Correlation of serum albumin and prognostic nutritional index with outcomes following pancreaticoduodenectomy

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Abstract

BACKGROUND
Pancreaticoduodenectomy (PD) is a complex surgical procedure with a high morbidity rate. The serious complications are major risk factors for poor long-term surgical outcome. Studies have reported an association between early postoperative prognostic nutritional index (PNI) and prediction of severe complications after abdominal surgery. However, there have been no studies on the use of early postoperative PNI for predicting serious complications following PD.

AIM
To analyze the risk factors and early postoperative PNI for predicting severe complications following PD.

METHODS
We retrospectively analyzed 238 patients who underwent PD at our hospital between January 2007 and December 2017. The postoperative complications were classified according to the Dindo-Clavien classification. Grade III-V postoperative complications were classified as serious. The risk factors for serious complications were analyzed by univariate analysis and multivariate logistic regression analysis.

RESULTS
Overall complications were detected in 157 of 238 patients (65.9%) who underwent PD. The grade III-V complication rate was 26.47% (63/238 patients). The mortality rate was 3.7% (9/238 patients). Multivariate logistic regression analysis revealed that preoperative serum albumin [odds ratio (OR): 0.883, 95% confidence interval (CI): 0.80-0.96; *P* < 0.01] and PNI on postoperative day 3 <

40.5 (OR: 2.77, 95%CI: 1.21-6.38, $P < 0.05$) were independent factors associated with grade III-V postoperative complications.

CONCLUSION
Perioperative albumin is an important factor associated with serious complications following PD. Low early postoperative PNI (< 40.5) is a predictor for serious complications.

Key words: Postoperative complications; Pancreatectomy; Serum albumin; Risk factors; Prognostic nutritional index

Core tip: Pancreaticoduodenectomy (PD) is a complex surgical procedure with a high morbidity rate. The serious complications are major risk factors for poor long-term surgical outcome. Studies have reported an association between early postoperative prognostic nutritional index (PNI) and prediction of severe complications after abdominal surgery. However, there have been no studies on the use of early postoperative PNI for predicting serious complications following PD. We retrospectively analyzed 238 patients who underwent PD at our hospital. The independent factors associated with serious postoperative complications following PD were preoperative serum albumin and PNI on postoperative day 3 of < 40.5. Thus, patients who undergo PD and have early postoperative low PNI should be monitored closely.

INTRODUCTION

The standard treatment for periampullary tumor is pancreaticoduodenectomy (PD)[1]. PD is a complex surgical procedure with a high morbidity rate of up to 50%[2-4]. However, the majority of complications are minor or grade I/II according to the Clavien-Dindo classification and do not affect long-term postoperative outcomes in patients with periampullary tumor[3-6]. Serious complications, Clavien-Dindo grade III-V, are major risk factors for poor long-term surgical outcome[2,7]. These complications increase length of hospital stay, reoperation and readmission, delay adjuvant treatment, and lead to mortality[8,9].

Several studies have investigated the use of inflammatory markers for prediction of severe postoperative complications following PD[10-13]. Prognostic nutritional index (PNI) is a common inflammatory marker previously reported to be associated with postoperative outcomes[14-16]. PNI is a simple inexpensive marker that is calculated from serum albumin and total lymphocyte count[17]. Kanda *et al*[13] and Kim *et al*[18] have reported that preoperative nutritional status affects postoperative outcomes following pancreatic surgery. Sato *et al*[19] have reported that the rapid change in PNI following distal pancreatectomy is significantly associated with postoperative pancreatic fistula (POPF). However, that study used PNI on postoperative day (POD) 7, which seemed to delay prediction of complications. Other studies have reported an association between early postoperative PNI and prediction of severe complications following gastrointestinal surgery[15,16,20]. There have been no studies of the use of early postoperative PNI for predicting serious complications following PD. Thus, the aim of our study was to analyze the risk factors and early postoperative PNI for predicting severe complications following PD.

MATERIALS AND METHODS

Patients and perioperative management
From January 2007 to December 2017, 244 consecutive patients underwent PD at the

Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand and were considered for inclusion in the study. Patients who underwent concomitant hepatic resection were excluded, which left 238 patients in the study. We retrospectively reviewed patient data, including age, gender, body mass index, underlying disease, ASA classification, history of smoking, serum albumin, preoperative total bilirubin, preoperative diagnosis and preoperative biliary intervention. We also reviewed the pancreatic texture, pancreatic duct size, operating time and operative blood loss. PNI was calculated as follows: albumin level (g/L) + 0.005 × total lymphocyte count (/μL). Ethical permission for this study was obtained from the Ethics Committee of Ramathibodi Hospital.

The surgical procedure has been described in a previous report[4]. PD was performed by surgeons with experience in pancreatic surgery. Pancreatic texture was classified as hard, firm or soft consistency based on palpation by the surgeon. After surgery, patients were transferred to a critical care unit or intermediate ward. Routine biochemical analyses of patients' blood were performed. An oral diet was started as soon as the output gastric content was < 400 mL and the occurrence of a bowel movement.

Postoperative complications

The postoperative complications were classified according to the Clavien-Dindo classification[6]. The complications were confirmed to occur in pancreatic surgery[21]. Serious complications were defined as higher than grade II in the Clavien-Dindo classification[6]. POPF was defined according to the International Study Group of Pancreatic Fistula (ISGPF) guidelines by amylase levels that were three times higher in the drainage fluid than serum[22]. POPF was classified into three categories: (1) grade biochemical leakage: transient pancreatic fistula with no clinical impact; (2) grade B: required a change in management or adjustment of the clinical course; and (3) grade C: required a major change in clinical management or deviated from the normal clinical course. Delay gastric emptying (DGE), as defined by the International Study Group of Pancreatic Surgery, within 30 d after the index operation[23]. DGE was assessed as present if either nasogastric tube insertion after POD 3 or as the inability to tolerate solid food intake by POD 7. Chyle leakage was defined as a milky drain output or triglyceride level > 110 mg/dL in the drain fluid on any POD. Postoperative mortality was recorded as the 90-d mortality and in-hospital mortality. The patients who the cause of death did not associated with the postoperative complication were excluded from the study.

Statistical analysis

Categorical and numerical variables were analyzed using Pearson's $\chi2$ or Fisher exact test and Mann-Whitney test, respectively. Univariate and multivariate (variable selection with stepwise and best subset approaches[24]) analyses were conducted using the logistic regression model. Odds ratios (OR) and 95% confidence interval (CI) were calculated to assess the strength of the associations between the various factors and postoperative outcome. $P < 0.05$ was considered statistically significant. Analyses were performed using STATA version 14 (StataCorp, College Station, TX, United States). The cut-off value for high and low PNI was determined by receiver operating characteristic (ROC) curve analysis.

RESULTS

The clinicopathological characteristics of the 238 patients and overall complications are summarized in Table 1. The overall complication rate was 65.97% (157/238 patients). The overall POPF rate was 49.57% (118/238 patients). The clinical relevant (grade B/C) POPF rate was 23.53% (56/238 patients). The overall grade III-V complication rate was 26.47% (63/238 patients). The postoperative mortality rate was 3.78% (9/238 patients). The median follow up period was twenty-four months.

Patient characteristics and operative outcomes in patients with grade 0-II and III-V complications

Table 2 compares the clinicopathological characteristic between patients with grade 0-II and III-V complications. Age, gender, diabetes mellitus, smoking, previous biliary intervention, total bilirubin, preoperative diagnosis, operating time, blood loss, pancreatic texture and pancreatic duct diameter did not differ significantly between the two groups. The grade III-V group had significantly higher body mass index (22.6 *vs* 21.85, $P < 0.05$) and lower serum albumin (34.1 *vs* 35.0, $P < 0.05$) than the grade 0-II group had. The patients in the grade III-V complications group had significantly higher ASA status than the grade 0-II group had ($P < 0.05$).

Table 1 Overall complications following pancreaticoduodenectomy	
Complications, *n* (%)	Total (*n* = 238)
No	81 (34.03)
yes	157 (65.97)
Postoperative pancreatic fistula	118 (49.58)
Grade BL	62 (26.05)
Grade B	38 (15.97)
Grade C	18 (7.56)
Surgical site infection	32 (13.45)
Intra-abdominal abscess	31 (13.02)
Delayed gastric emptying	23 (9.66)
Bile leak	15 (6.30)
Chyle leak	10 (4.20)
Intraperitoneal hemorrhage	9 (3.78)
Acute kidney injury	8 (3.36)
Cholangitis	7 (2.94)
Lung atelectasis	5 (2.10)
Septicemia	5 (2.10)
Gastrointestinal hemorrhage	4 (1.68)
Pleural effusion	4 (1.68)
Pneumonia	4 (1.68)
Intestinal obstruction	3 (1.26)
Pulmonary embolism	3 (1.26)
Acute pancreatitis	2 (0.84)
Delirium	2 (0.84)
Respiratory failure	2 (0.84)
Cerebrovascular accident	1 (0.42)
Hepatic failure	1 (0.42)
Urinary tract infection	1 (0.42)
Death	9 (3.78)

BL: Biochemical leakage.

Comparison of PNI between grade 0-II and III-V complications

Table 2 compares the pre- and postoperative PNI. Preoperative PNI did not differ between the two groups. The most significant difference in postoperative PNI between the two groups was on POD 3 (45.5 *vs* 30.0, $P < 0.01$). Accordingly, we used PNI on POD 3 for analysis of the factors predicting grade III-V postoperative complications. The cut-off value for PNI POD 3 was determined by ROC curve analysis (Figure 1). The area under the ROC curve was 0.72 (sensitivity 72.2%, specificity 68.0%, positive predictive value 0.62, and negative predictive value 0.53, 95%CI: 0.63-0.81). Patients with low PNI (< 40.5) had a significantly higher rate of severe complications than those with high PNI (≥ 40.5) (Figure 2). Thus, POD 3 PNI = 40.5 was considered as the optimal cut-off value.

Analysis of the risk factors for grade III-V complications

The results of univariate and multivariate analyses of potential predictors of grade III-V complications are shown in Table 3. Univariate analysis identified two variables significantly associated with grade III-V complications: preoperative serum albumin (OR: 0.943, 96%CI: 0.89-0.99; $P < 0.05$), and POD 3 PNI < 40.5 (OR: 2.619, 95%CI: 1.17-5.83; $P < 0.05$). Multivariate analysis identified two variables as significant predictive factors for grade III-V complications: preoperative serum albumin (OR: 0.88, 95%CI 0.80-0.96; $P < 0.01$) and POD 3 PNI < 40.5 (OR: 2.77, 95%CI: 1.21-6.38; $P < 0.05$).

DISCUSSION

Perioperative nutritional status is an important factor correlated with postoperative

Table 2 Clinicopathological characteristics in grade 0-II and III-V complication groups

Data		Total (*n* = 238)	Grade 0-II (*n* = 175)	Grade III-V (*n* = 63)	*P*
Age (yr), mean (SD)		60.01 (11.01)	59.89 (11.40)	60.33 (9.91)	0.788
Gender, *n* (%)					
	Male	125 (52.52)	95 (54.29)	30 (47.62)	0.364
	Female	113 (47.48)	80 (45.71)	33 (52.38)	
BMI (kg/m^2), median (range)		22.10 (15.11-38.95)	21.85 (15.11-38.95)	22.65 (16.22-35.34)	< 0.05
Diabetes mellitus, *n* (%)					
	No	173 (72.69)	123 (70.29)	50 (79.37)	0.165
	Yes	65 (27.31)	52 (29.71)	13 (20.63)	
ASA class, *n* (%), *n* = 234					
	I	6 (2.56)	3 (1.75)	3 (4.76)	< 0.05
	II	80 (34.19)	64 (37.43)	16 (25.40)	
	III	135 (57.69)	97 (56.73)	38 (60.32)	
	IV	10 (4.27)	6 (3.51)	4 (6.35)	
	V	3 (1.28)	1 (0.58)	2 (3.17)	
Smoking, *n* (%)					
	No	163 (68.49)	115 (65.71)	48 (76.19)	0.125
	Yes	75 (31.51)	60 (34.29)	15 (23.81)	
Previous biliary intervention, *n* (%)					
	No	84 (35.29)	60 (34.29)	24 (38.10)	0.587
	Yes	154 (64.71)	115 (65.71)	39 (61.90)	
Total bilirubin (mg/dL), median (range)		1.20 (0.10-35.0)	1.20 (0.10-35.0)	1.30 (0.20-25.0)	0.956
Albumin (g/L), median (range)		34.9 (18.7-49.0)	35 (18.7-49.0)	34.1 (23.1-45.0)	< 0.05
	≥ 35	116 (48.47)	91 (52.0)	25 (39.68)	0.093
	< 35	122 (51.26)	84 (48.0)	38 (60.32)	
Preoperative diagnosis, *n* (%)					
	Benign	55 (23.11)	43 (24.57)	12 (19.05)	0.372
	Malignant	183 (76.89)	132 (75.43)	51 (80.95)	
Pancreatic, *n* (%)					
	Pancreatic	131 (55.04)	95 (54.29)	36 (57.14)	0.696
	Nonpancreatic	107 (44.96)	80 (45.71)	27 (42.86)	
	Operating time, median (range)	465 (240-900)	420 (240-900)	480 (270-840)	0.175
	Blood loss (mL), median (range), *n* = 237	800 (100-13 000)	800 (100-8000)	1000 (150-13 000)	0.051
Pancreatic texture, *n* (%) *n*=227					
	Hard firm	113 (49.78)	88 (52.69)	25 (41.67)	0.143
	Soft	114 (50.22)	79 (47.31)	35 (58.33)	
Pancreatic diameter (mm) median (range), *n* = 225		3 (1-20)	3 (1-20)	4 (1-20)	0.718
PNI, median (range)					
	Preoperative, *n* = 230	98.9 (0.4-382.2)	98.9 (0.4-382.2)	101.5 (39.2-204.9)	0.456
	POD 1, *n* = 140	49.3 (0.2-111.6)	56.3 (0.2-425.6)	45.3 (0.2-111.6)	0.060
	POD 2, *n* = 81	43.1 (0.2-331.1)	45.5 (0.2-331.1)	35.2 (0.2-78.2)	< 0.05
	POD 3, *n* = 133	40.5 (0.1-290.2)	45.5 (0.2-290.2)	30.0 (0.1-85.9)	< 0.01
	POD 4, *n* = 53	31.7 (0.2-205.8)	36.8 (0.2-205.8)	27.1 (0.2-61.4)	0.112
	POD 5, *n* = 70	41.0 (0.1-147.4)	38.7 (0.1-147.4)	41.8 (0.2-123.2)	0.396

BMI: Body mass index; PNI: Prognostic nutritional index; POD: Postoperative day; SD: Standard deviation.

outcomes[25]. Serum albumin is a common indicator for ongoing inflammatory processes, and hypoalbuminemia is a predictor of postoperative morbidity[25-28]. It has been demonstrated that the survival of patients with cachexia is significantly reduced after undergoing resection of pancreatic cancer[29]. In the present study, the independent factors associated with serious postoperative complications following PD were preoperative serum albumin and POD 3 PNI < 40.5.

Albumin is a negative acute phase protein synthesized in the liver at a level of 12-25 g/d and half-life of 20 d. Serum albumin level is affected by multiple factors including

Area under ROC curve = 0.7251
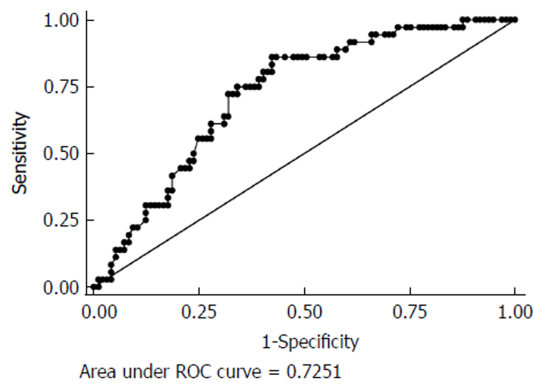
Figure 1 Receiver operating characteristic curves for predicting grade III-V complications with postoperative day 3 prognostic nutritional index < 40.5. ROC: Receiver operating characteristic.

malignancy, inflammatory state, trauma and surgery[30]. Hypoalbuminemia is associated with poor tissue healing, decreased collagen synthesis in surgical wounds or at anastomoses, and impairment of immune responses such as macrophage activation and granuloma formation[31,32]. Preoperative hypoalbuminemia is significantly associated with postoperative complications following various types of surgery[25,33,34]. Lyu *et al*[2] reported the risk factors for reoperation in 15549 patients following pancreatic resection, and preoperative serum albumin < 3.5 mg/dL was a predictor for unplanned 30-d reoperation. Moreover, Agustin *et al*[35] reported the factors related to life-threatening complications and mortality after pancreatic resection in a large population study. They demonstrated that serum albumin < 3.5 g/dL was an independent factor associated with Clavien-Dindo grade IV complications and mortality in the pancreatic surgery patients[35]. According to these reports, we conclude that preoperative hypoalbuminemia is a significant risk factor for serious postoperative complications, especially after pancreatic resection.

C-reactive protein and procalcitonin are inflammatory markers and accurate predictors for infectious complications following surgery[10,36]. However, in hospitals with limited resources, such as in Thailand, those markers are expensive. Moreover, procalcitonin examination is not available in all hospitals. So, those markers are not routinely used in our hospital. However, there is the simple inexpensive inflammatory marker PNI. PNI was first proposed by Onodera *et al*[17] as a predictor of surgical complications and mortality. PNI depends on two parameters, serum albumin and total lymphocyte count from peripheral blood smears[17]. Several studies have reported that low preoperative PNI is associated with postoperative complications[13,16,37,38]. However, for postoperative PNI, only one study has reported the association between decreased PNI on POD 7 following distal pancreatectomy, which showed that decreased PNI on POD 7 was a predictor for POPF[19]. However, the definitive diagnosis of POPF was on POD 3. Evaluation on POD 7 seemed to delay diagnosis. In our study, POD 3 PNI < 40.5 was a significant independent factor associated with serious postoperative complications following PD. This evidence was supported by Noji *et al*[39], who reported that infectious complications following PD could be predicted by amylase levels in drain effluent, body temperature, and leukocyte count on POD 3[39].

Postoperative PNI value might be associated with hypoalbuminemia because serum albumin level is an important parameter in PNI[40]. It has been shown that early postoperative serum albumin is associated with postoperative complications[40,41]. The stress response to injury is a factor that contributes to low postoperative serum albumin[28,42]. Labgaa *et al*[43] reported that patients who had a > 10 g/L decrease in serum albumin on POD 1 showed a threefold increased risk of overall postoperative complications after major surgery that lasted > 2 h. They concluded that the decrease in serum albumin was a marker of surgical stress response and early predictor of clinical outcomes. Moreover, the decrease in serum albumin significantly correlated with the extent of surgery, and the maximal increase in other stress markers such as C-reactive protein, procalcitonin and lactate[43].

There is evidence that low postoperative serum albumin is associated with outcome following PD[44,45]. Kawai *et al*[44] reported that serum albumin level ≤ 3.0 g/dL on POD 4 and leukocyte count > 9800/mm were independent predictive factors of clinically relevant pancreatic fistula following PD. Similarly, Fujiwara *et al*[45] reported that low postoperative serum albumin was an independent risk factor for POPF after PD[45]. According to these reports, low PNI in the early postoperative period could be a
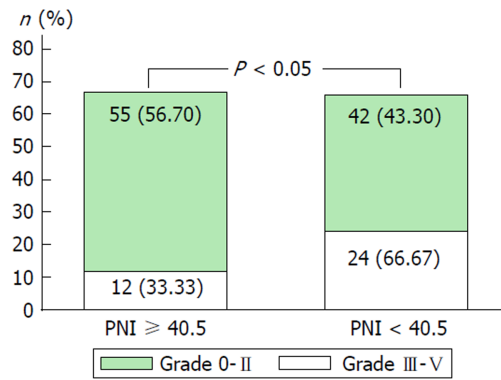
Figure 2 Comparison between low (< 40.5) and high (≥ 40.5) postoperative day 3 prognostic nutritional index in grade 0-II and III-V groups. PNI: Prognostic nutritional index.

predictor for serious complications following PD. Post-PD patients who have low PNI on POD 3 should be closely monitored for serious complications. In our hospital, routine CT is not performed following PD. According to the present study, computed tomography should be selectively performed in patients who have low PNI on POD 3, especially in those with POPF. However, the prospective studies are needed to validate this hypothesis.

This study had several limitations. First, because of its retrospective nature, there could have been some selection bias. Second, postoperative serum albumin could have been affected by exogenous intravenous albumin that was administered to some patients. However, our hospital policy is that only patients with serum albumin < 25 g/L are eligible for intravenous albumin. Third, the lower serum albumin between two groups (34.1 versus 35.0 g/L) is a modest difference. Fourth, the further prospective studies are needed to enhance the ability of POD 3 PNI < 40.5 to predict serious complications following PD.

In conclusion, Perioperative albumin is an important factor associated with serious complications following PD. POPF is a common complication following PD; however, most POPFs are minor complications and do not need any intervention. The most important consideration in clinical practice is that physicians should be aware of serious complications after PD. Our study suggests that PNI, which is a simple and inexpensive marker, is a good predictor for serious complications. Thus, patients who undergo PD and have early postoperative low PNI should be closely monitored.

Table 3 Univariate and multivariate analysis of the factors associated with grade III-V complications

Data		Univariate		Multivariate	
		OR (95%CI)	*P*	OR (95%CI)	*P*
Age (yr)		1.003 (0.97-1.03)	0.787		
Gender					
	Male	1			
	Female	1.306 (0.73-2.32)	0.364		
BMI (kg/m^2)		1.055 (0.98-1.13)	0.135		
Diabetes mellitus					
	No	1			
	Yes	0.615 (0.31-1.22)	0.168		
ASA class					
	I	1			
	II	0.250 (0.04-1.35)	0.108		
	III	0.391 (0.07-2.02)	0.264		
	IV	0.667 (0.08-5.12)	0.697		
	V	2.00 (0.11-35.80)	0.638		
Smoking					
	No	1			
	Yes	0.598 (0.31-1.15)	0.127		
Previous biliary intervention					
	No	1			
	Yes	0.847 (0.46-1.53)	0.588		
Total bilirubin (mg/d/L)		0.994 (0.93-1.05)	0.850		
Albumin (g/L)		0.943 (0.89-0.99)	< 0.05	0.883 (0.80-0.96)	< 0.01
Preoperative diagnosis					
	Benign	1			
	Malignant	1.384 (0.67-2.83)	0.374		
Pancreatic					
	Pancreatic	1			
	Nonpancreatic	0.890 (0.49-1.59)	0.696		
Operating time		1.002 (0.99-1.01)	0.154		
Blood loss (mL)		1.254 (1.02-1.54)	0.030		
Pancreatic texture					
	Hard/firm	1			
	Soft	1.559 (0.85-2.83)	0.144		
Pancreatic diameter (mm)		0.994 (0.88-1.12)	0.921		
PNI (POD 3)		0.981 (0.96-0.99)	< 0.05		
	≥ 40.5	1		1	
	< 40.5	2.619 (1.17-5.83)	< 0.05	2.776 (1.21-6.38)	< 0.05

BMI: Body mass index; CI: Confidence interval; OR: Odds ratio; PNI: Prognostic nutritional index; POD: Postoperative day.

ARTICLE HIGHLIGHTS

Research background

Pancreaticoduodenectomy (PD) is an example of major surgery and is a complicated operation to perform for the general surgeon. The perioperative morbidity rate previously reported reaching up to 50%. However, only serious complications are major risk factors for poor long-term surgical outcome. Majority of the serious complications is the infectious complication.

Research motivation

There are several studies have investigated the use of inflammatory markers for prediction of severe postoperative complications following PD. However, the common biomarkers previously reported are C-reactive protein and procalcitonin. These biomarkers are expensive in the limited resource country. Our goal is to find the simple and non-expensive marker for this complicated

operation. Prognostic nutritional index (PNI) is one of a simple inexpensive marker. There are previously reported of early postoperative PNI predicted the outcome following surgery.

Research objectives
The objective of our study was to analyze the risk factors and early postoperative PNI for predicting serious complications following PD.

Research methods
From January 2007 to December 2017, 244 consecutive patients underwent PD at the Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand and were retrospectively reviewed. The patients were classified into two groups (grade I-II and III-V complication groups according to Dindo-Clavien classification). Univariate and multivariate analyses were conducted. The cut-off value for high and low PNI was determined by receiver operating characteristic curve analysis

Research results
The independent factors associated with serious postoperative complications following PD were preoperative serum albumin and POD 3 PNI value < 40.5. To the best of our knowledge, we first time reported the early postoperative prognostic index as a predictor of the serious postoperative complication following PD. The hypoalbuminemia is the main factor associated with serious postoperative complications according to previous reports.

Research conclusions
PNI, which is a simple and inexpensive marker, is a good predictor for serious complications. Thus, patients who undergo PD and have early postoperative low PNI should be aware of serious complication especially infectious complications.

Research perspectives
The well designed prospective studies are needed to validate this predictor.

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