Preoperative and intraoperative risk factors of postoperative pancreatic fistula after pancreaticoduodenectomy – systematic review and meta-analysis

Kajetan Kiełbowski 1ABCDEF, Estera Bakinowska 1DEF, Rafał Uciński 2DEF
1Students' Scientific Society, Pomeranian Medical University, Szczecin, Poland; Head: Jerzy Sieńko MD PhD
2West Pomeranian Oncology Center, Szczecin, Poland; Head: Rafał Uciński MD PhD

ABSTRACT:
Introduction: Postoperative pancreatic fistula (POPF) is a potentially life-threatening complication after pancreaticoduodenectomy (PD). It is observed when the amylase activity in the drain fluid exceeds three times the normal upper value. Grades B and C of POPF are considered as clinically relevant POPF.

Aim: Since many papers evaluated the possible factors associated with POPF and some of those remain controversial, this meta-analysis assesses the strength of those results.

Materials and methods: This analysis was conducted through systematically searching databases for eligible articles published between 2015 and 2020. Search results were reviewed using inclusion criteria. To investigate potential risk factors associated with the occurrence of POPF, odds ratios (OR) with 95% confidence intervals (CI) were calculated. To compare continuous data, mean differences (MD) were calculated.

Results: Twenty retrospective and prospective studies published between 2015 and 2020 were included in this meta-analysis. A total number of patients was 6225. Thirteen factors were divided into preoperative and intraoperative groups. Our analysis proved that male sex (OR 1.55; 95% CI 1.27 to 1.90), BMI (MD 0.91; 95% CI 0.47 to 1.35), soft pancreatic texture (OR 4.35; 95% CI 3.04 to 6.22) and main pancreatic duct <3 mm (OR 2.72; 95% CI 1.43 to 5.19) can be considered as significant risk factors of POPF while vascular resection is a protective factor (OR 0.44; 95% CI 0.25 to 0.79). Age, smoking, drinking habit, diabetes, albumin level, biliary drainage, operation time and transfusions did not affect the development of pancreatic fistula.

Conclusions: Evaluating significant risk factors for POPF occurrence might help surgeons screen patients with a higher risk of developing fistula and select adequate postoperative care or treatment.

KEYWORDS: contest PPCH, pancreaticoduodenectomy, postoperative pancreatic fistula

INTRODUCTION
Pancreaticoduodenectomy (PD) is a challenging surgery performed in patients with benign or malignant tumors of pancreatic head, duodenum, gastric antrum) or with a pylorus-preserving technique when possible [1]. In the past, pancreatic surgery was considered as demanding procedure with high mortality rates. According to Mikulicz-Radecki, the famous Polish surgeon (1850–1905), the lack of progress was a result of three barriers. The first was the anatomical position of the pancreas. Second, frequent diagnosis of end-stage pancreatic cancer and third – high morbidity as a result of limitations in perioperative care. Research in the end of the 19th and in the 20th centuries was focused on overcoming those barriers [2]. The first partial resections of the pancreas and duodenum were performed in the end of the 19th century by Codivilla and Halsted while the first pancreaticoduodenectomy was carried out by Whipple in 1935. Currently, the mortality rate after PD has been decreased to less than 2% [3]. Nonetheless, early diagnosis of pancreatic cancer still represents a clinical problem and requires further research. After surgery, several complications might develop. Among others, there are: postoperative pancreatic fistula (POPF), delayed gastric emptying, hemorrhage, hepatic abscess or biliary stricture [4]. POPF is a common and dangerous complication and may lead to sepsis or bleeding, which in some cases would require re-operation [4, 5]. POPF is a leakage of pancreatic enzymes into the abdomen. It is recognised when amylase...
activity in the drain fluid exceeds 3 times the normal upper value. It might originate from failure of healing of a pancreatic anastomosis or from raw pancreatic surface.

Former classification divided POPF into three stages: A, B and C. However, in 2016 the International Study Group on Pancreatic Surgery redefined the grading system. Since then, instead of grade A POPF, there is a biochemical leak which is not a pancreatic fistula and does not have a clinical impact. Clinically relevant fistulas, affecting the postoperative course, include grades B and C (Fig. 1.) [6].

Since clinically relevant fistulas might lead to the development of other serious complications, it is crucial to fully understand and verify the risk factors of POPF after PD. Many surgical centers have reported their experience with POPF and many risk factors were considered as significant in the process of developing such fistulas. However, some factors remain controversial, and, in some studies, sample sizes were limited. Furthermore, since only grades B and C are considered as clinically relevant, it is significant to evaluate risk factors of CR-POPF only. Thus, we performed a systematic review and meta-analysis to assess the role of preoperative and intraoperative factors in developing POPF.

METHODS

Fig. 2. represents identification and selection processes for this meta-analysis. Search was conducted using PubMed, Embase and Cochrane Library. The following terms were used in searching: postoperative pancreatic fistula after pancreaticoduodenectomy/pancreatoduodenectomy; risk factors of POPF after pancreaticoduodenectomy; risk factors of pancreatic fistula. We developed eligibility criteria using a PICO acronym. Population: patients with pancreatic or duodenum diseases qualified for pancreatic resection; Intervention: pancreaticoduodenectomy; Comparator: biochemical examination; Outcome: occurrence of postoperative pancreatic fistula. Retrospective analyses, case-control and prospective studies published between 2015 and 2020 were included. In addition, the study had to present factors associated with POPF only after pancreaticoduodenectomy. Furthermore, biochemical leakage (former grade A POPF) had to be classified in the non-POPF group. Only articles in English were included. Characteristics of included studies are presented in Tab. I. Two reviewers independently screened titles and abstracts of searched studies and data was extracted manually. Discrete data and means with standard deviations (continuous data) were included. Medians with ranges were not used in this meta-analysis. In case of uncertainty, a third reviewer double-checked the indicated studies.

STATISTICAL ANALYSIS

This meta-analysis was performed using Review Manager software (version 5.4; Cochrane Collaboration, Oxford, United Kingdom). To evaluate the effects of discrete data on the risk of developing POPF, odds ratios (OR) with 95% Confidence Intervals (CI) were calculated. As data was presented in the form of means and standard deviations (SD), mean differences (MD) with 95% CI were calculated. Heterogeneity was quantified using the I² statistic. The statistical estimates of effect were determined using fixed effect in calculations with low heterogeneity (<25%). Random effect model was applied to the remaining ones. To assess publication bias, funnel plot was used.

RESULTS

As many as 539 studies were identified after initial search. Narrowing timeline to years 2015–2020 left 340 potential studies. After scanning titles and abstracts, 48 studies remained for full text assessment. A total of 20 studies with 6225 patients (range from 46 to 2503) were included. Seven (35%) studies investigated patients from Japan, 4 (20%) from China, 2 (10%) from Italy, 2 (10%) from France, 2 (10%) from Turkey, 1 (5%) from Spain, South Korea and Sweden.

Gender

All included studies (20) depicted association between gender and POPF. In 3 of them male sex was a significant risk factor for developing pancreatic fistula and pooled OR with 95% CI supported this view (OR 1.55 95% CI 1.27 to 1.90; Fig. 3A.).

Age

11/20 studies evaluated the effect of age (continuous variable) on POPF including 1667 patients. According to our analysis, there was no significant difference in age between two groups (MD 0.66 95%CI -0.93 to 2.25; Fig. 3B.).

Smoking

9 out of 20 studies assessed the impact of smoking on developing POPF. According to only one study smoking increased the risk of pancreatic fistula. Pooled OR did not indicate cigarette smoking to affect POPF (OR 1.06 95%CI 0.87 to 1.30; Fig. 3C.).
Tab. I. Characteristics of included studies.

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>YEAR</th>
<th>COUNTRY</th>
<th>STUDY DESIGN</th>
<th>DEFINITION OF POPF</th>
<th>SAMPLE SIZE</th>
<th>PATIENTS WITH POPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujiwara Y et al. [17]</td>
<td>2015</td>
<td>Japan</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>247</td>
<td>43</td>
</tr>
<tr>
<td>Chen Y et al. [18]</td>
<td>2015</td>
<td>China</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>921</td>
<td>89</td>
</tr>
<tr>
<td>Furukawa K et al. [19]</td>
<td>2016</td>
<td>Japan</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>46</td>
<td>16</td>
</tr>
<tr>
<td>Fang CH et al. [20]</td>
<td>2016</td>
<td>China</td>
<td>Prospective</td>
<td>ISGPF</td>
<td>90</td>
<td>18</td>
</tr>
<tr>
<td>Kinaci E et al. [21]</td>
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<td>Turkey</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>85</td>
<td>20</td>
</tr>
<tr>
<td>Takeishi K et al. [22]</td>
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<td>Japan</td>
<td>Prospective</td>
<td>ISGPF</td>
<td>120</td>
<td>27</td>
</tr>
<tr>
<td>Gagnière J et al. [23]</td>
<td>2017</td>
<td>France</td>
<td>Prospective</td>
<td>ISGPF</td>
<td>191</td>
<td>70</td>
</tr>
<tr>
<td>Casadei R et al. [24]</td>
<td>2017</td>
<td>Italy</td>
<td>Prospective</td>
<td>ISGPF</td>
<td>84</td>
<td>34</td>
</tr>
<tr>
<td>Gruppo M et al. [25]</td>
<td>2018</td>
<td>Italy</td>
<td>Prospective</td>
<td>ISGPS</td>
<td>86</td>
<td>23</td>
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<tr>
<td>Ke ZX et al. [26]</td>
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<td>China</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>241</td>
<td>50</td>
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<tr>
<td>Zarzavadjian Le Bian A et al. [27]</td>
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<td>France</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>270</td>
<td>74</td>
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<tr>
<td>Di Martino M et al. [28]</td>
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<td>Spain</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>107</td>
<td>30</td>
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<tr>
<td>Li YT et al. [29]</td>
<td>2019</td>
<td>China</td>
<td>Retrospective</td>
<td>ISGPS</td>
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<td>38</td>
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<tr>
<td>Aksel B et al. [30]</td>
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<td>Turkey</td>
<td>Retrospective</td>
<td>ISGPS</td>
<td>98</td>
<td>10</td>
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<tr>
<td>Paik KY et al. [31]</td>
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<td>South Korea</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>163</td>
<td>25</td>
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<tr>
<td>Abe K et al. [32]</td>
<td>2020</td>
<td>Japan</td>
<td>Retrospective</td>
<td>ISGPS</td>
<td>257</td>
<td>67</td>
</tr>
<tr>
<td>Abe T et al. [33]</td>
<td>2020</td>
<td>Japan</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>136</td>
<td>42</td>
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<tr>
<td>Sakamoto T et al. [34]</td>
<td>2020</td>
<td>Japan</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>192</td>
<td>54</td>
</tr>
<tr>
<td>Utsumi M et al. [35]</td>
<td>2020</td>
<td>Japan</td>
<td>Retrospective</td>
<td>ISGPF</td>
<td>97</td>
<td>29</td>
</tr>
<tr>
<td>Williamson C et al. [36]</td>
<td>2020</td>
<td>Sweden</td>
<td>Prospective</td>
<td>ISGPS</td>
<td>2503</td>
<td>245</td>
</tr>
<tr>
<td><strong>Total n of patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>6225</strong></td>
<td><strong>1004</strong></td>
</tr>
</tbody>
</table>

POPF – postoperative pancreatic fistula; ISGPS – International Study Group of Pancreatic Surgery; ISGPF – International Study Group of Pancreatic Fistula

**Drinking habit**

6/20 studies evaluated the influence of drinking alcohol on pancreatic fistula and none of them reported that drinking habit increases the risk. Meta-analysis supported this view (OR 0.98 95% CI 0.58 to 1.65; Fig. 3D.).

**Diabetes**

4751 patients in 9 studies were evaluated for the association of diabetes and POPF. One study indicated that diabetes increased the risk of POPF while another study indicated that this comorbidity lowered the risk. Pooled OR however showed that diabetes was not a risk factor for the development of fistula (OR 0.80 95% CI 0.52 to 1.25). Further assessment of subgroup analysis based on region (Europe vs Asia) showed that diabetes lowered the risk of POPF in Europe while the results from Asian countries did not indicate diabetes as a significant risk factor (Fig. 3E.).

**Albumin**

4/20 studies reported preoperative albumin values (continuous variable). Our analysis did not indicate that two groups differed regarding the albumin level. (MD 0.83 95%CI -0.07 to 1.74; Fig. 3E.).

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**Fig. 2.** Flow diagram illustrating selection of articles included in the meta-analysis.
## META-ANALYSIS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Male Events Total</th>
<th>Female Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3621</td>
<td>2604</td>
<td>100.0%</td>
<td>1.55 (1.27, 1.90)</td>
<td></td>
</tr>
</tbody>
</table>

### Comparison (95% CI)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>POFF</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.38</td>
<td>(0.38, 0.38)</td>
</tr>
</tbody>
</table>

### Bivariate Meta-Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Smokers</th>
<th>Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1035</td>
<td>3587</td>
<td>100.0%</td>
<td>1.06 (0.87, 1.30)</td>
<td></td>
</tr>
</tbody>
</table>

### Test for overall effect: Z = 0.82 (P = 0.41)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Drinkers</th>
<th>Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>372</td>
<td>1354</td>
<td>100.0%</td>
<td>0.98 (0.58, 1.65)</td>
<td></td>
</tr>
</tbody>
</table>

### Test for overall effect: Z = 0.82 (P = 0.41)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Diabetics</th>
<th>Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>857</td>
<td>3894</td>
<td>100.0%</td>
<td>0.80 (0.52, 1.25)</td>
<td></td>
</tr>
</tbody>
</table>

### Test for overall effect: Z = 0.82 (P = 0.41)
Preoperative biliary drainage

9/20 studies investigated the influence of preoperative biliary drainage on POPF. Increased risk of POPF after drainage was depicted in 2 studies while decreased risk was observed in one study. Meta-analysis showed no significant risk of fistula after biliary drainage (OR 0.97 95% CI 0.57 to 1.64; Fig. 3G.).

BMI

13/20 studies assessed the influence of BMI on POPF. Pooled effects of eight studies that presented data with continuous variables showed a significant difference in BMI between POPF and non-POPF groups (MD 0.91 95% CI 0.47 to 1.35; Fig. 3H.). In addition, 4 studies depicted BMI with discontinuous data. In one of them BMI>24 did not prove to be a significant risk factor. However, in the rest of them BMI greater than 22, 25 and 28 increased the risk of POPF occurrence.

Pancreatic duct diameter

9/20 studies evaluated the diameter of the main pancreatic duct (MPD) and its influence on the occurrence of fistula with a total of 2020 patients. Six studies used discontinuous and 3 used continuous variables. MPD < 3 mm was considered as a significant factor (OR 2.72 95% CI 1.43 to 5.19; Fig. 4B.). According to 3 other studies, pooled effects showed a significant difference in MPD diameter between the analyzed groups (MD -1.02 95% CI -1.44 to -0.61; Fig. 4C.).

Operation time

8 out of 20 studies examined the association between operation time and occurrence of the fistula. Pooled effects did not reveal that operation time significantly differed between two groups. (MD 5.87 95% CI -1.44 to 27.05; Fig. 4D.).

Blood transfusions

According to 5 studies that evaluated the influence of blood transfusions, it did not increase risk of POPF. Pooled OR supported this view (OR 0.94 95% CI 0.72 to 1.21; Fig. 4E.).
Fig. 4. Forest plots of the association between CR-POPF and intraoperative factors: A – pancreatic texture, B – MPD diameter, C – Operation time, D – Blood transfusions, E – Vascular resection.

- **A**: Forest plot for pancreatic texture.
- **B**: Forest plot for MPD diameter.
- **C**: Forest plot for operation time.
- **D**: Forest plot for blood transfusions.
- **E**: Forest plot for vascular resection.
study, patients with POPF were associated with an increase of BMI compared to the non-POPF group. Enhanced BMI correlates positively with increased amount of intrapancreatic fat. Furthermore, obesity is said to affect pancreatic texture and quality of pancreatic anastomosis [8]. Additionally, cytokines of adipose tissue may be activated as a result of surgical stress. This would cause pancreatitis and may lead to fistula formation [9]. However, according to the study performed by Rosso et al., infiltration of pancreatic fat of more than 10% is a risk factor for pancreatic fistula in non-overweight patients as well [10]. Apart from higher BMI, increased age, cystic fibrosis and Cushing syndrome are considered as risk factors for fat infiltration [9]. Diabetes remains a controversial factor associated with the occurrence of POPF. In this meta-analysis diabetes proved to lower the risk of POPF only in Europe (based on subgroup analysis). According to the articles from Asia, diabetes does not affect the development of fistulas. In the review by Nakata B et al., several studies are compared, and results are inconclusive. However, these results are based on studies carried out before a new grading of POPF defined by ISGPS [11]. In other study, by Xia X et al., diabetes lowered the risk of clinically relevant POPF. This might be a result of smaller amount of pancreatic fat or more advanced fibrosis in patients with DM compared to non-DM patients [12]. Soft pancreatic texture is a broadly accepted risk factor associated with the occurrence of POPF and still requires further research. In this

**Vascular resection**

5/20 studies investigated the association between vascular resection and the occurrence of POPF. This procedure decreased the risk of developing POPF as stated by 3 studies and this meta-analysis agreed with this view (OR 0.44 95% CI 0.25 to 0.79; Fig. 4F).
Nevertheless, assessment of the texture of the pancreas is mostly subjective and based on surgeon’s opinion. Therefore, it is difficult to introduce standardized definitions of a soft or firm gland. Higher heterogeneity may be a result of lack of these definitions.

A small main pancreatic duct is considered when its diameter is lower than 3 mm and it has been frequently correlated with the development of POPF. Narrow ducts might become more frequently obstructed. Furthermore, a smaller duct can contain only a certain number of sutures. Combined with soft pancreas reconstruction, this becomes technically complex [13].

Vascular resection is performed based on surgeon’s decision when the tumor adheres to a blood vessel. The procedure mainly affects veins; portal vein (PV) or superior mesenteric vein (SMV). Resection of visceral arteries may cause loss of small intestine innervation and fast gastrointestinal transit [14]. In the study performed by Shyr BU et al., this intervention did not increase risk of POPF [15]. On the contrary, according to this analysis, vascular resection procedure decreased the risk of POPF. Our institutional experience indicates that soft pancreas texture and narrow Wirsung duct are the most meaningful risk factors for the development of pancreatic fistula. POPF occurrence may also depend on surgeon’s experience and the number of pancreaticoduodenectomies performed in a particular center. Funnel plot was performed to assess publication bias using patients’ gender as an index. The funnel plot of 20 studies appeared to be symmetrical (Fig. 5). There were some limitations in this meta-analysis. Firstly, 14 studies were retrospective. More prospective cohort studies would be required to increase the reliability of reported data. Secondly, there was a significant heterogeneity as regards age, drinking habit, biliary drainage, diabetes, pancreatic texture, pancreatic duct diameter and operation time. All included studies were published between 2015 and 2020. POPF was defined by ISGPS in 2005, and its classification was redesigned in 2016. To examine the causes of heterogeneity, a subgroup analysis based on region was performed. It revealed that diabetes is a protective factor in papers published in Europe but in case of other factors, it did not change the initial result. Heterogenous results regarding pancreatic texture may follow from subjective assessment of soft pancreas. Other sources of heterogeneity are: patients’ characteristics or operative technique. This includes different indications for pancreaticoduodenectomy, such as pancreatic cancer, duodenal cancer, stromal tumor or intraductal papillary mucinous neoplasm IPMN among others. Additionally, different anastomoses performed in some studies (pancreaticojejunostomy, PJ vs pancreaticogastrostomy, PG) might contribute to the presence of heterogeneity. However, according to a recent phase 3 randomized control trial evaluating POPF rates after PJ and PG, there were no significant differences in fistula occurrence between these two groups (P = 0.48) [16]. Furthermore, many other factors may be associated with the development of POPF but they were not assessed in this meta-analysis due to the lack of articles or data.

**CONCLUSIONS**

This meta-analysis examined the risk factors of postoperative pancreatic fistula development after pancreaticoduodenectomy. Recently, the grading system of pancreatic fistula was redesigned which indicates that further research is required to fully understand the pathophysiology of the fistula. In this meta-analysis, male sex, soft pancreas and small pancreatic duct were identified as risk factors for POPF. Vascular resection lowers the risk of POPF but further research is needed to assess the influence of diabetes. In addition, patients with POPF were associated with an increased BMI compared to patients without pancreatic fistula.

We strongly believe that this study might allow surgeons to screen patients with a higher risk of POPF development and to introduce adequate treatment. Further research might focus on evaluating additional protective factors or impact of different surgical methods such as laparoscopic or robotic pancreaticoduodenectomy.

**REFERENCES**
