REVIEW ARTICLE

# Post-operative morbidity following pancreatic duct occlusion without anastomosis after pancreaticoduodenectomy: a systematic review and meta-analysis

Mariano C. Giglio[1], Gianluca Cassese[1], Federico Tomassini[2], Nikdokht Rashidian[2], Roberto Montalti[3] & Roberto I. Troisi[1]

[1]Division of HPB, Minimally Invasive and Robotic Surgery, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy, [2]Department of Human Structure and Repair, Ghent University Faculty of Medicine, Ghent, Belgium, and [3]Department of Public Health, Federico II University Naples, Naples, Italy

## Abstract

**Background:** Pancreatic duct occlusion (PDO) without anastomosis is a technique proposed to mitigate the clinical consequences of postoperative pancreatic fistulas (POPF) after pancreaticoduodenectomy. The aim of this study was to appraise the morbidity following PDO through a systematic review and meta-analysis.

**Methods:** A systematic search of MEDLINE, Embase, and Web Of Science identified studies reporting outcomes of PDO following pancreaticoduodenectomy. Pooled prevalence rates of postoperative complications and mortality were computed using random-effect modeling. Meta-regression analyses were performed to examine the impact of moderators on the overall estimates.

**Results:** Sixteen studies involving 1000 patients were included. Pooled postoperative mortality was 2.7%. A POPF was reported in 29.7% of the patients. Clinically relevant POPFs occurred in 13.5% of the patients, while intra-abdominal abscess and haemorrhages occurred in 6.7% and 5.5% of the patients, respectively. Re-operation was necessary in 7.6% of the patients. Postoperatively new onset diabetes occurred in 15.8% of patients, more frequently after the use of chemical substances for PDO ($p = 0.003$).

**Conclusions:** PDO is associated with significant morbidity including new onset of post-operative diabetes. The risk of new onset post-operative diabetes is associated with the use of chemical substance for PDO. Further evidence is needed to evaluate the potential benefits of PDO in patients at high risk of POPF.

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## Correspondence

Roberto I. Troisi, Division of HPB, Minimally Invasive and Robotic Surgery, Department of Clinical Medicine and Surgery, Federico II University of Naples, Address: via Sergio Pansini 5, 80131, Naples, Italy. Tel: + (39) 081 746 27 76. Fax: + (39) 081 746 2461. E-mail: roberto.troisi@unina.it

## Introduction

Postoperative pancreatic fistula (POPF) remains the main cause of morbidity following pancreaticoduodenectomy (PD).[1,2] The occurrence of POPF relates to several factors, including patient characteristics, such as pancreatic texture, size of the main pancreatic duct, body mass index, but also surgeon experience and hospital volume of pancreatic surgery.[3–5] The surgical technique used for the pancreatic-enteric anastomosis has long been investigated as a determinant of POPF, however to date, no technique has consistently proven to be superior to others.[3]

Pancreatic duct occlusion (PDO) without re-establishing pancreatic-enteric continuity has previously been proposed as a method to mitigate the clinical consequences of POPF.[6] The technique involves ligating or chemically occluding the pancreatic duct. The theory behind the technique is to prevent mixture

 

of pancreatic juice and enteric content thus preventing activation of pancreatic enzymes.[7]

In 2002, a randomized controlled trial involving 169 patients comparing pancreatic duct occlusion (PDO) (n = 86) and pancreaticojejunostomy (n = 83) after PD was performed.[8] No differences in the postoperative morbidity (36% vs 24%, p = 0.69) or mortality (8.1% vs 4.7%, p = 0.536) were observed, while a higher prevalence of de-novo endocrine pancreatic insufficiency was observed following PDO (34% vs 14%, p = 0.001)[8]. Based on this trial, a consensus of experts stated that there was no advantage to be expected from PDO after PD (level of recommendation-strong).[3]

Despite this recommendation several further studies have since been published, suggesting there remains significant interest in this technique.[9,10] A recent global survey involving more than 800 surgeons from all continents reported that 7% of the surgeons who responded occasionally perform PDO following PD.[11] Recently, the results from a prospective trial conducted in a high-volume center showed that patients at high risk of POPF receiving PDO had postoperative outcomes similtar to those of patients at low risk of POPF receiving pancreaticojejunal anastomosis.[10]

The aim of the current study was to appraise all published data regarding the morbidity following PDO through a systematic review and meta-analysis.

## Methods

This systematic review was performed in accordance with the Preferred reporting items for systematic reviews and meta-analyses (PRISMA)[12] and meta-analysis of observational studies in epidemiology (MOOSE) guidelines.[13]

### Search strategy

MEDLINE, Embase, and Web Of Science electronic databases were searched using the following terms: "pancrea*", "remnant", "stump", "duct", "closure", "occlusion" and related Medical Subject Headings (Supplementary file 1, Search strategy for Medline). The last search was run on October 7, 2019 with no language or publication status restriction. Additional potentially relevant studies were identified from the reference list of selected studies.

### Study selection

To be included, studies had to: (1) Include patients undergoing PD for any disease, with no reconstruction between the bowel and the pancreatic stump. (2) The pancreatic stump needed to be left in-situ and be occluded. (3) Report postoperative outcomes. (4) Include at least ten patients. Studies in which external drainage of the pancreatic stump was performed were excluded, as well as studies where PDO was performed as rescue after a failed pancreatic anastomosis. Conference abstracts, as well as nonhuman studies, were also excluded.

Two reviewers (MCG and GC) independently screened the results of the electronic search at the title and abstract levels. The full text of the selected references was then retrieved for further analysis and data extraction.

### Data extraction and quality assessment

Two reviewers (MCG and GC) extracted data from each selected study regarding the first author, publication year, country of origin, hospital volume with regard pancreatic surgery, study design, number of patients undergoing PDO, patients characteristics (age, sex), underlying disease requiring PD, technique used to achieve PDO, data regarding patients risk of POPF, including duct diameter, pancreatic texture and overall risk of POPF as judged by the authors, data on postoperative morbidity, including prevalence, definition, and grading of the clinical severity of POPF, prevalence of intra-abdominal abscess, delayed gastric emptying, postoperative pancreatitis (POP), reoperation rate, need of total pancreatectomy, de-novo onset of diabetes mellitus, presence of pancreatic insufficiency.

Data on the yearly volume of PDs performed at each center were obtained by dividing the total number of PDs performed by the time window (years) in which these procedures were accomplished. These data were calculated only when information on all the consecutive PDs in a given period of time was available in the article. Centers were classified in very high, high, medium and low volume for pancreatic surgery according to the classification of Gouma et al.,[4] which is specific for PD.

The quality of each study was evaluated by a modified version of the Newcastle–Ottawa scale for the assessment of the quality of non-randomized studies.[14–16] By this tool, each study quality was appraised by exploring four domains related to patient selection, outcome measurement tools, outcome assessment and adjustment for confounders. The adoption of a precise definition of POPF was chosen as the index outcome for quality assessment.

### Statistical analysis

The primary outcome was postoperative mortality. Secondary outcomes were prevalence of POPF (all grades and clinically relevant), intra-abdominal abscess, intra-abdominal hemorrhage, reoperation rate, need of total pancreatectomy, delayed gastric emptying, the de-novo onset of diabetes mellitus, the occurrence of pancreatic insufficiency.

The prevalence of each postoperative event was calculated for each study by dividing the number of patients experiencing the event by the total number of patients undergoing PDO. Pooled prevalence rates with 95% confidence intervals were computed using a random-effect model according to the DerSimonian and Laird method.[17] Prevalence was expressed as a percentage, rounded to the first decimal position. The Freeman-Tukey double arcsine transformation of the prevalence was used, in order to incorporate in the pooled analysis studies with the prevalence of 0%.[18] The presence of heterogeneity among the

studies was assessed by the Cochrane $Q$ test and quantified with the inconsistency index ($I^2$), with $I^2$ values of 25, 50 and 75 percent considered as indicative of low, moderate and high statistical heterogeneity.[19]

Random-effect meta-regression analyses using the restricted maximum likelihood method were performed to examine the impact of potential moderators (continuous or dichotomous).[20] Influence analysis was performed by leaving each study out in turn and re-computing the summary effect, in order to assess the impact of each study on the overall estimate and on heterogeneity. Publication bias was assessed by using the Egger's linear regression method.[21] A p-value $\leq 0.05$ was considered as statistically significant. R version 3.6.1 (2019, The R Foundation for Statistical Computing) was used for statistical analyses.

## Results

### Study selection

A total of 16 studies met the inclusion criteria and were selected for this meta-analysis[8–10,22–34] (Fig. 1).

### Study characteristics

The characteristics of the included studies are reported in Table 1. A total of 1000 patients undergoing PDO after PD were included in this meta-analysis.

In 4 studies PDO was selectively performed in patients judged to be at high risk for POPF, based on the size of the main pancreatic duct or pancreatic texture,[23,34,35] or using in one study[10] the Fistula Risk Score.[5] The remaining studies did not report any criteria for patient selection. The definition of POPF adopted in each study is reported in Supplementary File 2.

### Quality assessment and publication bias

The results of the quality assessment are presented in Supplementary File 3. The funnel plot showed symmetry (Supplementary File 4), confirmed by Egger's regression test ($p = 0.910$), which indicates the absence of publication bias.

### Methods for pancreatic stump occlusion

In the majority of the studies, the main pancreatic duct was either ligated or sutured and the pancreatic stump was oversewn or stapled (Table 2). In addition, in 11 studies chemical

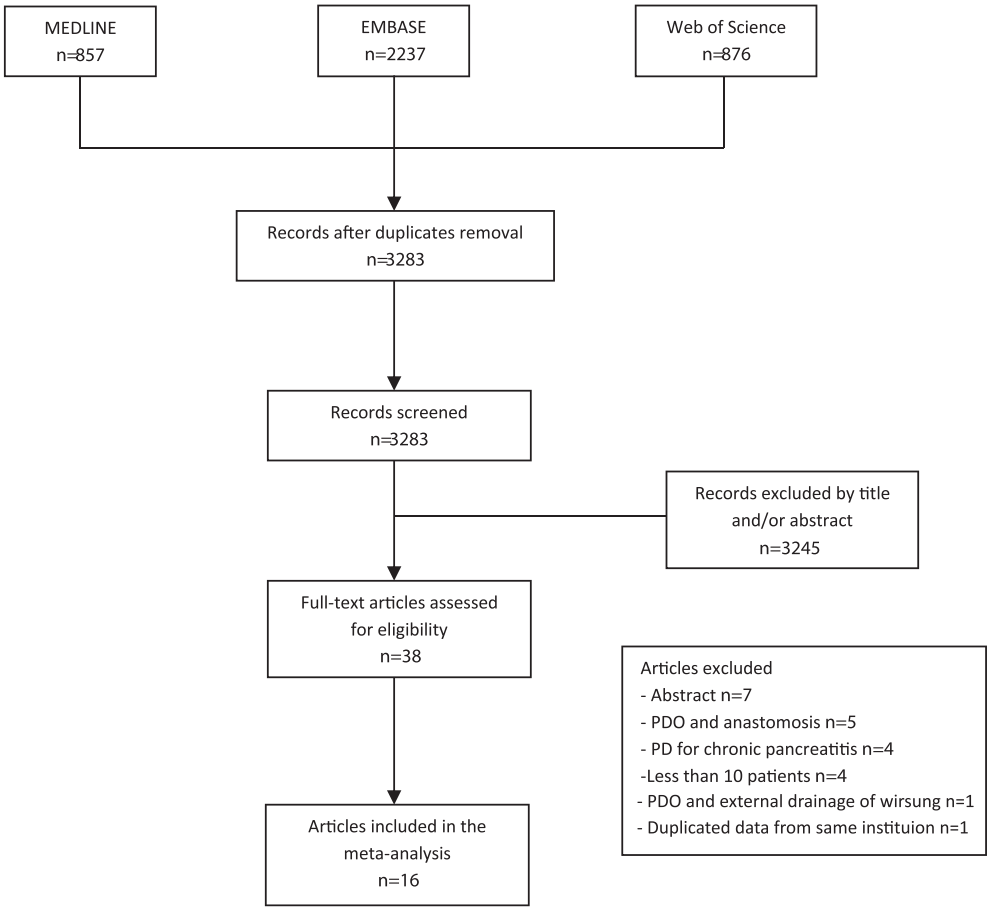


**Figure 1** PRISMA diagram showing study selection

**Table 1** Study characteristics

| Author | Year | Type | N | Malignant disease n (%) | Age | Sex (F) | Patients risk for POPF | Center Volume[a] (PD/Year)[b] |
|---|---|---|---|---|---|---|---|---|
| Papachristou et al. | 1980 | R | 43 | – | – | – | – | Medium (7) |
| Ahren et al. | 1990 | R | 26 | 26 | 62 (40–80) | 9 | Mixed | Very high (35) |
| Marczell et al. | 1992 | R | 44 | 44 | 67 | 19 | Mixed | – |
| Marcus et al. | 1995 | R | 19 | – | – | – | High (19[d]) | Medium (9) |
| Di Carlo | 1998 | R | 223 | 204 (91) | 60 (31–82) | 82 | – | High (15) |
| La Guardia et al. | 1999 | R | 95 | 85 (89) | 59 (35–84) | 46 | – | High (11) |
| Tran et al. | 2002 | P | 86 | 72 (84) | 59 | 30 | Mixed (11[d]) | High (20) |
| Felekouras et al. | 2004 | R | 16 | 14 | 68 (56–74) | 5 | – | Medium (8) |
| Farsi et al. | 2007 | R | 22 | 20 | 68 (38–79) | 10 | – | High (10) |
| Benzoni et al. | 2008 | R | 52 | 52 (100) | 62 ± 10 | – | – | High (12) |
| Tersigni et al. | 2014 | R | 33 | 33 | 63 (33–86) | 61 | Mixed | High (14) |
| Mezza et al. | 2015 | R | 24 | 24 | 63 ± 13 | 27 | High (24[d]) | – |
| Alfieri et al. | 2016 | R | 204 | 168 (82) | 65 (26–85) | 106 | Mixed (106[d]) | High (13) |
| Mauriello et al. | 2016 | R | 44 | 44 | 59 ± 11 | 24 | High (44[d]) | – |
| Gonzalez-Heredia et al. | 2018 | R | 18 | – | 64 ± 12 | 8 | – | Medium (8) |
| Mazzaferro et al. | 2019 | P | 51 | 51 (100) | 68 (62–75) | 40 | High[c] | Very high (34) |
| *Total* | | | *1000* | *837(83.7)* | | *467* | | |

N, number of included patients; POPF, postoperative pancreatic fistula; R, retrospective; P, prospective.
[a] According to Gouma et al.[4]
[b] Calculated from data reported in the study; number of procedures was rounded up to the next integer.
[c] Defined on Fistula risk score ≥6.[5]
[d] Patients with soft pancreatic texture.

substances were injected into the main pancreatic duct to achieve a permanent occlusions.[8–10,22,26,27,29,31,33,34] No authors reported conflicts of interest regarding the substances used, neither sponsorship from manufacturing companies. In one study both chemical and mechanical occlusion were employed in two different groups of patients.[32]

## Postoperative mortality

Pooled postoperative mortality from all 16 studies was 2.7% (95% CI, 0.9 to 5) (Fig. 2), with moderate heterogeneity ($I^2$ = 58%). The study by Papachristou et al. significantly contributed to the heterogeneity, with the reporting of 8/43 patients dying (Influence analysis, Supplementary File 5). After its exclusion, the results were more consistent ($I^2$ = 41%) with a pooled mortality of 2.1% (95% CI, 0.7 to 3.9, 8/957).

Meta-regression analyses showed that mortality remained constant over the years (p = 0.304) and was not related to centre volume (p = 0.679), also according to classification by Gouma et al. (p = 0.73). Pooled mortality rates according to subgroup analysis based on center volume are reported in Supplementary file 6.

Subgroup analysis showed no difference in mortality after PDO between patients at mixed risk of POPF (2.9%, 95% CI, 0.8 to 5.9) and those at high risk of POPF (2.1%, 95% CI, 0 to 7.5) of POPF (p = 0.729). Mortality was comparable (p = 0.298) when PDO was performed with chemical substances (2.3%, 95% CI, 0.6 to 4.8) or using suturing or staplers (5.6%, 95% CI, 0.7 to 13.3).

## Postoperative morbidity

All studies reported data on the occurrence of POPF, with a pooled rate of 29.7% (95% CI, 18.5 to 42.2) (Fig. 3a). Significant heterogeneity was present (Table 3), probably because of different definitions of POPF. As shown by meta-regression, POPF occurrence was independent of the method used for PDO (stapler or suture versus glue injection, p = 0.231).

Five studies adopted the International Study Group of Pancreatic Fistula (ISGPF) definition,[9,22,23,33,34] with a pooled rate of POPFs (all grades) of 47.8% (95% CI, 37.4 to 58.3). The pooled rate of Clinically relevant POPF (ISGPF grades B and C) from 5 studies[10,22,23,33,34] was 13.6% (95% CI, 10 to 17.5) (Fig. 3b).

Pooled rates of the occurrence of other postoperative complications are reported in Table 3.

## Postoperative exocrine function

Eight studies[8,22,24,26,28–30,34] reported the occurrence of postoperative exocrine insufficiency, with a pooled prevalence of 75.1% (95% CI, 48.8 to 94.4). There was high heterogeneity ($I^2$ = 97%), due to the absence of a shared definition of exocrine

**Table 2** Techniques for pancreatic stump occlusion

| Author | Technique | |
|---|---|---|
| Ahren | Suture | Stapler closure followed by PDL[a]and running 2-0 polipropylen suture on the pancreas edge |
| Alfieri | Glue injection | Cyano-acrylate (Glubran 2®) and PDL with 3-0 suture polipropylen suture[a] |
| Benzoni | Suture or glue injection | Polychlorprene homopolymer (Neoprene®) injection or stapler closure (Tyco® TA™ 60–90) |
| Di Carlo | Glue injection | Polychlorprene homopolymer (Neoprene®) injection, followed by a 3.0 purse string suture (Dexon) and transfixed stitches on the pancreatic edge |
| Farsi | Glue injection | Cyanoacrylate or Prolamine (Ethibloc®) injection, and PDL with polipropylen 3-0 suture |
| Gonzalez-Heredia | Glue injection | Cyanoacrylate glue injection, followed by PDL (3-0 silk purse-string suture) and oversewn of the pancreatic edge with interrupted stiches[a] |
| La Guardia | Glue injection | Prolamine (Ethibloc®) or Polychlorprene homopolymer (Neoprene®) injection |
| Marczell | Glue injection | Tisseel® injection, followed by PDL |
| Marcus | Suture | PDL with a purse-string suture and oversewn with polipropylen suture[a], interrupted silk sitches on the pancreatic stump |
| Mauriello | Suture | Linear stapler[b] |
| Mazzaferro | Glue injection | Polychlorprene homopolymer (Neoprene®) injection followed by oversewn of the pancreatic stump with a continuous polypropylene suture |
| Mezza | Glue injection | Cyano-acrylate (Glubran 2®) injection |
| Felekouras | Suture | PDL[a] followed by polypropylene oversewn suture of the pancreatic stump[c] |
| Papachristou | Suture | Interrupted silk sutures on the pancreatic stump (n = 40), with direct PDL with silk suture in some patients (n = 19), or closure with stapler†† (n = 3) |
| Tran | Glue injection | Prolamine (Ethibloc®) injection, or Polychlorprene homopolymer (Neoprene®) injection, or Tissucol® combined with aprotinin (Trasylol®) followed by PDL with 3–0 polydoxanone suture (PDS) and oversewn of the pancreatic stump |
| Tersigni | Glue injection | Cyano-acrylate (Glubran 2®) injection, followed by PDL (purse-string suture)[a] and interrupted stiches[a] on the pancreatic stump |

PDL, pancreatic duct ligation.
[a] Suture material and/or caliber not specified.
[b] Stapler cartridge characteristics not specified.
[c] Some patients injection of fibrin sealant.

insufficiency. Using this expression, most of the studies referred to the need for pancreatic enzymes supplementation,[8,22,24,29] while others intended the presence of diarrhea or steatorrhea[26,30] or a weight-loss > 10%.[26] Furthermore, the time of assessment also varied among the studies. At 3 months after surgery, the presence of diarrhea (≥3/defecation day) was reported in 42.1% of the patients.[26] The need for pancreatic enzymes supplementation was reported in 87% of the patients at 3 months[8] and in 59%[8] and 88%[22] of the patients at 12 months. However, during the first 12 months, no significant differences in the postoperative body weight were observed after PDO and pancreatic-enteric anastomosis.[10,26]

### Postoperative endocrine function

Nine studies reported on postoperative endocrine function, with data from one study not suitable for the meta-analysis.[29] The pooled prevalence rate of new-onset diabetes from eight studies[8,10,22,24,26,28,30,34] was 15.8% (95% CI, 8.7 to 24.4). New-onset diabetes occurred up to 18 months after surgery,[10] with insulin required in 50%–58% of the patients.[8,10,34]

Onset of postoperative diabetes depended on the surgical technique used for PDO (p = 0.003, Fig. 4), with an higher prevalence following injection of chemical substances (22.3%, 95%CI, 14.9 to 30.6) than after only suturing or stapling of the pancreatic remnant (6.1%, 95%CI, 1.5 to 12.9).

## Discussion

This meta-analysis summarizes the evidence on the postoperative outcomes of PDO.

Pooled postoperative mortality was 2.7%, although with heterogeneity between invidividual centers. Nine and four of the included studies were from medium and high/very high volume centers, respectively (Table 1). Although statistically non-significant, a trend towards lower mortality was observed in centers having a higher volume of PD surgery, according to Gouma et al.[4] (Supplementary File 6). It is, however, important to note that subgroup analysis according to the volume of surgery showed pooled mortality rates which were below the reference rates reported in the literature (Supplementary File 6).

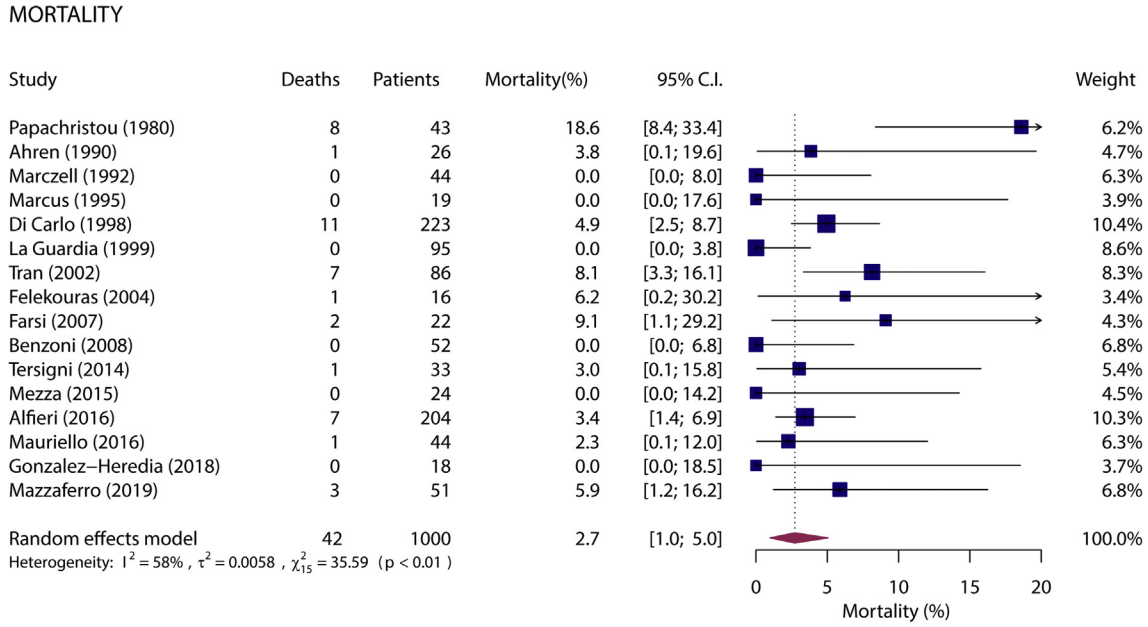


**Figure 2** Forest plot showing pooled estimate of postoperative mortality from all studies

The POPF prevalence (all grades) was highly variable across studies, the likely cause being that until 2005 there was no widely accepted definition of POPF.[36] A subgroup analysis of studies using the 2005 ISGPF definition[36] showed that POPF was diagnosed in 48% of the patients, although most patients had only grade A POPF. Clinically relevant POPF occurred in 13.5% of the patients, a rate that is almost identical to those (12% and 13%) observed in patients receiving a pancreatico-enteric anastomosis in two multicentre studies.[5,37] Although this is an indirect comparison of two treatments, this finding suggests that PDO does not decrease clinically relevant POPFs as much as one would expect. These data contrast with the concept that PDO mitigates the clinical course of a POPF by limiting the effluent to a pure, non-active, pancreatic-juice secretion. However, this may be the result of selection bias (i.e. PDO in high risk patients) and a direct comparison with pancreatico-enteric anastomosis needs to be carried after matching for the risk of POPF. A recent study from a high volume center showed that PDO can equalize the postoperative outcomes of patients at high risk of POPF to those of patients at low risk of POPF receiving a pancreatico-enteric anastomosis.[10] This evidence is corroborated by the present finding that pooled mortality in patients at high risk of POPF was almost identical to that observed in patients with any risk of POPF. These findings are of interest and probably foreshadow the reemergence of this surgical technique.

A surprising finding is the reported rare occurrence of post operative pancreatitis POP reported in less than 1% of the patients, while an higher incidence of "retention pancreatitis" would have been expected following PDO.[29] This suggests POP may be an overlooked complication, due to the absence of a specific definition.[38] There is now evidence that POP is at the origin of a significant proportion of POPF[38] and frequently occurs following PD in patients receiving pancreatico-enteric anastomosis.[39] Further studies will need to systematically appraise the occurrence of POP in patients undergoing PDO and to highlight its clinical relevance, especially in relation to the genesis of POPF in this context.

Although in 14 centers the main pancreatic duct was ligated and the pancreatic stump oversewn by a running suture or stapled, several authors, in addition, injected chemical substances into the ductal system (Table 2). This action aims to permanently occlude the duct, ideally preventing a high output POPF deriving from suture dehiscence. In addition, glues also reach the distal ductal branches, theoretically preventing side-branch POPF by almost completely obstructing pancreatic exocrine secretion. Conversely, chemical substances may also trigger POP, which might cause POPF.[38] The present study showed that the rate of POPF (all grades) was independent of the method used for PDO, suggesting the futility of injecting chemical substances for PDO. It was however evident that glue injection was associated with a higher postoperative onset of diabetes. This is probably a consequence of the progressive fibrosis triggered by these substances, which results in the loss of pancreatic endocrine cells. Accordingly, Mazzaferro and colleagues showed that postoperative diabetes occurs up to 18 months after PDO.[10]

PDO exposes patients to exocrine insufficiency, reported in 75% of the patients, although there was some expected heterogeneity[40] due to a varying definition of this outcome. The need for enzymes supplementation was frequent with up to 88% of the patients at 1 year requiring supplementation. It is worth noting

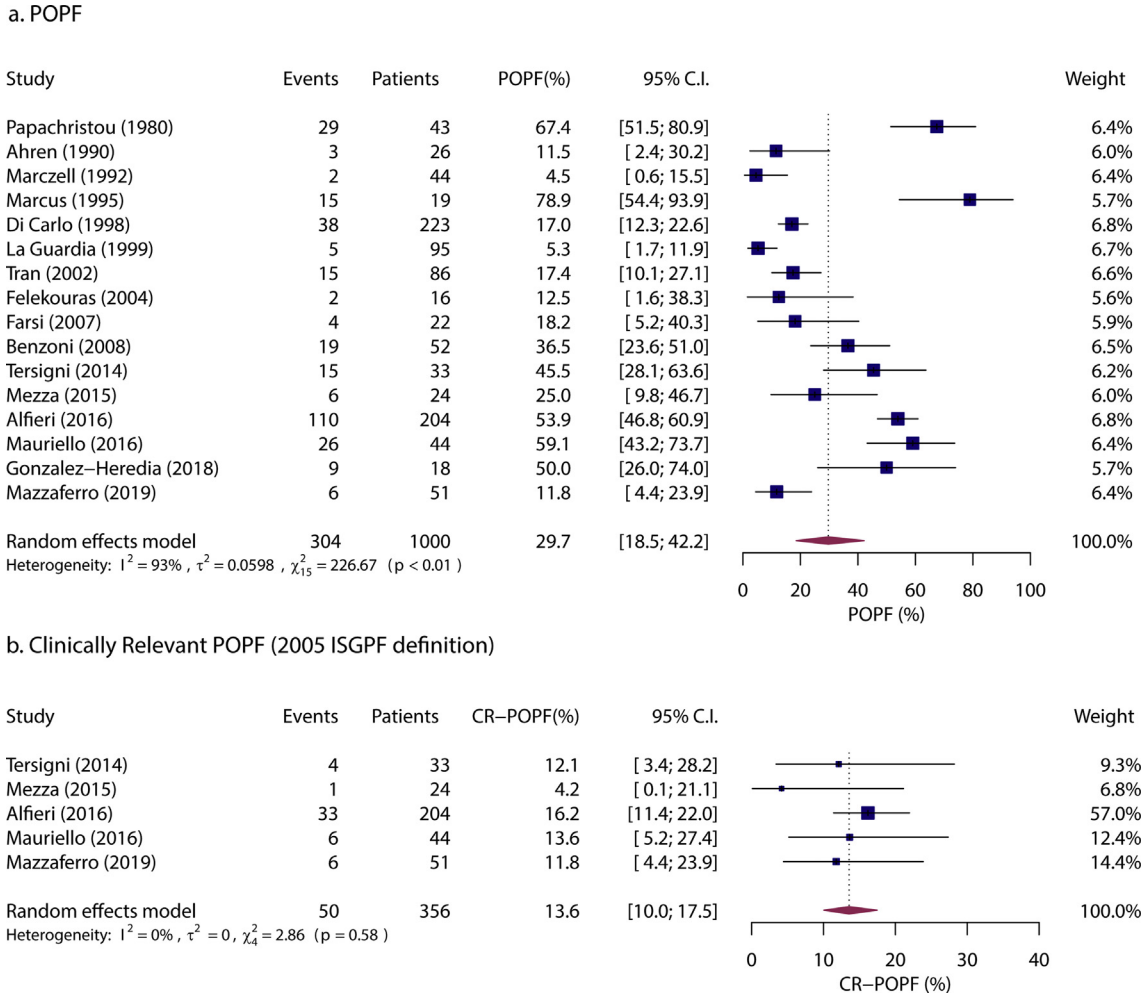


**Figure 3** Forest plot showing pooled estimate of a) postoperative pancreatic fistula (POPF) and b) clinically relevant POPF (CR-POPF), according to the 2005 International Study Group of Pancreatic Fistula (ISGPF) definition

that enzymatic replacement is also required in 74% of patients who receive a pancreatic-enteric anastomosis,[40] as a consequence of an obstruction of the pancreatic duct, loss of pancreatic tissue, pancreatic denervation, and loss of duodenum, which co-ordinates the release of pancreatic enzymes.[41] In addition, three comparative studies showed a similar trend in the postoperative weight between patients receiving PDO and those receiving a pancreatico-jejunostomy,[8,10,26] although patients were not matched according to the quality of the pancreatic remnant, which also influences the risk of exocrine insufficiency. Albeit not definitive, these data together suggest that the impact of PDO on postoperative exocrine insufficiency could be less prominent than expected, and caution should be taken in using it as an argument against this surgical technique.

In light of the above postoperative outcomes, the indication to PDO in the daily clinical practice needs to be discussed. As shown, PDO has non-negligible rates of postoperative clinically relevant POPF, intra-abdominal hemorrhage, and the need for re-operation. Hence, the clinical course after PD with PDO is other than straightforward, with the adjunct high risk of new onset diabetes, which increases healthcare costs and presumably reduce patients' quality of life. As discussed above, PDO was recently shown to improve outcomes in selected patients at high risk of POPF. This subgroup of patients, especially if insulin-dependent at the time of the operation, could represent the ideal candidates for this technique. Notably, the majority of the patients contributing to the present study received PDO in high volume centers (Table 1). Therefore, the present results apply to these contexts and the apparent ease of the PDO technique should not induce inexperienced centers to attempt elective PDs. A trend towards lower mortality in centers at higher volume, although statistically non-significant, suggests that outcomes of PDO still depend on the center experience.

**Table 3** Pooled estimates

| Outcome | Studies | Events | Pooled estimate (95% CI) | Test of heterogeneity | | Quantification of Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | | Q test | p | | |
| Deaths | 16[8,9,29–34,10,22–28] | 42/1000 | 2.7% (0.9, 5.1) | 35.6 | 0.002 | $\tau^2$ = 0.006; $I^2$ = 58% | M |
| POPF | 16[8,9,29–34,10,22–28] | 304/1000 | 29.7% (18.5, 42.2) | 226.7 | <0.001 | $\tau^2$ = 0.062 $I^2$ = 93% | H |
| POPF (ISGPF definition) - All grades | 5[9,22,23,33,34] | 165/323 | 47.8% (37.4, 58.3) | 9.42 | 0.051 | $\tau^2$ = 0.007; $I^2$ = 57% | M |
| Clinically relevant POPF (ISGPF definition - Grade BC) | 5[10,22,23,33,34] | 50/356 | 13.6% (10, 17.5) | 2.9 | 0.581 | $\tau^2$ = 0; $I^2$ = 0% | N |
| Intra-abdominal haemorrage | 13[8,10,32–34,22–28,30] | 55/843 | 5.5% (3.6, 7.6) | 14.4 | 0.277 | $\tau^2$ = 0.001; $I^2$ = 16% | N |
| Intrabdominal abscesses | 10[8,10,22–27,30,33] | 55/724 | 7% (4.6, 9.7) | 11.5 | 0.245 | $\tau^2$ = 0.001; $I^2$ = 21% | N |
| Reoperation | 10[8,10,22,24,26–30,34] | 66/742 | 8% (4.6, 12.2) | 23.4 | 0.005 | $\tau^2$ = 0.001; $I^2$ = 61% | M |
| Postoperative pancreatitis | 7[8,10,23,24,26,29,33] | 5/306 | 0.8% (0, 3.1) | 9.1 | 0.167 | $\tau^2$ = 0.003; $I^2$ = 34% | N |
| Total pancreatectomy | 5[10,22,29,30,34] | 1/342 | 0% (0, 0.3) | 3.4 | 0.999 | $\tau^2$ = 0; $I^2$ = 0% | N |
| Delayed Gastric Emptying | 7[10,22–25,27,34] | 89/588 | 15.6% (10.2, 21.8) | 15.6 | 0.159 | $\tau^2$ = 0.005; $I^2$ = 62% | N |
| Exocrine insufficiency | 8[8,22,24,26,28–30,34] | 347/468 | 75.1% (48.8, 94.4) | 206.1 | <0.001 | $\tau^2$ = 0.140; $I^2$ = 97% | H |
| Postoperative diabetes | 8[8,10,22,24,26,28,30,34] | 90/422 | 15.8% (8.7, 24.4) | 25.3 | <0.001 | $\tau^2$ = 0.142; $I^2$ = 72% | M |

CI, confidence interval; POPF, post-operative pancreatic fistula; ISGPF, International Study Group on Pancreatic Fistula; M, moderate; H, High; N, none.

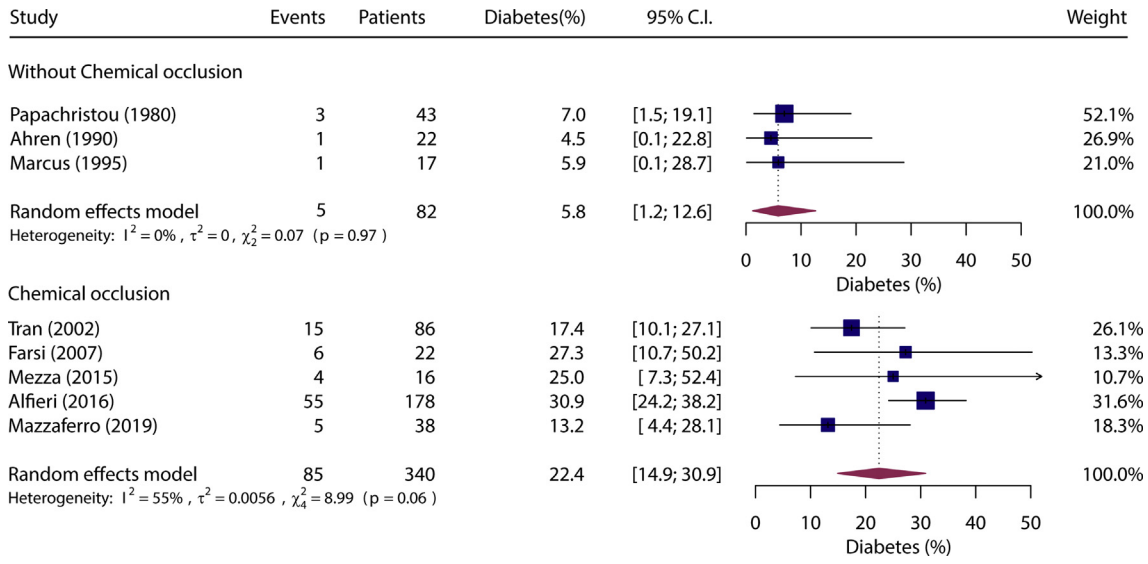


**Figure 4** Forest plot showing pooled estimate of de-novo onset of postoperative diabetes according to the method used for pancreatic duct occlusion

This meta-analysis has some limitations. A formal comparison between the outcomes of PDO and pancreatic-enteric anastomoses following PD was not performed. The risk of selection bias was judged to be very high and the data available (risk of POPF in each group) and number of comparative studies was insufficient to apply statistical methods (e.g. meta-regression) in order to control for this bias. Only a few recent studies reported POPF according to the ISGPF definitions, so there was not enough statistical power to perform a moderator analysis to explore the impact of different PDO methods on well-defined POPF. The studies used a variety of definitions of postoperative exocrine insufficiency and this translated into significant heterogeneity, which limited the interpretation of the data. Furthermore, the impact of neoadjuvant treatment on post-operative outcomes could not be explored, as data on pre-operative chemotherapy was scarcely reported and most of the studies were from the pre-neoadjuvant chemotherapy era. Despite these limitations, this study is the first to offer a comprehensive review of the evidence

on this technique. This meta-analysis also highlighted the potential relationship between the use of chemical substances for PDO and the de-novo onset of postoperative diabetes, which future studies will need to address.

In conclusion, PDO following PD is associated with significant morbidity, including a high risk of the de-novo onset of diabetes, which likely depends on the methods used for PDO. Further evidence is needed to establish the adjunct value of this technique in patients at high risk of POPF.

## Conflicts of interest

None declared.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.04.014.