disseminated Cancer					
- No	70	51 (72,9%)	19 (27,1%)		0.615
- Yes	5	3 (60%)	2 (40%)	1.79 (0.277-11.554)	
Preoperative SIRS					
- No	61	48 (78.7%)	13 (21.3%)	1	0.017*
- Yes	14	6 (42.9%)	8 (57.1%)	4.92 (1.449-16.727)	

RESULTS

The in-house mortality rate after pancreaticoduodenectomy in Dr. Soetomo General Hospital between January 2012-October 2022 was 28% (21 out of 75). New cut-off value that was analyzed for variables with no clear cut-off value previously are shown in table 1. The characteristics of risk factors for in-house mortality are shown in table 2. Bivariate analyses are shown in table 3. Variables with p-value <0,25 were then included in the multivariate analysis.

The following variables were statistically significant predictors of in-house mortality on multivariate logistic regression analysis with Wald method: ASA ≥ 3, total bilirubin ≥ 16,6 mg/dL, age > 52 years old, and comorbidities. These are shown in table 4.

Each variable was then with a score earned from the calculation based on Exp value from the multivariate analysis. The calculation of score number are shown in table 5. The final score are shown in table 6.

The ROC curve for this scoring system is shown in figure 1. A value of 1 for area under the curve (AUC) level indicates the perfect model. The AUC of this scoring system was 0,911 (95% CI 0,823-0,965, p < 0,001). The cut-off value of this scoring systems was >4. Sensitivity was 81% and specificity was 88,9% (Figure 1). External validation of the existing scoring systems is shown in table 7.

DISCUSSION

Surgical resection is the only curative treatment for non-metastatic resectable

Table 4. Logistic regression model for score formulation.

Variable	B	S.E	Wald	df	p	Exp B	CI 95%
Age> 54 year	2.006	0.969	4.286	1	0.038	7.435	1.11-49.6
Comodbidities	1.757	0.840	4.371	1	0.037	5.793	1.16-30.06
ASA status	2.190	0.972	5.075	1	0.024	8.932	1.32-43.98
Bilirubin total	2.120	0.849	6.234	1	0.013	8.329	1.57-43.98

Table 5. Calculations of score number for each risk factors based on Exp score.

Score number	Lower limit	Upper limit
1	5.793	6.578
2	>6.578	7.363
3	>7,363	8.147
4	>8,147	8.932

Table 6. Final scoring system with score number based on Exp score from multivariate analysis.

Variables	EXP value	Point
ASA status ≥ 3	8.932	4
Total bilirubin > 16,6 mg/dL	8.329	4
Age > 52 years	7.435	3
Comorbidities	5.793	1
Total		**12**

Table 7. External validation of the existing scoring systems.

Scoring systems	AUC	95% CI	Sensitivity	Specificity
Parikh	0.684	0.567-0.787	47.62%	87.04%
Nugroho	0.829	0.724-0.906	76.19%	83.02%
Whipple-ABACUS	0.736	0.62-0.832	76.19%	62.26%
New scoring system	0.911	0.823-0.965	81%	88.9%

pancreatic cancer. As one of the surgical techniques, pancreaticoduodenectomy still carries high morbidity and mortality. Post pancreaticoduodenectomy morbidity is still as high as 30-60% with in-house mortality rate as high as 1-5% (4.2% in Netherlands and 2.5-5.9% in Japan).[6,7] While in Indonesia, mortality following pancreaticoduodenectomy was 19.6% based on a study conducted in Jakarta and 28% based on our study.

Aside from technical factor, few conditions surrounding pancreatic cancer patients could worsen the outcome of surgery. Liver dysfunction due to chronic jaundice could lead to multiple complications. High-risk patients increase mortality rate following surgery.[7]

An accurate assessment of multiple risk factors that might contribute to surgery's outcome is essential before performing one. This will help surgeons with informed consent and patients decide on surgery.

A scoring system is a method that can be used to assess high-risk patients. There are currently a few scoring systems with preoperative risk factors to predict mortality rates following pancreaticoduodenectomy. However, these scoring systems failed to achieve good predictive value consistently. Each of these scoring systems has different risk factors, different cut-off values for every risk factor, and some risk factors may rarely be found in pancreatic cancer patients in our center.[4–6] We retrospectively gathered data in our center to develop a novel scoring system to predict mortality following pancreaticoduodenectomy.

The bivariate analysis concluded that eight variables were statistically significant risk factors to mortality following pancreaticoduodenectomy. Those variables were as follows: age > 52 years, comorbidities, hematocrit ≤ 30.1%, total bilirubin > 16.6 mg/dL, creatinine serum > 0.9 mg/dL, albumin ≤ 2.64 g/dL, American Society of Anesthesiologist (ASA) status ≥ 3, and preoperative systemic inflammatory response syndrome (SIRS). All these variables were included in multivariate logistic regression analysis.

The multivariate analysis concluded that only four factors were statistically significant risk factors to mortality following pancreaticoduodenectomy. Those variables were age > 52 years, comorbidities, total bilirubin > 16.6 mg/dL, and ASA status ≥ 3. Each variable was assigned to a score based on Exp value from the multivariate analysis. The final scoring system had a total score of 12, with cut-off value > 4. The final scoring system produced an AUC level of 0.911 with sensitivity 81% and specificity 88.9%.

Compared with worldwide data, mortality in our center is relatively high. This could happen due to the fact that our center is a low volume center hospital with total pancreaticoduodenectomy cases less than 9 per year. Panni et al. stated that odd ratio of mortality following pancreaticoduodenectomy in hospital with total case between 9-35 were 0.647 (95% CI 0.595-0.702, p<0.0001) and in hospital with total case more than 35/year were 0.458 (95% CI 0.399-0.525, p<0.0001).[8]

Our study's cut-off value for age was relatively young compared to worldwide data. This could happen due to differences in life expectancy. Based on WHO, Indonesia's life expectancy from 2010-2022 are 69-72.14 years, while in the US, Germany, Italy, and Japan, life expectancy from 2010-2022 is between 79-84 years.[9] Besides life expectancy, age differences existed when diagnosis was made. In Indonesia, the average age of people diagnosed with pancreatic cancer is 55 years. In the US, Italy, and Japan, the average age was above 65 years.[5,8,10–13]

Comorbidities, mainly diabetes mellitus, heart and lung disease, increased the mortality rate following

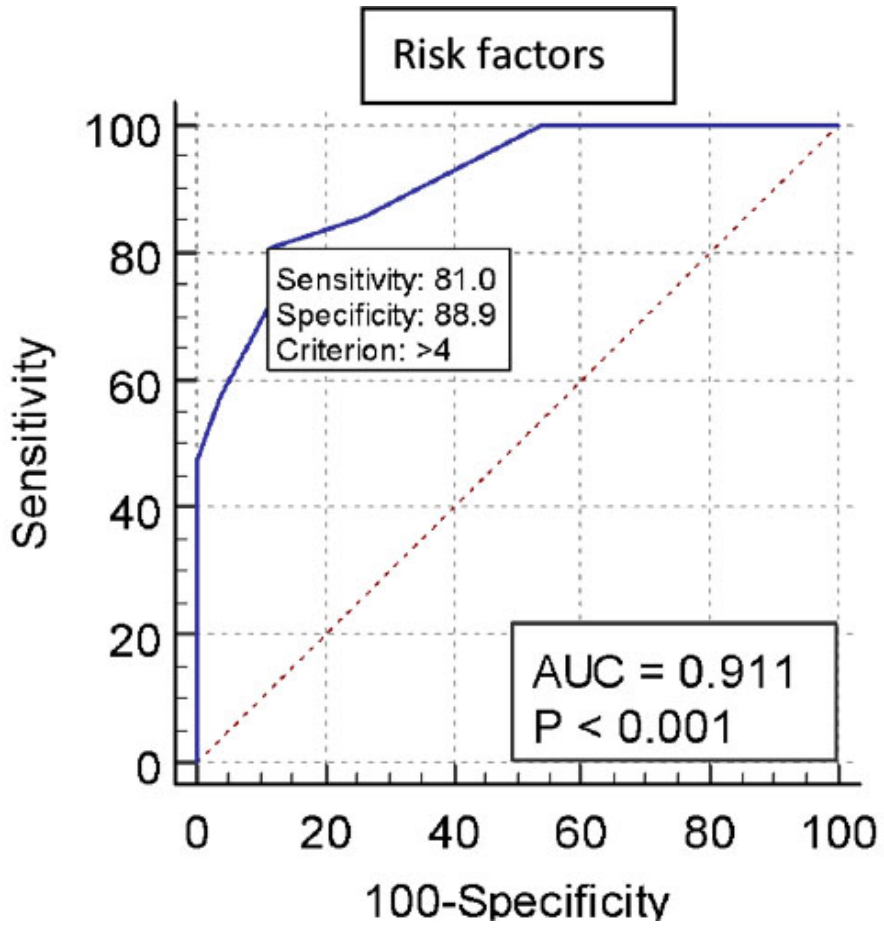

Figure 1. ROC curve for the new scoring system.

pancreaticoduodenectomy in our study. This could happen to oxidative stress and pro-inflammatory cytokine that was released following major trauma. In the case of major and complex surgery such as pancreaticoduodenectomy, comorbidities would decrease recovery and rehabilitation following surgery, further increasing poor outcomes.[14–16]

ASA status was also a significant factor in our study. ASA status reflects functional status. Higher ASA status reflects poorer functional status. Poor functional status was associated with the body's inability to recover optimally.[17]

Hyperbilirubinemia is the most common symptom in pancreatic cancer, and it was a significant factor for in-house mortality following pancreaticoduodenectomy in our study. Progressive hyperbilirubinemia could increase the risk of cholangitis, endotoxemia, liver failure, renal dysfunction, coagulopathy, organ failure, sepsis, and death. Therefore, preoperative biliary drainage could be considered in patients with comorbidities and liver impairment due to hyperbilirubinemia, especially in patients with bilirubin levels> 15 mg/dL. The goal was to optimize patient's condition before proceeding to surgery.[18–21]

CONCLUSION

Using four relatively easy variables, we have developed a novel scoring system to predict mortality rate following pancreaticoduodenectomy accurately. However, because this study was conducted in a low volume center hospital with a small number of patients, we believe an external validation is required before implementation in daily practice.

CONFLICT OF INTEREST

No conflict of interest.

FUNDING

None.

ETHICAL CONSIDERATION

Ethical Committee Faculty of Medicine have approved this study, Universitas Airlangga with ethicalclearance reference number 1085/LOE/301.4.2/X/2022.

AUTHOR CONTRIBUTION

All authors have been contributed for manuscript writing and agreed for the final version of the manuscript for publication.

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