Risk factors for pancreatic fistula following pancreaticoduodenectomy: A retrospective study in a Thai tertiary center

Narongsak Rungsakulkij, Somkit Mingphruedhi, Pongsatorn Tangtawee, Chonlada Krutsri, Paramin Muangkaew, Wikran Suragul, Penampai Tannaphai, Suraida Aeesoa

AIM
To analyze the risk factors of postoperative pancreatic fistula following pancreaticoduodenectomy in a Thai tertiary care center.

METHODS
We retrospectively analyzed 179 patients who underwent pancreaticoduodenectomy at our hospital from January 2001 to December 2016. Pancreatic fistula were classified into three categories according to a definition made by an International Study Group on Pancreatic Fistula. The risk factors for pancreatic fistula were analyzed by univariate analysis and multivariate logistic regression analysis.
RESULTS
Pancreatic fistula were detected in 88/179 patients (49%) who underwent pancreatocoduodenectomy. Fifty-eight pancreatic fistula (65.9%) were grade A, 22 cases (25.0%) were grade B and eight cases (9.1%) were grade C. Clinically relevant pancreatic fistula were detected in 30/179 patients (16.7%). The 30-d mortality rate was 1.67% (3/179 patients). Multivariate logistic regression analysis revealed that soft pancreatic tissue (odds ratio = 3.598, 95%CI: 1.77-7.32) was the most significant risk factor for pancreatic fistula. A preoperative serum bilirubin level of > 3 mg/dL was the most significant risk factor for clinically relevant pancreatic fistula according to univariate and multivariate analysis.

CONCLUSION
Soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

Key words: Risk factors; Pancreatic fistula; Pancreas; Pancreatectomy; Pancreatocoduodenectomy

Rungsakulkij N, Mingphruedhi S, Tangtawee P, Krutsri C, Muangkaew P, Suragul W, Tannaphai P, Aeesoa S. Risk factors for clinically relevant pancreatic fistula following pancreatocoduodenectomy: A retrospective study in a Thai tertiary center. World J Gastrointest Surg 2017; 9(12): 270-280. Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i12/270.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i12.270

INTRODUCTION
Pancreatocoduodenectomy (PD) is the standard treatment for resectable periampullary and pancreatic tumors. PD is an example of major surgery and is a complicated operation to perform for the general surgeon. Current mortality rates are low; previous reports have suggested a perioperative mortality rate of less than 5%[1-3]. However, high morbidity rates have also been reported, some reaching up to 50%[3-7]. The most common complication following PD is postoperative pancreatic fistula (POPF). POPF is the major cause of complications such as delayed gastric emptying (DGE), postoperative hemorrhage, intra-abdominal infection and increased length of hospital stay (LOH)[8].

Many risk factors have been reported for POPF, including obesity, soft pancreatic texture, small pancreatic duct and low volume center[9-15]. Some studies have investigated ways to improve the surgical outcome and reduce POPF, including the placement of an external and internal trans-anastomotic pancreatic duct[16,17], pancreatogastrostomy[18-20], omental roll-up around pancreaticenteric (PE) anastomosis[21], application of fibrin sealants around PE anastomosis[22,23] and prophylaxis with somatostatin analogs[24-25]. However, the outcomes of these different methods remain controversial.

Recently, a soft pancreas and high body mass index (BMI) were reported as the most common risk factors for POPF[9-12]. However, POPF risk factors have not been studied in a Thai population before. The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

MATERIALS AND METHODS

Patients
From January 2001 to December 2016, 210 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 a concomitant hepatic resection were excluded; in the end, a total of 179 patients were included. Patient data were retrospectively reviewed. These included age, gender, weight, BMI, underlying disease, serum albumin, preoperative total bilirubin levels and preoperative biliary drainage (PBD). In addition, we recorded the use of percutaneous trans-hepatic biliary drainage or placement of an endoscopic internal biliary stent. We also reviewed the type of operation, pancreatic texture, pancreatic duct size, type of PE anastomosis, use of trans-anastomotic pancreatic duct stent, pathological diagnosis, operative time and operative blood loss. Ethical permission for this study was obtained from the hospital's ethics committee.

Preoperative evaluation
The general condition of patients and any co-morbid conditions were preoperatively assessed by a physician, surgeon and internist. The diagnosis and clinical staging of the disease were reviewed preoperatively by a multidisciplinary team including surgeons, radiologists and gastroenterologists.

Operative approach
Routine antibiotic prophylaxis was administered 30 min before the incision. PD is classified into classical PD and pylorus-preserved PD (PPPD) and the type of surgery depended on the surgeon’s own preference. Reconstruction after resection was performed using...
Patient characteristics and operative outcomes in patients with and without POPF

POPF were detected in 88 patients (49%). Fifty-eight patients (65.9%) had grade A POPF, 22 patients (25%) had grade B POPFs and eight patients (9.1%) had grade C POPFs. CR-POPF were detected in 30/179 patients (16.7%). The 30-d mortality rate was 1.67% (3/179). Table 1 compares the post-PD complications between POPF and no POPF groups. Age, serum albumin levels, operative blood loss, gender, diabetes mellitus and PBD were not statistically different between the two groups. However, statistically significant differences were observed in BMI, preoperative total serum bilirubin, pancreatic duct diameter, operative time, cardiovascular disease, pancreatic texture and trans-anastomotic stent between the two groups. The POPF group had a higher rate of other complications (5.5% vs 25%, \( P < 0.001 \)) and a longer LOH (15 d vs 25 d, \( P < 0.001 \)).

Risk factors for POPF

Univariate and multivariate analyses were used to identify risk factors for POPF (Table 2). Univariate analyses of the 88 patients with pancreatic fistula revealed the following risk factors for POPF: BMI > 25 (OR 2.38, 95%CI: 1.13-5.03, \( P = 0.005 \)), pancreatic duct diameter (OR 2.765, 95%CI: 1.47-5.18, \( P = 0.002 \)), operative time (OR 2.39, 95%CI: 1.26-4.55, \( P = 0.008 \)), history of cardiovascular disease (OR 3.41, 95%CI: 1.48-7.86, \( P = 0.004 \)), soft pancreatic texture (OR 4.682, 95%CI: 1.31-15.09, \( P = 0.002 \)) and placement of a trans-anastomotic pancreatic duct stent (OR 2.38, 95%CI: 1.13-5.03, \( P = 0.005 \)) as the most significant risk factor for POPF.

Effect of POPF grade on patient characteristics and operative outcomes and predictive factors for CR-POPF

Preoperative total bilirubin and pancreatic reconstruction techniques (duct to mucosa vs invagination) were significantly different between grade A POPF and CR-POPF (Table 3). Univariate analysis revealed preoperative total serum bilirubin levels of more than 3 mg/dL as a potential risk factor for grade A POPF (OR 3.49, 95%CI: 1.48-9.51, \( P = 0.005 \)). Multivariate analysis revealed total serum bilirubin levels of more than 3 mg/dL as the most significant predictive factor for CR-POPF (OR 4.50, 95%CI: 1.54-13.15, \( P = 0.006 \)) (Table 4).

DISCUSSION

The most common perioperative complication of PD is...
Table 1  Patient characteristics in postoperative pancreatic fistula and no postoperative pancreatic fistula groups

| Characteristic data                             | No POPF (n = 91) | POPF (n = 88) | P-value | 95%CI          |
|------------------------------------------------|------------------|---------------|---------|----------------|
| Age, mean (SD)                                 | 60.7 (10.6)      | 59.1 (11.2)   | 0.33    | 58.22-61.44    |
| BMI, median (IQR)                              | 21.4 (20, 23.9)  | 23.1 (20.8, 25.5) | 0.005  | 22.05-23.22    |
| Albumin, median (IQR)                          | 34.1 (31, 38.3)  | 34.9 (32, 37.95) | 0.667  | 33.38-35.10    |
| Total bilirubin, median (IQR)                  | 4.1 (3, 13.2)    | 1.3 (0.7, 5.6) | 0.002  | 5.01-7.16      |
| Pancreatic duct diameter (mm), median (IQR)    | 3 (3, 5)         | 3 (2, 5)      | 0.048  | 3.44-3.99      |
| Operative time, median (IQR)                   | 420 (360, 540)   | 480 (420, 570) | 0.014  | 448.46-486.23  |
| Blood loss (mL), median (IQR)                  | 1000 (600, 1500) | 800 (500, 1500) | 0.236  | 1082-1459.66   |
| LOH day, median (IQR)                          | 15 (12, 20)      | 25 (17, 39.5) | < 0.001 | 23.14-52.87   |
| Gender, n (%)                                  |                  |               |         |                |
| Male                                          | 49 (53.8)        | 46 (52.3)     | 0.833  |                |
| Female                                        | 42 (46.2)        | 42 (47.7)     |         |                |
| DM, n (%)                                     |                  |               |         |                |
| No                                            | 64 (70.3)        | 69 (78.4)     | 0.216  |                |
| Yes                                           | 27 (29.7)        | 19 (21.6)     |         |                |
| Hx of cardiovascular disease, n (%)            |                  |               |         |                |
| No                                            | 82 (90.1)        | 64 (72.7)     | 0.003  |                |
| Yes                                           | 9 (9.9)          | 24 (27.3)     |         |                |
| PBD, n (%)                                     |                  |               |         |                |
| No                                            | 36 (39.6)        | 25 (28.4)     | 0.116  |                |
| Yes                                           | 55 (60.4)        | 63 (71.6)     |         |                |
| Pancreatic texture, n (%)^1                    |                  |               |         |                |
| Hard/firm                                     | 60 (68.2)        | 27 (31.4)     | < 0.001 |                |
| Soft                                          | 28 (31.8)        | 39 (68.6)     |         |                |
| Type of resection, n (%)                       |                  |               |         |                |
| PPPD                                          | 20 (22.0)        | 31 (35.2)     | 0.05   |                |
| Classical PD                                  | 71 (78.0)        | 57 (64.8)     |         |                |
| Duct to mucosa vs Invagination                 |                  |               |         |                |
| Duct to mucosa                                | 56 (61.5)        | 63 (71.6)     | 0.154  |                |
| Invagination                                   | 35 (38.5)        | 25 (28.4)     |         |                |
| Stert, n (%)                                   |                  |               |         |                |
| No                                            | 73 (80.2)        | 54 (61.4)     | 0.005  |                |
| Yes                                           | 18 (19.8)        | 34 (38.6)     |         |                |
| External vs Internal, n (%)                    |                  |               |         |                |
| External                                      | 4 (22.2)         | 12 (36.4)     | 0.298  |                |
| Internal                                      | 14 (77.8)        | 21 (63.6)     |         |                |
| Malignant, n (%)                               |                  |               |         |                |
| No                                            | 18 (19.8)        | 16 (18.2)     | 0.785  |                |
| Yes                                           | 73 (80.2)        | 72 (81.8)     |         |                |
| Final diagnosis, n (%)                         |                  |               |         |                |
| CA ampulla                                    | 25 (27.5)        | 37 (42.1)     | 0.04   |                |
| CA pancreas                                   | 28 (27.5)        | 12 (13.6)     |         |                |
| CA duodenal                                   | 8 (8.8)          | 3 (3.4)       |         |                |
| CA distal CBD                                 | 7 (7.7)          | 11 (12.5)     |         |                |
| Other                                         | 26 (28.5)        | 25 (28.4)     |         |                |
| Grading, n (%)                                 |                  |               |         |                |
| No                                            | 91 (100)         | 0             | 0       |                |
| A                                             | 0                | 58 (65.9)     |         |                |
| B                                             | 0                | 22 (25.0)     |         |                |
| C                                             | 0                | 8 (9.1)       |         |                |
| Other complications                            |                  |               |         |                |
| No                                            | 86 (94.5)        | 66 (75.0)     | < 0.001 |                |
| Yes                                           | 5 (5.5)          | 22 (25.0)     |         |                |
| 30-d mortality, n (%)                          |                  |               |         |                |
| No                                            | 91 (100)         | 85 (96.6)     | 0.117  |                |
| Yes                                           | 0                | 3 (3.4)       |         |                |
| Age, n (%)                                     |                  |               |         |                |
| < 70                                          | 73 (80.2)        | 73 (82.9)     | 0.637  |                |
| ≥ 70                                          | 18 (19.8)        | 15 (17.1)     |         |                |
| BMI, n (%)                                     |                  |               |         |                |
| < 25                                          | 78 (85.7)        | 63 (71.6)     | 0.021  |                |
| ≥ 25                                          | 13 (14.3)        | 25 (28.4)     |         |                |
| Albumin, n (%)                                 |                  |               |         |                |
| ≥ 30                                          | 75 (82.4)        | 77 (87.5)     | 0.342  |                |
| < 30                                          | 16 (17.6)        | 11 (12.5)     |         |                |
| Total bilirubin, n (%)                         |                  |               |         |                |
| < 3                                           | 41 (45.1)        | 56 (63.6)     | 0.013  |                |
| ≥ 3                                           | 50 (54.9)        | 32 (36.4)     |         |                |

Rungsakulkij N et al.  Risk factors of pancreatic fistula
Table 2  Univariate and multivariate logistic regression analysis of postoperative pancreatic fistula risk factors

| Variable                              | Univariate OR (95%CI) | Univariate P-value | Multivariate OR (95%CI) | Multivariate P-value |
|---------------------------------------|-----------------------|--------------------|------------------------|----------------------|
| Age (yr)                              |                       |                    |                        |                      |
| < 70                                   | 0.833 (0.39-1.78)     | 0.637              |                        |                      |
| ≥ 70                                   |                       |                    |                        |                      |
| Body mass index (kg/cm²)              |                       |                    |                        |                      |
| < 25                                   | 2.381 (1.13-5.03)     | 0.023              | 2.081 (0.86-5.03)      | 0.104                |
| ≥ 25                                   |                       |                    |                        |                      |
| Albumin                               | 0.669 (0.29-1.54)     | 0.344              |                        |                      |
| < 30                                   |                       |                    |                        |                      |
| Total bilirubin                       |                       |                    |                        |                      |
| < 3                                   | 0.468 (0.26-0.85)     | 0.013              | 1.455 (0.38-5.55)      | 0.583                |
| ≥ 3                                   |                       |                    |                        |                      |
| Pancreatic duct diameter              |                       |                    |                        |                      |
| ≥ 5 mm                                | 2.765 (1.47-5.18)     | 0.002              | 3.148 (0.81-12.27)     | 0.098                |
| < 5 mm                                |                       |                    |                        |                      |
| Operative time                        | 2.393 (1.26-4.55)     | 0.008              | 1.355 (0.59-3.07)      | 0.465                |
| < 420 min                             |                       |                    |                        |                      |
| ≥ 420 min                             |                       |                    |                        |                      |
| Blood loss                            | 0.616 (0.34-1.12)     | 0.11               |                        |                      |
| < 1000                                |                       |                    |                        |                      |
| ≥ 1000                                |                       |                    |                        |                      |
| Gender                                |                       |                    |                        |                      |
| Male                                  | 1.065 (0.59-1.92)     | 0.833              |                        |                      |
| Female                                |                       |                    |                        |                      |
| DM                                    | 0.653 (0.33-1.29)     | 0.218              |                        |                      |
| No                                    |                       |                    |                        |                      |
| Yes                                   | 3.417 (1.48-7.86)     | 0.004              | 2.612 (0.96-7.08)      | 0.059                |
| Hx of cardiovascular disease          |                       |                    |                        |                      |
| No                                    | 1.649 (0.88-3.08)     | 0.117              |                        |                      |
| Yes                                   |                       |                    |                        |                      |
| Preop biliary stent (no)              |                       |                    |                        |                      |
| No                                    | 4.682 (2.47-8.87)     | < 0.001            | 3.598 (1.77-7.32)      | < 0.001              |
| Yes                                   |                       |                    |                        |                      |
| Pancreatic texture                    |                       |                    |                        |                      |
| Hard/firm                             | 0.518 (0.27-1.00)     | 0.051              | 0.807 (0.37-1.78)      | 0.597                |
| Soft                                  | 0.635 (0.34-1.19)     | 0.156              |                        |                      |
| Type of resection                     | 2.553 (1.31-4.99)     | 0.006              | 1.272 (0.52-3.09)      | 0.595                |
| Pylorus-preserved pancreaticoduodenectomy |                       |                    |                        |                      |
| Pancreatoduodenectomy                 | 0.500 (0.13-1.87)     | 0.303              |                        |                      |
| Duct to mucosa                        |                       |                    |                        |                      |
| Invagination                          | 1.109 (0.52-2.34)     | 0.785              |                        |                      |
| Stent (no)                            | 0.324 (0.14-0.76)     | 0.01               | 0.439 (0.16-1.19)      | 0.105                |
| No                                    | 0.253 (0.06-1.05)     | 0.058              | 0.533 (0.11-2.59)      | 0.435                |
| Yes                                   | 1.062 (0.36-3.11)     | 0.913              | 1.188 (0.33-4.29)      | 0.793                |
| Other                                 | 0.650 (0.31-1.37)     | 0.258              | 0.543 (0.22-1.35)      | 0.189                |

1n = 174 patients. Other complications: DGE, postoperative hemorrhage, chyle leakage. POPF: Postoperative pancreatic fistula; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.
Table 3  Relationships between patient characteristics, operative outcome and postoperative pancreatic fistula grade

| Characteristic data                                | POPF (grading)         | P-value | 95%CI       |
|---------------------------------------------------|------------------------|---------|-------------|
|                                                   | A (n = 58)             | B + C (n = 30) |             |
| Age, mean (SD)                                    | 59.2 (11.3)            | 58.8 (11.4) | 0.874       |
|                                                   |                        |          | 56.67-61.46 |
| Body mass index, median (IQR)                     | 23.1 (20.4, 25.1)      | 23.1 (21.1, 26.5) | 0.805 |
|                                                   |                        |          | 22.62-24.45 |
| Albumin, median (IQR)                             | 34.7 (32, 38)          | 35.4 (32, 37.9) | 0.603 |
|                                                   |                        |          | 33.38-35.58 |
| Total bilirubin, median (IQR)                     | 0.9 (2, 5)             | 3.3 (1.2, 12) | 0.01 |
|                                                   |                        |          | 3.44-6.66   |
| Pancreatic duct diameter (mm), median (IQR)       | 3 (2, 5)               | 3 (2, 4)  | 0.175       |
|                                                   |                        |          | 3.07-3.79   |
| Operative time, median (IQR)                      | 480 (420, 600)         | 480 (360, 540) | 0.49 |
|                                                   |                        |          | 462.22-511.75 |
| Blood loss (mL), median (IQR)                     | 800 (500, 1500)        | 900 (600, 1500) | 0.071 |
|                                                   |                        |          | 985.10-1616.95 |
| LOH day, median (IQR)                             | 21 (14, 30)            | 42.5 (30, 60) | < 0.001 |
|                                                   |                        |          | 28.14-46.32 |
| Gender, n (%)                                     | Male 34 (58.6)         | 12 (40.0) | 0.097       |
|                                                   | Female 24 (41.4)       | 18 (60.0) |             |
|                                                   |                        |          |             |
| DM, n (%)                                         | No 45 (77.6)           | 24 (80.0) | 0.794       |
|                                                   | Yes 13 (22.4)          | 6 (20.0)  |             |
|                                                   |                        |          |             |
| Hx of cardiovascular disease, n (%)               | No 42 (72.4)           | 22 (73.3) | 0.927       |
|                                                   | Yes 16 (27.6)          | 8 (26.7)  |             |
|                                                   |                        |          |             |
| PBD, n (%)                                        | No 20 (34.5)           | 5 (16.7)  | 0.079       |
|                                                   | Yes 38 (65.5)          | 25 (83.3) |             |
|                                                   |                        |          |             |
| Pancreatic texture, n (%)                         | Hard/Firm 20 (35.1)    | 7 (24.1)  | 0.301       |
|                                                   | Soft 37 (64.9)         | 22 (75.9) |             |
|                                                   |                        |          |             |
| Type of resection, n (%)                          | PPPD 24 (41.4)         | 7 (23.3)  | 0.093       |
|                                                   | PD 34 (58.6)           | 23 (76.7) |             |
|                                                   |                        |          |             |
| Duct, n (%)                                       | Duct to mucosa 46 (79.3) | 17 (56.7) | 0.026       |
|                                                   | Invagination 12 (20.7)  | 13 (43.3) |             |
|                                                   |                        |          |             |
| Srent, n (%)                                      | No 32 (55.2)           | 22 (73.3) | 0.097       |
|                                                   | Yes 26 (44.8)          | 8 (26.7)  |             |
|                                                   |                        |          |             |
| External vs Internal, n (%)                       | External 8 (32.0)      | 4 (50.0)  | 0.42        |
|                                                   | Internal 14 (60.0)     | 4 (50.0)  |             |
|                                                   |                        |          |             |
| Malignant, n (%)                                  | No 12 (20.7)           | 4 (13.3)  | 0.396       |
|                                                   | Yes 46 (79.3)          | 26 (86.7) |             |
|                                                   |                        |          |             |
| Final diagnosis, n (%)                            | CA ampulla 23 (39.6)   | 14 (46.7) | 0.33        |
|                                                   | CA pancreas 8 (13.8)   | 4 (13.3)  |             |
|                                                   | CA duodenal 3 (5.2)    | 0         |             |
|                                                   | CA distal CBD 5 (8.6)  | 6 (20.0)  |             |
|                                                   | Other 19 (32.8)        | 6 (20.0)  |             |
|                                                   |                        |          |             |
| Age, n (%)                                        | < 70 47 (81.0)         | 26 (86.7) | 0.505       |
|                                                   | ≥ 70 11 (19.0)         | 4 (13.3)  |             |
|                                                   |                        |          |             |
| BMI, n (%)                                        | < 25 42 (71.4)         | 21 (70.0) | 0.812       |
|                                                   | ≥ 25 16 (27.6)         | 9 (30.0)  |             |
|                                                   |                        |          |             |
| Albumin, n (%)                                    | < 30 50 (86.2)         | 27 (90.0) | 0.743       |
|                                                   | ≥ 30 8 (13.8)          | 3 (10.0)  |             |
|                                                   |                        |          |             |
| Total bilirubin, n (%)                            | < 3 43 (74.1)          | 13 (43.3) | 0.004       |
|                                                   | ≥ 3 15 (28.9)          | 17 (56.7) |             |
|                                                   |                        |          |             |
| Pancreatic duct diameter, n (%)                   | ≥ 5 12 (20.7)          | 11 (36.7) | 0.106       |
|                                                   | < 5 46 (79.3)          | 19 (63.3) |             |
|                                                   |                        |          |             |
| Operative time, n (%)                             | < 420 12 (20.7)        | 9 (30.0)  | 0.331       |
|                                                   | ≥ 420 46 (79.3)        | 21 (70.0) |             |
|                                                   |                        |          |             |
| Blood loss, n (%)                                 | < 1000 37 (63.8)       | 17 (56.7) | 0.515       |
|                                                   | ≥ 1000 21 (36.2)       | 13 (43.3) |             |

POPF: Postoperative pancreatic fistula; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.
POPF. POPF remains the leading cause of complications such as DGE and postoperative hemorrhage, which increase mortality\cite{1-3} and the LOH. Many risk factors for POPF have been reported previously\cite{4-9}. In the present study, the incidence of POPF and the 30-d mortality rate were similar to previous studies. In addition, we identified soft pancreatic texture as a main risk factor for POPF\cite{8-12}. Our multivariate analysis showed that a soft pancreas is the most independent predictive factor for POPF. This is in agreement with previous studies\cite{5,9-12,27}. There are many reasons why soft pancreatic tissue increases the risk of POPF. First, a soft pancreas makes it more difficult to secure PEA because friable pancreatic tissue cannot

| Variable                                      | Univariate OR (95%CI) | Univariate P-value | Multivariate OR (95%CI) | Multivariate P-value |
|-----------------------------------------------|-----------------------|--------------------|-------------------------|----------------------|
| Age (yr)                                      |                       |                    |                         |                      |
| < 70                                          | 0.657 (0.19-2.27)     | 0.507              |                         |                      |
| ≥ 70                                          |                       |                    |                         |                      |
| BMI (kg/cm$^2$)                               |                       |                    |                         |                      |
| < 25                                          | 1.125 (0.43-2.96)     | 0.812              |                         |                      |
| ≥ 25                                          |                       |                    |                         |                      |
| Albumin                                      |                       |                    |                         |                      |
| < 30                                          | 0.694 (0.17-2.84)     | 0.611              |                         |                      |
| ≥ 30                                          |                       |                    |                         |                      |
| Total bilirubin                               |                       |                    |                         |                      |
| < 3                                           | 3.749 (1.48-9.51)     | 0.005              | 4.506 (1.54-13.15)      | 0.006                |
| ≥ 3                                           |                       |                    |                         |                      |
| Pancreatic duct diameter (mm)                 |                       |                    |                         |                      |
| < 5                                           | 0.451 (0.17-1.20)     | 0.11               |                         |                      |
| ≥ 5                                           |                       |                    |                         |                      |
| Operative time (min)                          |                       |                    |                         |                      |
| < 420                                         | 0.609 (0.22-1.66)     | 0.334              |                         |                      |
| ≥ 420                                         |                       |                    |                         |                      |
| Blood loss                                    |                       |                    |                         |                      |
| < 1000                                        | 1.347 (0.55-3.31)     | 0.516              |                         |                      |
| ≥ 1000                                        |                       |                    |                         |                      |
| Gender                                        |                       |                    |                         |                      |
| Male                                          | 2.125 (0.86-5.22)     | 0.1                |                         |                      |
| Female                                        |                       |                    |                         |                      |
| DM                                            |                       |                    |                         |                      |
| No                                            | 0.865 (0.29-2.56)     | 0.794              |                         |                      |
| Yes                                           |                       |                    |                         |                      |
| Hx of cardiovascular disease                  |                       |                    |                         |                      |
| No                                            | 0.954 (0.35-2.58)     | 0.927              |                         |                      |
| Yes                                           |                       |                    |                         |                      |
| Preop biliary stent (no)                      |                       |                    |                         |                      |
| No                                            | 2.631 (0.87-7.92)     | 0.085              | 2.24 (0.67-7.49)        | 0.191                |
| Yes                                           |                       |                    |                         |                      |
| Pancreatic texture                            |                       |                    |                         |                      |
| Hard/firm                                     |                       |                    |                         |                      |
| Soft                                          |                       |                    |                         |                      |
| Type of resection                             |                       |                    |                         |                      |
| PPPD                                          |                       |                    |                         |                      |
| PD                                            | 2.319 (0.86-6.27)     | 1.787 (0.54-5.92)  | 0.342                   |                      |
| Duct to mucosa                                | 2.931 (1.12-7.67)     | 0.028              | 2.837 (0.89-9.08)       | 0.079                |
| Invagination                                  |                       |                    |                         |                      |
| Stent (no)                                    | 0.447 (0.17-1.17)     | 0.101              |                         |                      |
| No                                            |                       |                    |                         |                      |
| Yes                                           | 0.471 (0.09-2.38)     | 0.362              |                         |                      |
| External                                      |                       |                    |                         |                      |
| Internal                                      |                       |                    |                         |                      |
| Malignant (no)                                |                       |                    |                         |                      |
| No                                            | 1.695 (0.50-5.80)     | 0.4                |                         |                      |
| Yes                                           |                       |                    |                         |                      |
| Final diagnosis (CA ampulla)                  |                       |                    |                         |                      |
| CA pancreas                                   | 0.821 (0.21-3.24)     | 0.779              |                         |                      |
| CA duodenal                                   | -                     |                    |                         |                      |
| CA distal CBD                                 | 1.971 (0.51-7.68)     | 0.328              |                         |                      |
| Other                                         | 0.519 (0.17-1.61)     | 0.256              |                         |                      |
| POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.
hold suture tension. As a result, suture materials cut through the pancreatic parenchyma and anastomosis fails. A soft pancreas is also prone to ischemia when manipulated, which disrupts anastomosis. Finally, a soft pancreas has enriched exocrine function and pancreatic enzymes are released when leakage occurs\(^{9,11,27,28}\).

The assessment of pancreatic texture is controversial and subjective. Pancreatic texture is commonly assessed intraoperatively by palpation. Callery et al\(^{11}\) reported the clinical risk score for POPF based on pancreatic texture, pancreatic duct diameter and intraoperative blood loss. They classified the pancreatic texture as firm or soft\(^{11}\). Some studies have classified pancreatic texture as hard, firm or soft, but the distinction between a hard and firm pancreas remains unclear\(^{1,3}\).

Recently, Ansorge et al\(^{29}\) reported similar risk factors for POPF. They classified the pancreatic texture into four grades, including very hard (severe chronic pancreatitis), hard (fibrotic or atrophic obstructed pancreatic gland), soft (unaffected compact gland), and very soft (unaffected fatty pancreas). They found that 44/100 patients had a hard pancreas. The rate of POPF in the very hard/soft groups was significantly different to that in the soft/very soft groups\(^{29}\). There is a newly developed tissue strain imaging technology reflecting tissue fibrosis or stiffness and is integrated into a conventional ultrasound system called acoustic radiation force impulse (ARFI). Lee et al\(^{30}\) and Harada et al\(^{30}\) reported the high accuracy of ARFI for prediction of the stiffness of the pancreas preoperatively.

The relationship between soft and fatty pancreatic tissue has been well studied\(^{28-29,32}\). A fatty pancreas refers to the increasing infiltration of adipose tissue into the pancreas\(^{28}\). Ansorge et al\(^{29}\) found that the softness of pancreatic tissue was strongly associated with fat levels in the tissue. This was supported by previous reports that a fatty pancreas is a risk factor for POPF\(^{1,26,32}\). Taken together, these findings suggest that the infiltration of adipose tissue into the pancreas is associated with soft pancreatic texture.

The assessment of pancreatic texture is difficult and subjective. Currently, there are no standard procedures for the intraoperative assessment of pancreatic texture. Pancreatic texture has commonly been assessed intraoperatively by palpation\(^{5,11,20}\). In the present study, we also assessed pancreatic texture by palpation. This subjective assessment of pancreatic texture could have differed from surgeon to surgeon.

Unfortunately, it was not possible to assess pancreatic texture during the preoperative evaluation. Tranchart et al\(^{13}\) used computed tomography to predict the occurrence of severe pancreatic fistula following PD. They found that a visceral fat area of more than 84 cm\(^2\) was associated with a fatty pancreas (58.4% vs 48.1%, \(P = 0.005\)) and was a risk factor for CR-POPF (OR 8.16 95%CI: 2.2-3, \(P = 0.002\)). They suggested preoperative assessment of body fat distribution as a means of evaluating fat levels in the pancreas and predicting the occurrence of CR-POPF\(^{13}\). In our study, the incidence of CR-POPF is high when compared to previous studies\(^{5,6,11,12}\). This could be explained by the lower population of pancreatic cancer in this study that the pancreatic cancer is more likely to obstruct the pancreatic duct and therefore increase fibrosis of the pancreas\(^{11}\).

Obstructive jaundice was previously regarded as the main factor increasing perioperative morbidity and mortality. The pathophysiology of obstructive jaundice includes increased endotoxin concentrations in the portal circulation, altered Kupffer cell function affecting the reticuloendothelial system in the liver, over-activation of inflammatory cascades, decreased cellular immunity and renal dysfunction. These manifestations influence the nutritional status of patients. PBD decreased postoperative septic complications in mice by improving liver function, nutritional status, cell-mediated immune function, systemic endotoxemia, cytokine release and the overall immune response\(^{34}\). Regarding periampullary obstruction, endoscopic drainage approach today represents the procedure of choice with high succession rate\(^{36,38}\).

In this study, a preoperative serum bilirubin level of more than 3 mg/dL was a risk factor for CR-POPF. Kimura et al\(^{31}\) reported that serum bilirubin of more than 2.0 mg/dL was a significant preoperative risk factor for higher 30-d and in-hospital mortality rates following PD\(^{3}\). Gebauer et al\(^{37}\) found that patients with POPF who underwent repeated surgery had higher in-hospital mortality (0.6 vs 0.7, \(P = 0.002\)) and total serum bilirubin levels (0.7 vs 1.1, \(P = 0.003\)) than POPF patients that did not undergo reoperation. In a previous study, multivariate binary logistic regression model analysis revealed that a serum bilirubin level of > 2.0 mg/dL is an independent risk factor for reoperation (OR 25.053, 95%CI: 3.486-180.069)\(^{37}\). Some previous studies have identified higher serum bilirubin levels in CR-POPF patients, but these differences were not statistically significant. For example, El Nakeeb et al\(^{2}\) reported a preoperative bilirubin level of 4.6 mg/dL in patients with grade A POPF and 9.7 mg/dL in patients with CR-POPF, but this difference was not significant. This was supported by Braga et al\(^{38}\), who detected higher total serum bilirubin in patients with grade III-IV complications than patients with grade 0-II complications (3.5 mg/dL vs 1.6 mg/dL). Again, this difference was not statistically significant. Fujii et al\(^{39}\) found that endoscopic internal drainage posed a higher risk for POPF than endoscopic nasobiliary drainage.

In a recent systematic review, Scheufler et al\(^{40}\) reported that POPF rates do not differ between PBD and no drainage groups. However, a higher infectious complications rate was detected in the PBD group. Most of the studies included in this review were retrospective studies, and the most frequent complications were wound-related\(^{40}\). A few randomized control trial studies have now been performed by a Dutch group. In these studies, the POPF rate did not differ between PBD and surgery first groups following PD. However, the population in the POPF group was only 16%, which may
not have been high enough to obtain sufficient statistical power\(^{31}\). Current evidence does not recommend routine PBD because the rate of infectious (usually wound-related) complications is higher. However, a randomized control trial of a large population is needed to clarify this in the case of CR-POPF.

In this study, 66.8% of patients underwent PBD, which is higher than previous reports\(^{30-41}\). This could be explained by the fact that Thailand is a low to middle-income country, therefore patients with periampullary tumor and pancreatic cancer usually present with severe obstructive jaundice and have poor nutritional status. Serum bilirubin levels were higher than 15 mg/dL and serum albumin levels were less than 30 mg/dL in most patients. In addition, high-volume centers have patient congestion, limited resources and long waiting lists for operations.

This study was limited by the small study population. A larger population study might have revealed more significant risk factors of POPF.

In conclusion, we have identified a soft pancreas as an independent risk factor of POPF. A fatty pancreas is strongly associated with a soft pancreas and can be measured to predict CR-POPF. Preoperative detection of a fatty pancreas by CT and newly developed ultrasound technology is a potential method for predicting a soft pancreas preoperatively. However, this needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

**ARTICLE HIGHLIGHTS**

**Research background**

Many risk factors have been reported for postoperative pancreatic fistula (POPF), including obesity, soft pancreatic texture, small pancreatic duct and low volume center. Some studies have investigated ways to improve the surgical outcome and reduce POPF, including the placement of an external and internal trans-anastomotic pancreatic duct, pancreatogastrostomy, omental roll-up around PE anastomosis and prophylaxis with somatostatin analogs. However, the outcomes of these different methods remain controversial. Recently, a soft pancreas and high body mass index (BMI) were reported as the most common risk factors for POPF. However, risk factors for POPF have not been studied in a Thai population before. The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

**Research motivation**

The most common perioperative complication of pancreaticoduodenectomy is POPF. POPF remains the leading cause of complications such as DGE and postoperative hemorrhage, which increase mortality and the LOH. Many risk factors for POPF have been reported previously.

**Research objectives**

The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

**Research methods**

The retrospective study design were required by reviewed data from January 2001 to December 2016, 210 consecutive patients underwent PD at the Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand.

**Research results**

This is the study from tertiary care center from Thailand. To the best of the authors knowledge, this is the largest study from Thailand. The authors found that soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

**Research conclusions**

The authors have identified a soft pancreas as an independent risk factor of POPF. A fatty pancreas is strongly associated with a soft pancreas and can be measured to predict CR-POPF. Preoperative detection of a fatty pancreas by CT is a potential method for predicting a soft pancreas preoperatively. Recently, the newly developed technology of ultrasonography has high accuracy to prediction of the stiffness of pancreas preoperatively. However, this needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

**Research perspectives**

Preoperative detection of a fatty pancreas by CT and newly developed ultrasound technology is a potential method for predicting a soft pancreas preoperatively, which needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

**ACKNOWLEDGMENTS**

The authors would thank Mr. Napaphat Poprom for reviewed the biostatistics.

**REFERENCES**

1. McMillan MT, Vollmer CM Jr, Ashburn HI, Ball CG, Bassi C, Beane JD, Berger AC, Bloomston M, Callery MP, Christin JD, Dixon E, Drebina JA, Castillo CF, Fisher WE, Fong ZY, Haverick E, House MG, Hughes SJ, Kent TS, Kunstman JW, Malleo G, McElhany AL, Salem RR, Soares K, Sprés MH, Valero V 3rd, Watkins AA, Wolfgang CL, Behrman SW. The Characterization and Prediction of ISGPS Grade C Fistulas Following Pancreaticoduodenectomy. *J Gastrointest Surg* 2016; 20: 262-276 [PMID: 26169295 DOI: 10.1007/s11605-015-2884-2]

2. Hackert T, Hinz U, Pausch T, Fesehenke I, Strobel O, Schneider L, Fritz S, Büchler MW. Postoperative pancreatic fistula: We need to redefine grades B and C. *Surgery* 2016; 159: 872-877 [PMID: 26603847 DOI: 10.1016/j.surg.2015.09.014]

3. Kimura W, Miyata H, Gotoh M, Hirai I, Kenjo A, Kitagawa Y, Shimada M, Baba H, Tomita N, Nakagoe T, Sugihara K, Mori M. A pancreaticoduodenectomy risk model derived from 8575 cases from a national single-race population (Japanese) using a web-based data entry system: the 30-day and in-hospital mortality rates for pancreaticoduodenectomy. *Ann Surg 2014*; 259: 773-780 [PMID: 24253151 DOI: 10.1097/SLA.0000000000002263]

4. Roberts KJ, Sutcliffe PF, Marudanayagam R, Hodson J, Isaac J, Muesan P, Navarro A, Patel K, Jah A, Nepeta S, Adair A, Lazaridis S, Prachalias A, Shingler G, Al-Sarireh B, Storey R, Smith AM, Shah N, Fusi S, Ahmed J, Abu Hilal M, Mirza DF. Scoring System to Predict Pancreatic Fistula After Pancreaticoduodenectomy: A UK Multicenter Study. *Ann Surg 2015*; 261: 1191-1197 [PMID: 25371115 DOI: 10.1097/SLA.0000000000000997]

5. Addo P, Delpero JR, Payne F, Oussoultzoglou E, Fachhuber PR, Sauvanet A, Sa Cunha A, Le Treut YP, Mabrut JY, Le Treut Y, Cantin M, Sa Cunha A, Eloubeidi MA, Lambrinoudakis C, Ronsin O, Girard P, Sanchez-Ramos J, Adham M, Mabrut JY, Prachalias A, Shingler G, Al-Sarireh B, Storey R, Smith AM, Shah N, Fusi S, Ahmed J, Abu Hilal M, Mirza DF. Scoring System to Predict Pancreatic Fistula After Pancreaticoduodenectomy: A UK Multicenter Study. *Ann Surg 2015*; 261: 1191-1197 [PMID: 25371115 DOI: 10.1097/SLA.0000000000000997]
Büchler MW, Friess H, Wagner M, Kulli C, Wagener V, Z Graggcken K. Pancreatic fistula after pancreatic head resection. Br J Surg 2000; 87: 883-889 [PMID: 10993102 DOI: 10.1046/j.1365-2128.2000.01465.x]

Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg 2013; 220: 530-536 [PMID: 25724606 DOI: 10.1016/j.jamcollsurg.2012.12.031]

Frymerman AS, Schuld J, Ziehen P, Kollmar O, Justinger C, Menai M, Richter S, Schilling MK, Moussavain MR. Impact of postoperative pancreatic fistula on surgical outcome—the need for a classification-driven risk management. J Gastrointest Surg 2010; 14: 711-718 [PMID: 20894814 DOI: 10.1007/s11605-009-1147-5]

Hu BY, Wan T, Zhang WZ, Dong JH. Risk factors for postoperative pancreatic fistula: Analysis of 539 successive cases of pancreaticoduodenectomy. World J Gastroenterol 2016; 22: 7797-7805 [PMID: 27678363 DOI: 10.3748/wjg.v22.i47.7797]

Fang CH, Chen QS, Yang J, Xiang F, Fang ZS, Zhu W. Body Mass Index and Stump Morphology Predict an Increased Incidence of Pancreatic Fistula After Pancreatoduodenectomy. World J Surg 2016; 40: 1467-1476 [PMID: 26796868 DOI: 10.1007/s00268-016-4343-5]

Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreaticoduodenectomy. J Am Coll Surg 2013; 216: 1-14 [PMID: 23122535 DOI: 10.1016/j.jamcollsurg.2012.09.002]

El Nakeeb A, Salah T, Sultan A, El Hemaly M, Askr W, Ezzat H, Handey E, Afet E, El Hanafi E, El-Geidie A, Abdel Wahab M, Abdallah T. Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience). World J Surg 2013; 37: 1405-1418 [PMID: 23494109 DOI: 10.1007/s00268-013-1998-5]

Gaujoux S, Cortes A, Couvelard A, Noullet S, Clavel L, Rebour S, Levy P, Suvanant A, Rungsakulkij N, Hu BY. Preventive effect of omental flap in postoperative pancreatic fistula. J Gastrointest Surg 2012; 16: 1499-1507 [PMID: 22580842 DOI: 10.1007/s11605-012-1908-4]

Tian Y, Ma H, Peng Y, Li G, Yang H. Preventive effect of omental flap in pancreaticoduodenectomy against postoperative complications: a meta-analysis. Hepatogastroenterology 2015; 62: 187-189 [PMID: 26091894 DOI: 10.2147/HG.GS.S56648]

Barakat O, Ozaki CF, Wood RP. Topically applied 2-cyanoacrylate (Dermabond) for prevention of postoperative pancreatic fistula following pancreatic surgery. Cochrane Database Syst Rev 2016; 2: CD009621 [PMID: 26875671 DOI: 10.1002/14651858.CD009621.pub2]

Gurusamy KS, Koti R, Fusiad G, Davidson BR. Somatostatin analogues for pancreatic surgery. Cochrane Database Syst Rev 2013; (4): CD008370 [PMID: 23633353 DOI: 10.1002/14651858.CD008370.pub3]

Gans SL, van Westreenen HL, Kiewiet JJ, Rauws EA, Gouma DJ, Boeermeester MA. Systematic review and meta-analysis of somatostatin analogues for the treatment of pancreatic fistula. Br J Surg 2012; 99: 754-760 [PMID: 22203616 DOI: 10.1002/bjs.8709]

Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izziicki B, Neoptolomenos J, Sarr M, Traverso W, Buciker M. International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138: 8-13 [PMID: 1603039 DOI: 10.1016/j.surg.2005.05.001]

Lin JW, Cameron JL, Ye CJ, Rauli TS, Lillermo KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg 2004; 8: 951-959 [PMID: 15585382 DOI: 10.1016/j.gassur.2004.09.044]

Kang CM, Park MS, Choi SH, Chung YE, Choi JY, Kim MJ. Prediction of postoperative pancreatic fistulas after pancreatectomy: a study comparing acoustic radiation force impulse imaging of the pancreas for estimation of pathologic fibrosis and risk of postoperative pancreatic fistula. Br J Surg 2014; 246: 1058-1064 [PMID: 18043111 DOI: 10.1016/j.bjsurg.2009.09.044]

Ansoorge C, Strömmer L, Andrénd-Sandberg Å, Lundell L, Herrington MK, Segersvärd R. Structured intraoperative assessment of pancreatic gland characteristics in predicting complications after pancreatectomy. Br J Surg 2012; 99: 1076-1082 [PMID: 22556164 DOI: 10.1002/bjs.8784]

Lee TK, Kang CM, Park MS, Choi SH, Chung YE, Choi JY, Kim MJ. Postoperative pancreatic fistula with acute acoustic radiation force impulse elastography. J Ultrasound Med 2014; 33: 781-786 [PMID: 24764332 DOI: 10.7863/ultra.33.5.781]

Harada N, Inoue Y, Inoue A, Takakuma Y, Hasegawa K, Sugawara Y, Tanaka M, Fukayama M, Kokudo N. Acoustic radiation force impulse imaging of the pancreas for estimation of pathologic fibrosis and risk of postoperative pancreatic fistula. J Am Coll Surg 2014; 218: 887-894 [PMID: 25262282 DOI: 10.1016/j.jamcollsurg.2014.07.040]

Rossi E, Casneci S, Pessaux P, Oussoultzoglou E, Panaro F, Mahfud M, Jaek D, Bacheller P. The role of “fatty pancreas” and of BMI in the occurrence of pancreatic fistula after pancreatectomy. J Gastrointest Surg 2009; 13: 1845-1851 [PMID: 1963369 DOI: 10.1007/s11605-009-0794-8]

Tranchart H, Gaujoux S, Rebour S, Vuillermie MP, Dokmaz S, Levy P, Couvelard A, Belghiti J, Suvanant J. Preoperative CT scan helps to predict the occurrence of severe pancreatic fistula after pancreaticoduodenectomy. Br J Surg 2012; 256: 139-145 [PMID: 22609844 DOI: 10.1016/j.bjsa.2011.06.02362]

van der Gag NA, Klock J, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Prophylactic biliary drainage in patients with obstructive jaundice: history and current status. J Gastrointest Surg 2009; 13: 814-820 [PMID: 18726134 DOI: 10.1007/s11605-008-0618-4]

Iacono C, Ruzzenette A, Campagnaro T, Botolassi L, Valdegamberi A, Guglielmi A. Role of prophylactic biliary drainage in jaundiced patients who are candidates for pancreateoduodenectomy or hepatic resection: highlights and drawbacks. Ann Surg 2013; 257: 191-204 [PMID: 23013805 DOI: 10.1097/SLA.0b013e318268408]
Hans et al. Risk factors of pancreatic fistula

of Adverse Events for Endoscopic vs Percutaneous Biliary Drainage in the Treatment of Malignant Biliary Tract Obstruction in an Inpatient National Cohort. JAMA Oncol 2016; 2: 112-117 [PMID: 26513013 DOI: 10.1001/jamaoncol.2015.3670]
37 Gebauer F, Kloth K, Tachezy M, Vashi YK, Cataldogirmen G, Izbicki JR, Bockhorn M. Options and limitations in applying the fistula classification by the International Study Group for Pancreatic Fistula. Ann Surg 2012; 256: 130-138 [PMID: 22504279 DOI: 10.1097/SLA.0b013e318242d4e4]

38 Braga M, Capretti G, Pecorelli N, Balzano G, Doglioni C, Ariotti R, Di Carlo V. A prognostic score to predict major complications after pancreaticoduodenectomy. Ann Surg 2011; 254: 702-707, discussion 707-708 [PMID: 22042466 DOI: 10.1097/SLA.0b013e318235988b]

39 Fujii T, Yamanada S, Suenaga M, Kanda M, Takami H, Sugimoto H, Nomoto S, Nakao A, Kodera Y. Preoperative internal biliary drainage increases the risk of bile juice infection and pancreatic fistula after pancreaticoduodenectomy: a prospective observational study. Pancreas 2015; 44: 465-470 [PMID: 25423556 DOI: 10.1097/MPA.0000000000000265]

40 Scheufele F, Schorn S, Demir IE, Sargut M, Tieftrunk E, Calavrezos L, Jäger C, Friess H, Ceyhan GO. Preoperative biliary stenting versus operation first in jaundiced patients due to malignant lesions in the pancreatic head: A meta-analysis of current literature. Surgery 2017; 161: 939-950 [PMID: 28043693 DOI: 10.1016/j.surg.2016.11.001]

41 van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kuijper FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijl JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bosuyt PM, Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010; 362: 129-137 [PMID: 20071702 DOI: 10.1056/NEJMoa0903230]

P- Reviewer: Chow WK, Gong JS, Smith RC S- Editor: Kong JX L- Editor: A E- Editor: Lu YJ
