Predictors of surgical site infection after pancreaticoduodenectomy

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Abstract

Background: Surgical site infection (SSI) is one of the most common complications after pancreaticoduodenectomy (PD). Thus, it is beneficial to preoperatively identify patients at high risk of developing SSI. The primary aim of the present study was to identify the factors associated with SSI after PD, and the secondary aim was to identify the adverse outcomes associated with the occurrence of SSI.

Methods: A single-centre retrospective study was conducted. All 280 patients who underwent PD at our institution from January 2008 to December 2018 were enrolled. Demographic and perioperative data were reviewed, and the potential risk factors for developing SSI and the adverse outcomes related to SSI were analysed.

Results: A total of 90 patients (32%) developed SSI. Fifty-one patients developed incisional SSI, and 39 developed organ/space SSI. Multivariate logistic analysis revealed that the significant risk factors for developing incisional SSI were preoperative biliary drainage (odds ratio, 3.04; 95% confidence interval, 1.36–6.79; p < 0.05) and postoperative pancreatic fistula (odds ratio, 2.78; 95% confidence interval, 1.43–5.38; p < 0.05), and the risk factors for developing organ/space SSI were preoperative cholangitis (odds ratio, 10.07; 95% confidence interval, 2.31–49.75; p < 0.05) and pancreatic fistula (odds ratio, 6.531; 95% confidence interval, 2.30–18.51; p < 0.05). Enterococcus spp., Escherichia coli and Klebsiella pneumoniae were the common bacterial pathogens that caused preoperative cholangitis as well as SSI after PD. The patients in the SSI group had a longer hospital stay and a higher rate of delayed gastric emptying than patients in the non-SSI group.

Conclusions: The presence of postoperative pancreatic fistula was a significant risk factor for both incisional and organ/space SSI. Any efforts to reduce postoperative pancreatic fistula would decrease the incidence of incisional SSI as well as organ/space SSI after pancreaticoduodenectomy. Preoperative biliary drainage should be performed in selected patients to reduce the incidence of incisional SSI. Minimizing the occurrence of preoperative cholangitis would decrease the incidence of developing organ/space SSI.

Keywords: Pancreaticoduodenectomy, Risk factors, Surgical wound infection

Background

Pancreaticoduodenectomy (PD) is a standard operation for the treatment of peripancreatic cancer and some benign diseases. Despite the substantial improvement in mortality related to this operation, the morbidity is still as high as nearly 50% [1–3]. One of the most common complications after PD is surgical site infection (SSI). SSI prolongs the length of hospital stay, increases costs [4], and may also influence overall survival [5]. Therefore, it is crucial to understand the factors that contribute to SSI after PD.

The Guidelines for Prevention of SSI (1999) published by the Centers for Disease Control define SSI as an
infection that occurs within 30 or 90 days postoperatively (depending on the type of surgery) that involves the skin or subcutaneous tissue of the incisional region, deep soft tissues (e.g., fascial and muscle layers), or any part of the anatomy (e.g., organs or spaces) other than the incision that was opened or manipulated intraoperatively [6].

The factors identified in previous studies as risk factors for SSI after PD include preoperative biliary drainage [2, 7], pancreatic fistula [8], a high body mass index (BMI) [8], diabetes mellitus [7], blood transfusion [9], malnutrition, and a low serum albumin level [10–12]. As previous studies have revealed varying results, the primary aim of the present study was to identify the factors associated with SSI after PD, and the secondary aim was to identify adverse outcomes related to SSI after PD.

Methods

Patients and data collection

A single-centre retrospective study was conducted. The data from 280 patients who underwent PD at Ramathibodi Hospital from 2010 to 2018 were retrospectively reviewed. The demographic and clinical data collected included age, sex, comorbidity, BMI, American Society of Anesthesiology classification, history of smoking, preoperative biliary drainage, preoperative laboratory test results, duration of surgery, blood loss, perioperative complications, history of preoperative cholangitis, length of hospital stay and final pathologic diagnosis. Postoperative pancreatic fistula (POPF) was defined in accordance with the guidelines of the International Study Group of Pancreatic Fistula [13]. Bile leakage was defined in accordance with the guidelines of the International Study Group of Liver Surgery [14]. The wounds and drains of all patients were routinely examined for signs of infection; when SSI was suspected, additional bacterial cultures were performed, and bacteriologic data were collected. SSI was defined in accordance with the guidelines for the prevention of SSI of the Centers for Disease Control [6]. Patients were further categorized into those with incisional SSI and those with organ/ space SSI. The incisional SSI group included those with infections of the skin, subcutaneous tissue, fascia, and muscle. The present study was approved by the Institutional Review Board of Ramathibodi Hospital.

Perioperative management

Preoperative biliary drainage (PBD) was carried out in patients with clinical cholangitis, jaundice with malnutrition, or a waiting time of longer than 2 weeks; endoscopic biliary drainage (EBD) was used in most cases, while some patients underwent percutaneous transhepatic biliary drainage (PTBD). Bile juice was collected at the time PBD was performed to isolate the causative bacterium in all patients who developed clinical cholangitis, and antibiotics were prescribed based on the bacterial culture results. The biliary stents or percutaneous catheters were changed in the patients who developed cholangitis after PBD. Oral nutritional supplements were given to the malnourished patients. All patients washed their body and hair with chlorhexidine soap (4% chlorhexidine gluconate) in the evening on the day before the operation and in the morning on the operative day. Hair removal was completed just before moving the patient to the operating room. The surgical field was scrubbed with 4% chlorhexidine gluconate and painted with 2% chlorhexidine gluconate in alcohol or 10% povidone-iodine before commencing the operations. Cefoxitin was used as a preoperative prophylactic antibiotic in all cases and was continued for 24 h postoperatively, in accordance with the protocol of Ramathibodi Hospital.

The surgical procedure comprised either pylorus-preserving PD or standard PD. The pancreaticojejunostomy anastomoses were created using both the duct-to-mucosa and the invagination techniques. Pancreatic duct stents were used in all cases, and the size of the stent was adjusted based on the diameter of the pancreatic duct. Prophylactic drains were routinely placed anterior to the pancreaticojejunostomy anastomosis and posterior to the hepaticojejunostomy anastomosis. Two types of drains, a tube drain and a closed-suction drain, were commonly used. However, the number and type of drains depended on surgeon preference. The peritoneal cavity and the subcutaneous tissue were irrigated with 2 l of normal saline before skin closure.

During the postoperative period, the surgical wounds and the clinical status were routinely examined. The drain amylase level was routinely checked on postoperative days 1, 3, and 5, and the drains were removed on postoperative day 5 if there was no pancreatic leakage. In the patients who developed pancreatic fistula, the drains were retained until pancreatic leakage ceased. The patients who developed SSI after surgery received antimicrobial therapy following the results of bacterial cultures of the intraoperative bile juice or the drainage fluid obtained from the infection area. Diet was resumed, depending on the return of bowel function and patient tolerance. There were no major changes in the clinical practices over these 9 years. However, over the last 3 years, the patients were allowed to resume diet earlier than in previous years; sipping water was allowed on postoperative day 1, a liquid diet was allowed on postoperative day 2, and a soft diet was started on postoperative day 3 or day 4 if tolerable by the patient. The modified Blumgart anastomosis technique for the pancreaticojejunostomy anastomosis was the most common technique used over the last 4 years compared to the
Statistical analysis
Categorical variables were analysed using Pearson’s $\chi^2$ test (or Fisher’s exact test if appropriate), while numerical variables were analysed using independent Student’s $t$-test (or the Mann-Whitney U test if appropriate). Risk factors with a $p$ value of $< 0.1$ in univariate analysis were entered into multivariable analysis with applied logistic regression. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the strength of the associations between the variables and the outcomes. The performance of the final model was described using receiver operating characteristic curves. A $p$ value of $< 0.05$ was considered statistically significant. Analyses were performed using the STATA program, version 14 (StataCorp, College Station, TX, USA).

Results
Patient characteristics and perioperative outcomes
A total of 280 patients underwent PD during the study period. Table 1 shows the demographic and perioperative data. SSI occurred in 90 of 280 patients (32%), comprising 51 patients (18%) with incisional SSI and 39 (14%) with organ/space SSI. POPF occurred in 143 patients (51%), comprising biochemical leakage in 73 (26%), grade B in 50 (18%), and grade C in 20 (7%). Among the 143 patients with POPF, 67 (46%) developed SSI, and half of them developed organ/space SSI. POPF was significantly more common in the SSI group than in the non-SSI group. Preoperative biliary drainage was performed in 192 of 280 patients (67%), with endoscopic retrograde cholangiopancreatography accounting for 62% of the drainage procedures. Preoperative cholangitis occurred in 18 patients (6.43%); fourteen of the cases were due to biliary stent occlusion, 2 of the cases were due to obstructive jaundice, and 12 out of 18 patients (68%) developed SSI after PD. The number of patients who underwent preoperative biliary intervention was significantly higher in the SSI group than in the non-SSI group. The incidence of delayed gastric emptying was significantly higher in the SSI group than in the non-SSI group, and the BMI of the patients was significantly higher in the SSI group than in the non-SSI group. The BMI of the patients was significantly higher in the SSI group than in the non-SSI group. The median duration of hospital stay in the SSI group was 28 days, which was twice as long as that in the non-SSI group. The median length of hospital stay was significantly longer in the SSI group than in the non-SSI group (28 days vs 14 days).

Factors related to surgical site infection after pancreaticoduodenectomy
The patients in the SSI group were divided into 2 groups depending on the depth of SSI: the incisional and the organ/space SSI groups. The independent risk factors for incisional SSI after PD were preoperative biliary drainage (OR 3.04) and POPF (OR 2.78). For the organ/space SSI, POPF (OR 6.53) and preoperative cholangitis (OR 10.72) were the independent risk factors. The results of uni- and multivariate analyses of the factors related to incisional and organ/space SSI are shown in Table 2 and Table 3, respectively.

Bacteriology
In the SSI group, the bacterial cultures were positive in 46 of 90 patients, with polymicrobial culture results in 22 patients (48%). Enterococcus was the most common species identified, followed by Escherichia coli and Klebsiella pneumoniae. The results of the bacterial cultures from SSI are shown in Table 4. The results of the bile cultures from the patients who experienced preoperative cholangitis are shown in Table 5. E. coli, Enterococcus, and Klebsiella pneumoniae were the common pathogens found to contaminate the bile juice.

Discussion
The postoperative mortality rate of PD has been decreasing for many years. However, the morbidity rate remains high, particularly regarding SSI, which is one of the most common problems after PD. The incidence of SSI after PD varies from 12 to 51% [7, 8, 15–17]. Many factors contribute to SSI, including multiple enteric anastomoses, extensive physiologic changes, blood loss, and a long operative time [17]. SSI results in a large burden on the healthcare system. One study found that SSI resulted in an additional 12 days of hospitalization and approximately 5000 USD in direct costs [18], while another showed that SSI resulted in a two-fold increase in the duration of hospitalization and a 2.5-fold increase in healthcare expenditures [19]. The present study found similar results; the incidence of SSI was 32%, and the length of hospital stay in the SSI group was 28 days, which was twice as long as that in the non-SSI group.

POPF is a common and concerning problem after PD. [20, 21] Clinically relevant POPF after PD reportedly occurs in 12% of patients and is associated with a mortality rate of 39% [22]. The autodigestive effect of leaky pancreatic juice causes circumferential tissue damage and promotes bacterial infection [23]. Therefore, POPF has been reported as an independent risk factor for SSI; the incidence of serious infection in patients with POPF is
| Patient characteristics and demographic data | Total (n = 280) | Non-SSI (n = 190) | SSI (n = 90) | p value |
|---------------------------------------------|---------------|-----------------|-------------|---------|
| **Age in years, mean ± SD**                 | 59.98 ± 10.79 | 59.81 ± 10.70   | 60.36 ± 11.01 | 0.687   |
| **BMI, median (range)**                     | 22.36 (15.11, 38.95) | 21.94 (15.11, 38.95) | 22.60 (16.22, 34.06) | 0.040   |
| **Sex, n (%)**                              |               |                 |             |         |
| Male                                        | 148 (52.86)   | 100 (52.63)     | 48 (53.33)  | 0.913   |
| Female                                      | 132 (47.14)   | 90 (47.37)      | 42 (46.67)  |         |
| **Comorbidities, n (%)**                    |               |                 |             |         |
| Diabetes mellitus                           | 81 (28.93)    | 62 (32.63)      | 19 (21.11)  | 0.047   |
| Hypertension                                | 108 (38.57)   | 70 (36.84)      | 38 (42.22)  | 0.388   |
| Dyslipidemia                                | 76 (27.14)    | 56 (29.47)      | 20 (22.22)  | 0.203   |
| Renal insufficiency                         | 7 (2.50)      | 4 (2.11)        | 3 (3.33)    | 0.539   |
| **ASA class, n (%), n = 275**               |               |                 |             |         |
| I                                           | 6 (2.18)      | 3 (1.62)        | 3 (3.33)    | 0.811   |
| II                                          | 104 (37.82)   | 69 (37.30)      | 35 (38.89)  |         |
| III                                         | 156 (56.73)   | 106 (57.30)     | 50 (55.56)  |         |
| IV(E)                                       | 8 (2.91)      | 6 (3.24)        | 2 (2.22)    |         |
| Smoking, n (%)                              | 84 (30.00)    | 56 (29.47)      | 28 (31.11)  | 0.780   |
| Previous biliary intervention, n (%)        | 192 (68.57)   | 119 (62.63)     | 73 (81.11)  | 0.002   |
| WBC, mean ± SD                              | 7838 ± 2670   | 7953 ± 2665     | 7605 ± 2680 | 0.321   |
| Platelet x 10^3, median (range)             | 300 (96, 715) | 302 (96, 715)   | 124 (140, 548) | 0.068 |
| Hb in g/dL, median (range)                  | 12 (3, 30.2)  | 12 (3, 30.2)    | 2.2 (8.5, 23.3) | 0.349 |
| BUN in mg/dL, median (range)                | 13 (4, 57)    | 13 (4, 57)      | 7 (5, 29)   | 0.712   |
| Creatinine in mg/dL, median (range)         | 0.8 (0.3, 12) | 0.8 (0.3, 11)  | 0.26 (0.33, 12) | 0.734 |
| Total bilirubin in mg/dL, median (range)     | 1.6 (0.1, 35) | 1.75 (0.2, 35) | 3.4 (0.1, 30.3) | 0.341 |
| Albumin in g/L, mean ± SD                   | 34.35 ± 5.32  | 34.55 ± 5.65    | 33.94 ± 4.57 | 0.377 |
| Pre-operative cholangitis, n(%)             | 18 (6.43)     | 6 (3.16)        | 12 (13.33)  | 0.001   |
| Operative time in min, median (range)       | 475 (240, 900) | 435 (240, 900)  | 480 (240, 840) | 0.078 |
| Blood loss in ml, median (range)            | 800 (100, 13000) | 800 (100, 8000) | 800 (150, 13000) | 0.757 |
| Complications, n (%)                        |               |                 |             |         |
| Pancreatic fistula                           |               |                 |             |         |
| No                                          | 137 (48.93)   | 114 (60.00)     | 23 (25.56)  | 0.000   |
| Yes                                         | 143 (51.07)   | 76 (40.00)      | 67 (74.44)  |         |
| Bile leakage                                | 20 (7.14)     | 10 (5.26)       | 10 (11.11)  | 0.076   |
| Delayed gastric emptying                    | 29 (10.36)    | 14 (7.37)       | 15 (16.67)  | 0.017   |
| Chyle leakage                               | 13 (4.64)     | 6 (3.16)        | 7 (7.78)    | 0.125   |
| Duration of drain placement (day), n = 238  | 13 (2, 266)   | 10 (2, 94)      | 23 (2, 266) | 0.000   |
| LOH in days, median (range)                 | 16 (5, 320)   | 14 (5, 87)      | 28 (8, 320) | 0.000   |
| Diagnosis, n (%)                            |               |                 |             |         |
| Benign                                      | 73 (26.07)    | 50 (26.32)      | 23 (25.56)  | 0.892   |
| Malignant                                   | 207 (73.93)   | 140 (73.68)     | 67 (74.44)  |         |

SSI Surgical site infection, SD Standard deviation, BMI Body mass index, WBC White blood cell count, Hb Hemoglobin, BUN Blood urea nitrogen, LOH Length of hospital stay
reportedly 61%, which is three times higher than that in patients without POPF [9]. The present study demonstrated similar results, with POPF identified as a risk factor for SSI. Nearly half of the patients with POPF developed SSI, whereas only 17% of patients without POPF developed SSI; the incidence of SSI in patients with POPF was three times higher than that in patients without POPF. Focusing on the depth of SSI, POPF was a risk factor for both incisional SSI (OR 2.78) and organ/space SSI (OR 6.531). In the organ/space SSI group, the incidence was five times higher than that in patients without POPF. A previous study demonstrated a significant correlation between POPF and organ/space SSI, which developed in 76% of patients with POPF. The

| Variable                              | Univariate     | Multivariate   |
|---------------------------------------|----------------|----------------|
| Age in years, mean ± SD               | 1.006 (0.97–1.03) | 1.006 (0.97–1.03) |
| BMI, median (range)                   | 1.015 (0.94–1.09) | 1.015 (0.94–1.09) |
| Sex, n (%)                            | 0.751 (0.41–1.37) | 0.751 (0.41–1.37) |
| Comorbidities, n (%)                  |                |                |
| Diabetes mellitus                     | 0.737 (0.37–1.43) | 0.737 (0.37–1.43) |
| Hypertension                          | 1.246 (0.68–2.27) | 1.246 (0.68–2.27) |
| Dyslipidemia                          | 0.638 (0.31–1.29) | 0.638 (0.31–1.29) |
| Renal insufficiency                   | 1.690 (0.30–9.47) | 1.690 (0.30–9.47) |
| ASA class, n (%), n = 242             |                |                |
| II                                    | 1.000           | 1.000           |
| III                                   | 0.833 (0.45–1.52) | 0.833 (0.45–1.52) |
| Smoking, n (%)                        | 1.504 (0.81–2.78) | 1.504 (0.81–2.78) |
| Previous biliary intervention, n (%)  | 3.182 (1.47–6.87) | 3.182 (1.47–6.87) |
| WBC, mean ± SD                        | 0.958 (0.85–1.08) | 0.958 (0.85–1.08) |
| Platelet x10^9, median (range)        | 0.794 (0.58–1.07) | 0.794 (0.58–1.07) |
| Hemoglobin in g/dL, median (range)    | 1.058 (0.94–1.17) | 1.058 (0.94–1.17) |
| BUN in mg/dL, median (range)          | 0.999 (0.95–1.05) | 0.999 (0.95–1.05) |
| Creatinine in mg/dL, median (range)   | 1.082 (0.84–1.38) | 1.082 (0.84–1.38) |
| Total bilirubin in mg/dL, median (range) | 0.971 (0.92–1.02) | 0.971 (0.92–1.02) |
| Albumin in g/L, mean ± SD             | 0.999 (0.94–1.05) | 0.999 (0.94–1.05) |
| Pre-operative cholangitis, n(%)       | 3.375 (0.20–54.82) | 3.375 (0.20–54.82) |
| Operative time in min, median (range) | 1.205 (0.96–1.50) | 1.205 (0.96–1.50) |
| Blood loss in ml, median (range)      | 0.980 (0.74–1.28) | 0.980 (0.74–1.28) |
| Complications, n (%)                  |                |                |
| Pancreatic fistula                     |                |                |
| No                                    | 1.000           | 1.000           |
| Yes                                   | 3.250 (1.73–6.09) | 3.250 (1.73–6.09) |
| Bile leakage                          | 2.117 (0.73–6.10) | 2.117 (0.73–6.10) |
| Delayed gastric emptying              | 3.006 (1.28–7.06) | 3.006 (1.28–7.06) |
| Chyle leakage                         | 2.586 (0.84–7.93) | 2.586 (0.84–7.93) |
| Diagnosis, n (%)                      |                |                |
| Benign                                | 1.040 (0.58–1.84) | 1.040 (0.58–1.84) |
| Malignant                             | 1.000           | 1.000           |

SSI Surgical site infection, OR Odds ratio, CI Confidence interval, BMI Body mass index, ASA American Society of Anesthesiologists, WBC White blood cell count, BUN Blood urea nitrogen
authors postulated that once POPF occurs, intra-abdominal infection may be inevitable; therefore, effective drainage and intensive antibacterial treatment should be performed to prevent further morbidity [8].

Obstructive jaundice is a common presentation of periampullary cancer. In the past, biliary drainage was routinely performed before PD, and some studies suggested that this method improved surgical outcomes [24, 

| Table 3 | Variable associated with organ/space surgical site infection (SSI) |
|---------------------------------|----------------|----------------|----------------|
| SSI                            | Univariate     | Multivariate   |                |
|                                | OR (95% CI)    | p value       | OR (95% CI)    | p value       |
| Age in years, mean ± SD        | 1.002 (0.96–1.03) | 0.891         | 1.107 (0.99–1.22) | 0.057         |
| BMI, median (range)            | 1.104 (1.01–1.20) | 0.024         |                |                |
| Sex, n (%)                     |                |                |                |
| Male                           |                |                |                |
| Female                         | 1.507 (0.71–3.18) | 0.281         |                |                |
| Comorbidities, n (%)           |                |                |                |
| Diabetes mellitus              | 0.284 (0.09–0.84) | 0.024         |                |                |
| Hypertension                   | 1.263 (0.59–2.67) | 0.542         |                |                |
| Dyslipidemia                   | 0.765 (0.32–1.80) | 0.541         |                |                |
| Renal insufficiency            | 1.453 (0.15–13.42) | 0.742         |                |                |
| ASA class, n (%), n = 242      |                |                |                |
| I                              | 1              |                |                |
| II                             | 0.144 (0.02–0.81) | 0.029         |                |                |
| III                            | 0.169 (0.03–0.90) | 0.038         |                |                |
| IV                             | 0.333 (0.03–3.20) | 0.341         |                |                |
| Smoking, n (%)                 | 0.531 (0.20–1.35) | 0.187         |                |                |
| Previous biliary intervention, n (%) | 1.864 (0.79–4.35) | 0.150         |                |                |
| WBC, mean ± SD                 | 0.933 (0.80–1.08) | 0.369         |                |                |
| Platelet ×10^3, median (range) | 0.741 (0.50–1.08) | 0.125         |                |                |
| Hemoglobin in g/dL, median (range) | 0.997 (0.85–1.15) | 0.970         |                |                |
| BUN in mg/dL, median (range)   | 1.001 (0.94–1.06) | 0.967         |                |                |
| Creatinine in mg/dL, median (range) | 0.734 (0.25–2.07) | 0.561         |                |                |
| Total bilirubin in mg/d/L, median (range) | 0.981 (0.92–1.04) | 0.538         |                |                |
| Albumin in g/L, mean ± SD      | 0.951 (0.89–1.01) | 0.128         |                |                |
| Preoperative cholangitis, n (%) | 12.193 (1.07–138.54) | 0.044         | 10.722 (2.31–49.75) | 0.002         |
| Operative time in min, median (range) | 1.126 (0.83–1.51) | 0.428         |                |                |
| Blood loss in ml, median (range) | 1.264 (1.01–1.59) | 0.046         |                |                |
| Complications, n (%)           |                |                |                |
| Pancreatic fistula              |                |                |                |
| No                             | 1              |                | 0              |
| Yes                            | 8.399 (3.10–22.71) | 0.000         | 6.531 (2.30–18.51) | 0.000         |
| Bile leakage                   | 2.482 (0.73–8.44) | 0.145         |                |                |
| Delayed gastric emptying       | 1.733 (0.53–5.63) | 0.360         |                |                |
| Chyle leakage                  | 1.978 (0.38–10.24) | 0.416         |                |                |
| Diagnosis, n (%)               |                |                |                |
| Benign                         | 1              |                |                |
| Malignant                      | 0.952 (0.41–2.18) | 0.908         |                |                |

SSI Surgical site infection, OR Odds ratio, CI Confidence interval, BMI Body mass index, ASA American Society of Anesthesiologists, WBC White blood cell count, BUN Blood urea nitrogen
ally, the present study demonstrated that preoperative/SteriC
tpared to non-preoperative cholangitis patients. Addition-
/risk for developing organ/space SSI by 10 times com-
pended risk factor for organ/space SSI. It increased the
bacterial infection in the biliary system, was an inde-
operative cholangitis, which is the result of severe
isms [27, 31]. The present study showed that pre-
results from intraoperative contamination by biliary or-
–100%), which suggests that postoperative infection
induces bile infection, with the bile infection rate in
stented patients is nearly twice that in non-stented pa-
tients (30% vs 18 and 78% vs 36%, respectively) [27, 28].
Another study revealed that bile infection is significantly
associated with overall morbidity, infection morbidity,
and mortality [29, 30]. Furthermore, isolated bacteria in
bile are strongly associated with infectious complications
(69–100%), which suggests that postoperative infection
results from intraoperative contamination by biliary or-
ganisms [27, 31]. The present study showed that pre-
operative cholangitis, which is the result of severe
bacterial infection in the biliary system, was an inde-
pendent risk factor for organ/space SSI. It increased the
risk for developing organ/space SSI by 10 times com-
pared to non-preoperative cholangitis patients. Addition-
ally, the present study demonstrated that preoperative
biliary drainage was a risk factor for overall SSI, as 81%
of patients with SSI had undergone preoperative biliary
drainage. However, when focusing on the depth of SSI,
the preoperative biliary intervention was the independ-
ent risk factor only for incisional SSI and not for organ/
space SSI. The result seemed extraordinary, but the data
in the literature showed a debatable result. Some studies
have reported that preoperative biliary drainage is asso-
ciated with a high incidence of intraabdominal abscess
formation after PD [32, 33], but some studies have re-
ported contradictory results. A study from Johns Hop-
kins reported no difference in the incidence of
intraabdominal abscess in the preoperative drainage
group compared to the non-drainage group (4% vs 6%)
[34]. Another study from the M.D. Anderson Cancer
Center reported that the rate of intraabdominal abscess
after PD was comparable in preoperative drainage and
non-drainage groups (7% vs 11%) [35]. Two other stud-
ies reported that preoperative biliary drainage was an in-
development risk factor for incisional SSI but was not a
risk factor for organ/space SSI in hepatobiliary and pan-
creatic surgery [16, 36]. Nonetheless, according to re-
cently published data, preoperative biliary drainage
appears to increase the morbidity rate in patients under-
going PD, particularly in terms of septic complications,
and routine biliary drainage should be avoided. A recent
literature review suggests that the indications for pre-
operative biliary drainage are 1) acute cholangitis, ob-
struction with a high bilirubin level, and severe pruritus;
2) anorexia with a poor nutritional status; 3) jaundice
associated with renal failure or other comorbidities; and 4)
PD delayed by more than 4 weeks [37].

In SSI patients, approximately half of the bacterial cul-
tures were positive, and 48% of these positive cultures
were polymicrobial. The bacteria that commonly caused
SSI were gut-derived species, such as Enterococcus,
Escherichia coli and Klebsiella pneumoniae, which were
the common pathogens causing preoperative cholangitis.
Extended-spectrum beta-lactamase-producing bacteria
were identified in 24% of positive cultures in SSI patients
and were identified in some preoperative cholangitis pa-
tients. Thus, when preoperative cholangitis or SSI is sus-
pected, antibiotics targeting these kinds of bacteria
should be considered until the responsible bacteria are
otherwise identified.

The incidence of DGE was significantly higher in the
SSI group than in the non-SSI group. Septic complica-
tions, especially intraabdominal collection, might affect
the function of the alimentary tract. Appropriate man-
agement, including appropriate antibiotics and abdom-
inal collection drainage, is mandatory to improve clinical
outcomes and reduce further morbidities. A long hos-
pital stay is an inevitable consequence in patients who
experience SSI because of the need for further

Table 4 Pathogens isolated from bile juice of patients who
developed preoperative cholangitis

| Bacterial species     | Number of cases in which each species was identified |
|-----------------------|------------------------------------------------------|
| Enterococcus          | 5                                                    |
| Escherichia coli      | 8                                                    |
| Klebsiella pneumoniae | 5                                                    |
| E. coli ESBL          | 1                                                    |
| Klebsiella ESBL       | 2                                                    |
| Pseudomonas           | 1                                                    |
| Others                | 5                                                    |

ESBL: Extended spectrum beta-lactamase-producing bacteria

25]. However, the wisdom of routine preoperative bil-
ary drainage has been questioned recently. A recent
meta-analysis demonstrated that preoperative biliary
drainage does not have a beneficial effect on postopera-
tive outcomes and actually increases overall complica-
tions and the incidence of wound infections [26]. Two
other studies demonstrated that biliary stent insertion
induces bile infection, with the bile infection rate in
stented patients is nearly twice that in non-stented pa-
tients (30% vs 18 and 78% vs 36%, respectively) [27, 28].
Another study revealed that bile infection is significantly
associated with overall morbidity, infection morbidity,
and mortality [29, 30]. Furthermore, isolated bacteria in
bile are strongly associated with infectious complications
(69–100%), which suggests that postoperative infection
results from intraoperative contamination by biliary or-
ganisms [27, 31]. The present study showed that pre-
operative cholangitis, which is the result of severe
bacterial infection in the biliary system, was an inde-
pendent risk factor for organ/space SSI. It increased the
risk for developing organ/space SSI by 10 times com-
pared to non-preoperative cholangitis patients. Addition-
ally, the present study demonstrated that preoperative

Table 5 Pathogens isolated from infected sites of surgical site
infection patients

| Bacterial species     | Number of cases in which each species was identified |
|-----------------------|------------------------------------------------------|
| Enterococcus          | 18                                                   |
| Escherichia coli      | 10                                                   |
| Klebsiella pneumoniae | 9                                                    |
| E. coli ESBL          | 6                                                    |
| Klebsiella ESBL       | 5                                                    |
| Pseudomonas           | 2                                                    |
| Acinetobacter         | 2                                                    |
| Others                | 22                                                   |

ESBL: Extended spectrum beta-lactamase-producing bacteria
treatments. In the SSI group, the duration of drain placement was longer than that in the non-SSI group. This might be because of the higher incidence of POPF in those patients. In our practice, the drains were removed only when the pancreatic fistula had completely disappeared.

Various risk factors for SSI have been reported in recent studies, which are shown in Table 6. Many studies have demonstrated that preoperative biliary drainage \[2, 7, 8, 16, 17, 36, 38\] and pancreatic fistula \[8, 10, 38\] are independent risk factors for SSI, which is consistent with the present study. Previous studies \[8, 30, 36\] have reported that a high BMI is a risk factor for SSI, which is consistent with another study in the literature showing that overweight and obesity increase the risk of SSI in many types of surgery \[39\]. The present study showed that the BMI in the SSI group was significantly higher than in the non-SSI group; however, it was not a significant risk factor for SSI in multivariate analysis. This might be because of the small number of patients included in the study. Two other previous studies \[8, 30\] also demonstrated that a long operative time (> 480 min, > 7 h) was a risk factor for developing SSI. The data of the present study did not reveal the same result. The difference in practice, for instance, the type and frequency of prophylactic antibiotic redosing, saline irrigation before abdominal closure and a different number of patients included in the studies, might have influenced the different results. Blood transfusion \[9, 30\] and neoadjuvant therapy \[2, 38\] have also been described as risk factors for SSI. The present study did not have sufficient data to discuss these factors. However, blood transfusion is still a debatable topic because studies in the literature have shown contradictory results \[40, 41\]. Neoadjuvant therapy has recently become an important modality of treatment in pancreatic cancer. To my knowledge, there have been few publications describing this issue, so more studies are needed to draw conclusions.

The present study had two main limitations. First, because of its retrospective nature, some selection bias may have been present. Second, the study population was relatively small compared with previous studies.

**Conclusions**

Preoperative biliary drainage, POPF, and preoperative cholangitis are significant risk factors for SSI. To lower the incidence of SSI, preoperative biliary drainage should be performed only in select cases, and every effort

### Table 6 Summarization of recent studies of risks of surgical site infection after pancreaticoduodenectomy

| Author (year) | Type of study | No. of patients | Incidence of SSI (%) | Percent of malignancy (%) | Risk factors of surgical site infection |
|---------------|---------------|-----------------|----------------------|---------------------------|----------------------------------------|
| Poluk K. E (2016) [37] | Single center retrospective | 679 | 17.2 | – | Pre-operative biliary drainage, Neoadjuvant chemotherapy |
| Zhang L (2016) [9] | Single center retrospective | 212 | 29\(^a\) | 80 | Pancreatic fistula, Blood transfusion |
| Barreto S. G (2015) [7] | Single center retrospective | 277 | 35 | 81 | Pre-operative biliary stent insertion, Non-diabetic endocrine co-morbidity. |
| De Pastena M (2017) [17] | Single center retrospective | 893 | 45.8\(\dagger\) | – | Pre-operative biliary drainage |
| Sugiura T (2012) [8] | Single center retrospective | 408 | 51 | 90 | Long operative time, High Body Mass Index, Pancreatic fistula, Semi-close suction drain, Main pancreatic duct < 3 mm, Abdominal wall fat thickness > 10 mm. |
| Burkhart R. A (2017) [2] | Single center retrospective | 394 | 19.8 | 71.1 | Pre-operative biliary drainage, neoadjuvant therapy, prior abdominal surgery |
| Shinkawa H (2018) [10] | Single center retrospective | 106 | 14.2 | – | Nutritional risk index, Pancreatic fistula |
| Gavazzi F (2016) [35] | Single center retrospective | 180 | 52.3 | 86 | Pre-operative biliary stent, Cardiac disease, BMI > 25 mg/m\(^2\) |
| Okano K (2015) [30] | Multi center retrospective | 4147 | 27.1 | 90 | Male sex, age 70 years or more, Body mass index at least 25 kg/m\(^2\), Other previous malignancy, Liver disease, Bile contamination, Duration of surgery 7 h or longer, Intraoperative blood transfusion, Soft pancreas |

\(\dagger\) Overall infectious complication

- Not stated
should be made to reduce the incidence of POPF and preoperative cholangitis.

Abbreviations
SSI: Surgical site infection; PD: Pancreatectoduodenectomy; BMI: Body mass index; POPF: Postoperative pancreatic fistula; OR: Odds ratio; CI: Confidence intervals

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Authors’ contributions
SW participated in the study design, data collection, data analysis and interpretation and manuscript writing; RH participated in the data collection and manuscript writing; MS participated in the data collection and data analysis; MP participated in the data collection and data analysis; AV participated in the data collection and data analysis; AS participated in the data analysis. The authors read and approved the final manuscript.

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