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Pancreatoduodenectomy (PD) and postoperative pancreatic fistula (POPF)

A systematic review and analysis of the POPF-related mortality rate in 60,739 patients retrieved from the English literature published between 1990 and 2015

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Abstract

Background: Pancreatoduodenectomy (PD) is one of the most technically demanding operations challenging surgeons, and a postoperative pancreatic fistula (POPF) can complicate an otherwise uneventful postoperative (PO) course. This review examined the methods and procedures used to prevent postoperative pancreatic fistula (POPF) after pancreatoduodenectomy (PD).

Methods: A comprehensive systematic search of the literature was performed using PubMed (Medline), Embase, Web of science, and the Cochrane databases for studies published between January 1, 1990 and December 31, 2015. English language articles involving at least 100 patients undergoing PDs carried out in centers performing at least 10 PDs/y were screened for data regarding the Grade of any POPFs according to the definition of the International Study Group on Pancreatic Fistula (ISGPF) and the overall rate of PO mortality related to POPF.

Results: We reviewed 7119 references through the major databases, and an additional 841 studies were identified by cross-checking the bibliographies of the full-text articles retrieved. After excluding 7379 out of 7960 studies, because they did not meet the eligibility criteria, the full texts of 581 articles were examined; 96 studies were excluded at this point, because they concerned partially or totally duplicate data that had already been reported. The remaining 485 articles were screened carefully for POPF-related mortality and POPF Grades as defined by the ISGPF. Of the 485 articles, 208 reported the POPF-related PO mortality rate and 162 the Grades (A, B, and C) of POPFs in 60,739 and 54,232 patients, respectively. The POPF-related mortality rates after pancreatojejunostomy and pancreatogastrostomy were similar but were less (0.5% vs. 1%; $P = .014$) when an externally draining, trans-anastomotic stent was placed intraoperatively. The incidence of the different Grades of POPF Grade was quite variable, but Grade C POPFs were associated with a PO mortality rate of 25.7% (range 0–100%).

Conclusions: The POPF-related mortality rate has remained at approximately 1% over the past 25 years. Only externally draining, trans-anastomotic stents decreased the POPF-related mortality rate. However, adequately designed venting drains were never tested in randomized controlled trials (RCTs).

Abbreviations: DFA = drain fluid-amylase, ISGPF = International Study Group on Pancreatic Fistula, PD = pancreatoduodenectomy, PG = pancreatogastrostomy, PJ = pancreatojejunostomy, PO = postoperative, POD = Postop day, POPF = postoperative pancreatic fistula, RCTs = randomized controlled trials.

Keywords: pancreatectomy, pancreatic surgery, pancreaticoduodenectomy, POPF, postoperative pancreatic fistulas, stent

1. Introduction

Pancreatoduodenectomy (PD) performed for benign or malignant diseases is one of the most technically demanding operations challenging surgeons, and a postoperative pancreatic fistula (POPF) can complicate an otherwise uneventful postoperative (PO) course. The development of a POPF involving extravasation of pancreatic enzymes outside of the pancreatic ductal system from a leaking pancreaticoenteric anastomosis into the peri-pancreatic tissue or peritoneal cavity can cause severe morbidity (intra-abdominal abscesses, sepsis, pseudoaneurisms leading to severe hemorrhage, etc.) and even mortality.

Multiple different operative techniques have been designed in attempt to prevent formation of a POPF; these techniques include pancreatic duct ligation or occlusion,[1] end-to-side duct-to-mucosa pancreatojejunostomy (PJ),[2] dunking PJ,[3] binding PJ,[4] and pancreatogastrostomy (PG)[5,6] all with or without an internally or externally draining pancreatic duct stent.[7] One group suggested wrapping the PJ and the local retroperitoneal vessels with omentum and/or the falciform ligament, a procedure popular in Austral-Asia but rarely used in Europe or the USA.[8] Fibrin glue and other topical hemostatic occlusive agents have also been evaluated as adjuncts to help "seal" the anastomosis making it water tight, and thereby preventing a POPF.[9]

Somatostatin and its multiple synthetic analogues (Octreotide, Vapreotide, Pasireotide, etc.) that are known to decrease pancreatic enzyme secretion have also been claimed to decrease the incidence of POPF.[10] The use of surgical drains has been challenged after many types of high risk operations (hepatectomy, splenectomy, colectomy, and more recently pancreatectomy) has been challenged, because these drains can be responsible for retrograde, intra-peritoneal infection, and hollow organ perforation.[11,12]

Inconsistencies in the reporting of complications after pancreatic surgery involving some form of pancreaticoenteric anastomosis coupled with incomplete data on intraoperative factors at the time of the pancreatectomy have confounded interpretation in many of these studies.[13] The crucial importance of standardized reporting of types of procedures and complications has, in fact, led several groups of investigators to work together to develop widely accepted definitions with regard to types of pancreatic anastomoses,[13] definition and incidence of POPF,[14] postoperative hemorrhage,[15] and delayed gastric emptying.[16]

The current study aimed to analyze the effect of different procedures and operative methods of the pancreatoenteric anastomosis on the POPF-related and overall postoperative mortality rate and the distribution of different Grades of POPF as defined by the International Study Group on Pancreatic Fistula (ISGPS).[14] We reviewed all published articles on this topic between January 1, 1990 and December 31, 2015.

2. Methods

A comprehensive systematic search of the literature was performed using PubMed (Medline), Embase, Web of science, and the Cochrane databases for studies published between January 1, 1990 and December 31, 2015 (including articles published electronically ahead of print). The terms used were: "pancreat(ic)oduodenectomy or PD," "Whipple," "Proximal pancreatectomy," "Pylorus preserving pancreatectomy," "Postoperative pancreatic fistula or POPF." Additional references were sought by cross-checking the bibliographies of the full-text articles that were reviewed. All causes for a proximal pancreatectomy for both malignant and benign diseases were included, excluding chronic pancreatitis and trauma.

2.1. Inclusion and exclusion criteria

Published studies were included if they: were case-control studies, cohort studies, or randomized controlled trials (RCTs) published in the English language in peer-reviewed journals, contained clearly defined pathology (benign or malignant pancreatic lesions) and surgical procedures that were carried out, and included at least 100 PDs carried out in centers performing a minimum of 10 PDs/y to avoid any bias linked to inadequate experience.

Studies were excluded if they: lacked any of the above mentioned criteria; involved studies that reported partially or totally duplicated data of the same patients described in already published work; concerned studies focusing exclusively on laparoscopic surgery; or were reviews, editorials, expert opinions, case reports, or letters-to the editor not containing the author's own data.

Statistical analysis was performed using Chi-squared testing and Fisher exact testing, and all statistical analyses were performed using the Stata v 13.1 software (StataCorp, 4905 Lakeway Drive, College Station, TX).

3. Results

We reviewed 7119 references through the major databases, and an additional 841 studies were identified by cross-checking the bibliographies of the full-text articles retrieved, leading to a total of 7960 possible references (Fig. 1). After excluding 7379 studies, because they did not meet the eligibility criteria, the full texts of 581 articles were examined; 96 studies were excluded at this point, because they concerned partially or totally duplicate data that had already been reported. The remaining 485 articles were screened carefully for POPF-related mortality and POPF Grades as defined by the International Study Group on Pancreatic Fistula (ISGPF).[14] After 277 and 323 articles were excluded because of missing data regarding these two variables, 208 articles reporting on POPF-related mortality rate and 162 articles reporting on POPF grading were retained. Only 84 of the 208 and the 162 articles contained adequate data on both.

The 208 articles reporting on POPF-related mortality included a total of 60,739 patients, including 193 single center studies that reported on 46,216 patients, and 14 multicenter studies that reported on 14,523 patients. The single center studies were divided into 4 groups depending on the mean number of patients undergoing PD operations yearly at the center: Group 1 referred to centers who performed 10 to 20 PD/y; Group 2 performed 20 to 30 PD/y, Group 3 performed 30 to 50 PD/y, and Group 4 performed >50 PD/y. A fifth Group included patients who participated in multicenter studies. The mortality rate corresponding to the time during which the study was performed were plotted (Fig. 2A–C). Overall, 590 of the 60,739 patients studied (0.97%) died because of a POPF including 435 of the 46,216 patients described in the single center studies (0.94%) and 155 of the 14,523 patients (1.07%) in the multicenter studies. The mortality rate before and after the year 2000 was virtually identical (1.07%), although there was an increase of approximately 325% in the number of PDs reported in the second period. A zero POPF-related mortality rate was reported by 77 studies (Fig. 2A–C) distributed equally amongst the 5 Groups.

A variety of anastomotic techniques were described in the 208 studies examining the POPF-related mortality rate. Adequate data on the method of pancreatic anastomoses utilized and the POPF-related mortality were available for 43,339 patients (71.4%) (Table 1). A PJ, which was performed in 37,772 patients, had a 1.0% rate of POPF-related mortality, which we used as a reference value. A PG, which was performed in 5567 patients, had a 0.8% rate of POPF-related mortality ($P = .856$). The overall, all cause operative mortality rates between groups did not differ (PJ = 831/37,467: 2.2%) and (PG = 121/5,567: 2.2%) ($P = .999$). The POPF-related mortality rate in the remaining 17,295 patients (Table 1: NR, NS, PJ†, PG†, NR†) was 1.0% and the POPF-related mortality rate in the 1160 in whom the type of operation was not specified was somewhat greater (2.1%; $P < .0001$). The overall all cause mortality rate in these 17,295 patients was similar (2.4%) to the PJ and PG groups (Table 1).

Data on the use of stents and the POPF-related mortality were available for 35,084 patients (57.8%). The POPF-related mortality rate in the 21,856 non-stented patients, was 1.0%, and was used as a reference value. The POPF-related mortality rate was not different in the 8154 patients with an internal stent ($P = .238$), the 312 patients with a externally venting stent ($P = .999$), the 9132 patients in whom the use of a stent was not reported ($P = .999$), the 7614 patients in whom the type of a stent was not specified ($P = .999$), nor in the 1370 patients in whom the use of a stent was variable ($P = .999$). The mortality rate was,
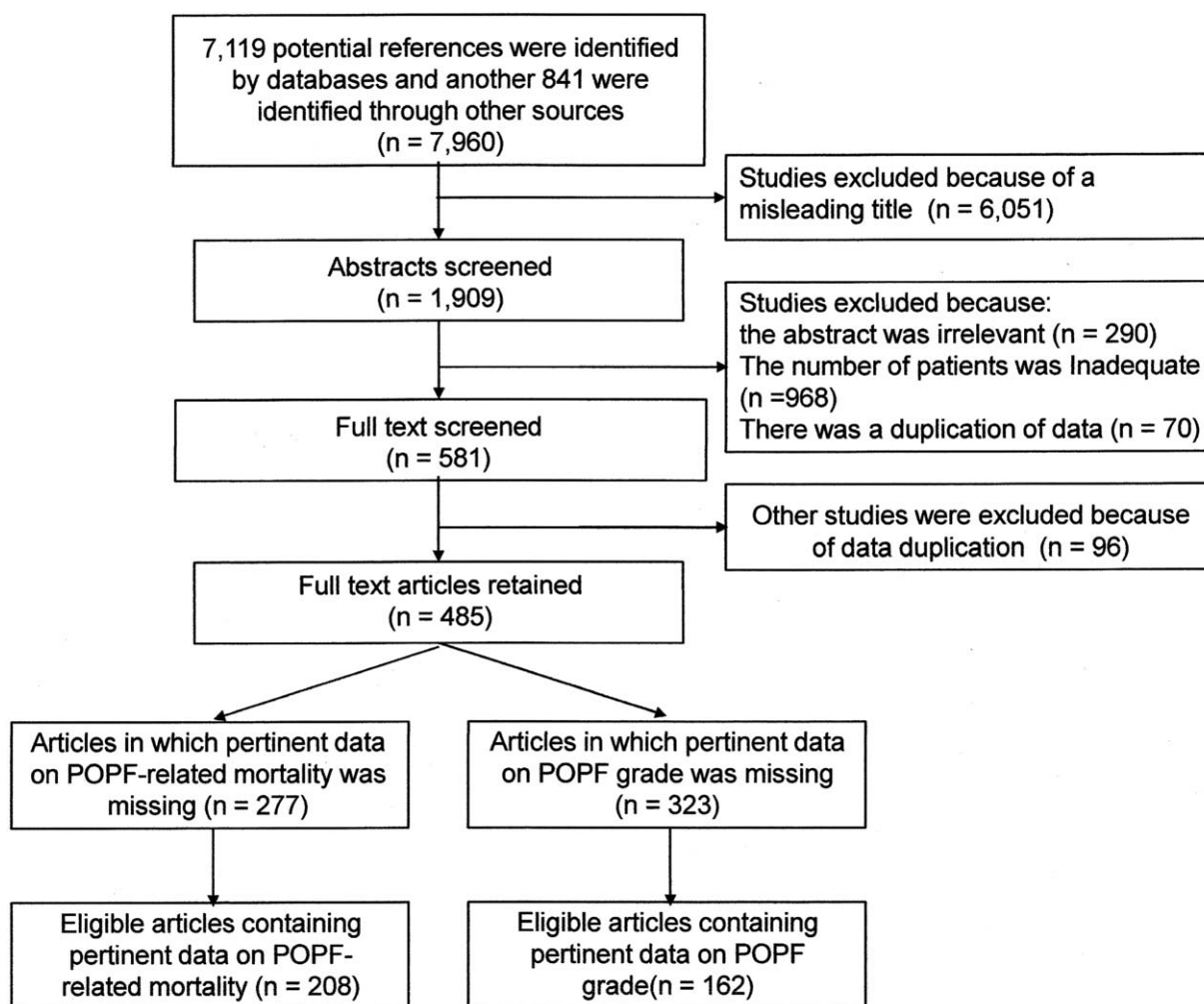
Figure 1. Strategy of literature search.

instead, somewhat less (0.5% vs. 1.0%) in the 4762 patients managed with an external stent ($P = .014$), and was slightly greater (1.61%; $P < .0001$) in the patients in the studies in which different stenting solutions were utilized, although the respective mortality rates of these latter studies were not specified.

Using the overall PO mortality rate from all causes in the 21,856 non-stented patients (2.4%) as a reference value, the overall PO mortality rates of the 8154 patients with an internal trans-anastomotic stent (1.3%) and the 4618 patients with an external trans-anastomotic stent (1.4%) were less ($P < .0001$), while that of the 1370 patients with variable stent solutions was greater (3.72%) ($P = .014$). The overall mortality rate of the remaining 23,489 patients who had another type of anastomosis (Venting, NR, NS, Internal drain‡, External drain‡, No stent‡, Venting‡, NR‡) was not significantly different from that in the non-stented patients (Table 1).

Prophylactic somatostatin analogues where used in approximately 16,409 of the 60,739 patients (27.0%), but 15 authors reporting on 6375 patients did not specify the exact number of patients treated. As a result, adequate data on the POPF-related mortality rate were available for only 10,034 patients, 103 of whom died (1.0%).

Fibrin glue to reinforce the PJ anastomosis was utilized in 497 of the 60,739 patients (0.8%) studied, but adequate data on the POPF-related mortality rate was available for only 350 patients, 5 of whom died (1.4%).

Data on the use of abdominal drains were available for 54,830 of the 60,739 patients (90.3%); 54,063 (98.6%) were treated with one or more drains. Adequate data on PO mortality were available for 52,185. The POPF-related mortality rate was 1.0% (530 patients), and the overall all cause mortality was 2.3% (1181 patients). Of the 767 patients not treated with drains, adequate data on the POPF-related mortality rate were available for only 474 (0.9%), 10 patients died directly because of a POPF (2.1%), and the overall mortality rate was 4.0% (19 patients). Use, or lack of use, of abdominal drains was not reported in 5909 of the PF patients.

Adequate data on the Grades of POPF were reported in 162 articles involving 54,232 patients. Overall, 4813 Grade A (8.9%), 4830 Grade B (8.9%), and 1872 Grade C (3.5%) POPFs were reported for a mean overall fistula rate of 21.3%. The incidence of the various Grades of POPF varied across the different studies reviewed (Fig. 3A–D). In particular, the incidence of Grades A and B POPFs varied from less than 2% to more than 20% with a minimum of 0% and a maximum of 42.5% for Grade A and a minimum of 0.7% and a maximum of 33.3% for Grade B POPF. The incidence of Grade C POPFs also varied from less than 1% to greater than 9% with a minimum of 0% and a maximum of 13.6%.
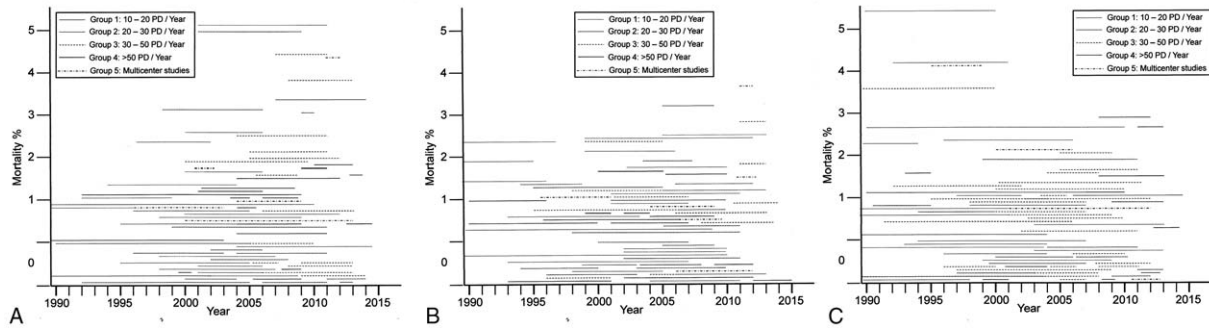
Figure 2. A–C: POPF-related mortality rate according to the 208 eligible studies which were classified into 5 groups (see explanation within the figs.). Characteristics of the lines corresponding to the 5 groups are shown at the top left (A), top central (B), top right (C). A zero POPF-related mortality rate was reported by 77 studies while POPF-related mortality rates ranged between 0.02% and 5.4% in the other 131 studies... There was no statistically significant differences among the 5 groups (Fisher exact test: $P = .215$; Chi-squared $= 5.87$, $P = .209$). POPF = postoperative pancreatic fistula.

The mortality rate linked directly to Grade C POPFs could be retrieved from 84 articles reporting adequate data on both the Grades of POPFs and direct mortality. The mean PO mortality rate was 25.7% (261 deaths of 1014 patients) with a wide range of 0% to 100%.

4. Discussion

This study represents the most extensive literature review on Grades of POPF[14] and associated postoperative mortality rates,

both direct POPF-related deaths and overall, all cause deaths. This comprehensive review included only studies examining a minimum of 100 patients in centers handling at least 10 patients/y in order to avoid the bias of inexperienced, low volume hospitals. Only 208 (43%) of the 485 full-text studies concerning POPF-related mortality rate (including 77 studies with a zero POPF-related mortality rate and 40 studies with a zero overall PO mortality rate) were eligible for inclusion, because only these studies contained all relevant data; only 162 (33%) of the 485 full

Table 1

Number and percentage of deaths of 60,739 patients according to the type of pancreatic anastomosis and the use of stents.

Type of anastomosis*	POPF-related mortality rate ($\chi^2 = 16.4442$; $P = .002$)					Overall mortality rate ($\chi^2 = 2.8077$; $P = .591$)				
	N. Pts.		N. deaths	% deaths	P	N. Pts		N. deaths	% deaths	P
PJ	37,772		371	1.0	Ref.	37,467§		831	2.2	Ref
PG	5567		45	0.8	.856	5567		121	2.2	.999
NR	6388		61	1.0	.999	6388		156	2.4	.999
NS	1160		24	2.1	<.0001**	1160		30	2.6	.999
PJ†	7647					7647				
PG†	1316	9747	89	0.9	.999	1316	9747	234	2.4	.999
NR†	784					784				

Type of stent	POPF-related mortality rate ($\chi^2 = 52.2840$; $P = .000$)					Overall mortality rate ($\chi^2 = 81.2383$; $P = .000$)				
	N. Pts.		N. deaths	% deaths	P	N. Pts		N. deaths	% deaths	P
No stent	21,856		209	1.0	Ref	21,856		524	2.4	Ref
Internal	8154		57	0.7	.238	8154		107	1.3	<.0001**
External	4762		24	0.5	.014**	4618¶		64	1.4	<.0001**
Venting	312		1	0.3	.999	312		6	1.9	.999
NR	9132		83	0.9	.999	8024‖		203	2.5	.999
NS	7614		80	1.1	.999	7614		206	2.7	.999
Variable	1370		13	1.0	.999	1370		51	3.7	.014**
Internal‡	1964					1964				
External‡	3874					3874				
No stent‡	1528	7539	122	1.6	<.0001**	1528	7539	210	2.8	.441
Venting‡	80					80				
NR‡	93					93				

NR = not reported; NS = not specified the number of PJ and PG or the number of different stent solution adopted; PJ = pancreatojejunostomy; PG = pancreatogastrostomy; POPF = postoperative pancreatic fistula.

* Thirty two patients in whom the anastomosis was not performed and 73 patients in whom the main pancreatic duct was occluded were excluded from our analysis.

† The POPF-related and overall mortality rates were not able to be calculated in these patients because the studies examined mixed groups of PJ and PG and mortality rates related to the specific type of anastomosis were not reported.

‡ The overall and POPF-related mortality rates in these patients were not able to be calculated because the studies examined various stenting techniques (internal, external, and venting) and non-stented anastomoses and specific mortality rates were not reported.

§ The overall mortality rate of 305 patients was not reported.

¶ The overall mortality rate of 144 patients was not reported.

‖ The overall mortality rate of 1.108 patients was not reported.
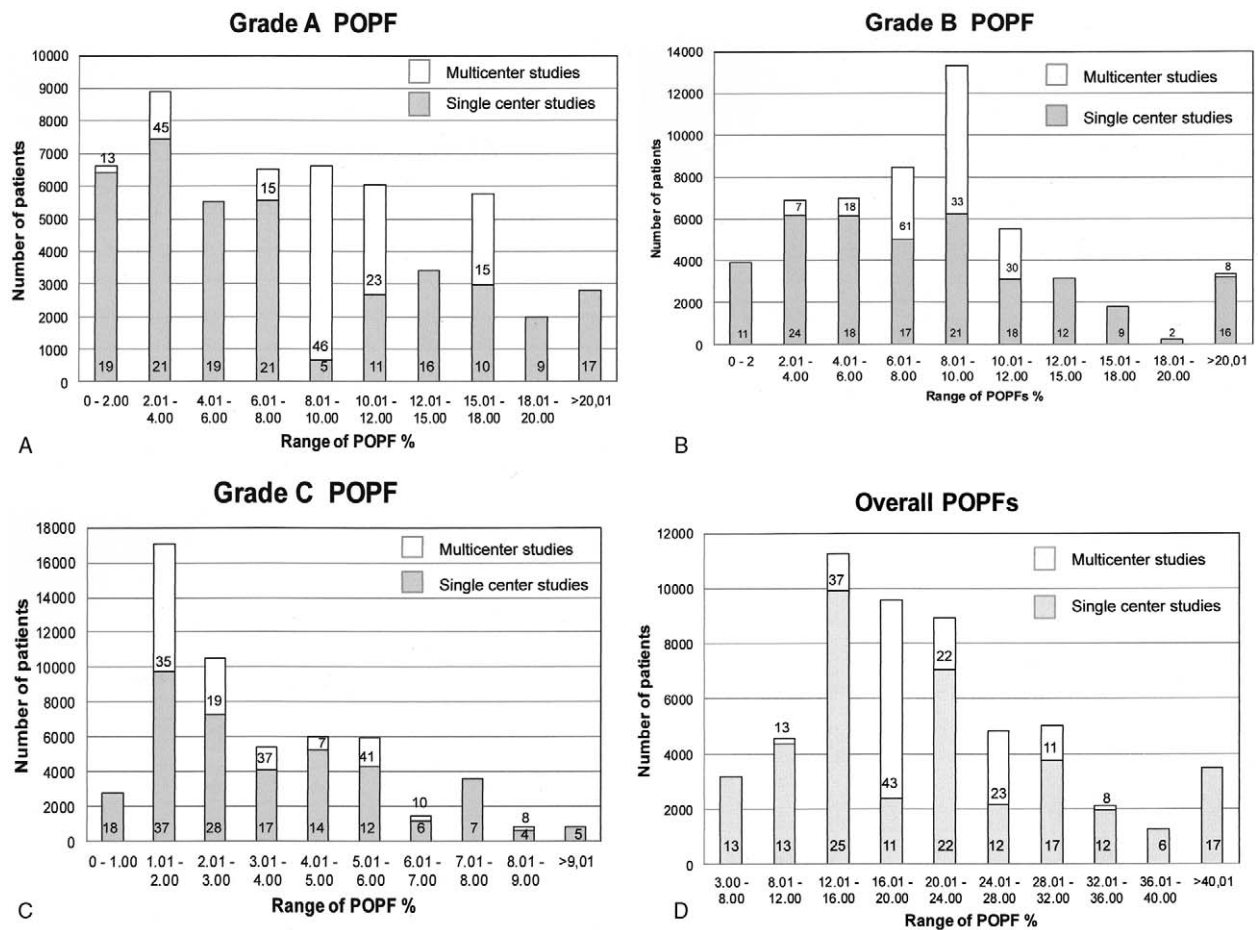
** Bonferroni's adjusted P values.

Figure 3. The range of reported incidence of Grades A, B, C POPFs and the overall range of POPF rates in 54,232 patients. Grey column: single center studies; white column: multicentre studies. The number of the medical centers included in each study is listed in the columns. POPF = postoperative pancreatic fistula.

text articles concerning the Grade of POPF according to the ISGPS definition[14] were retained, because they contained all relevant data, although 83% were published on or after 2008, at least 3 years after the ISGPF classification was originally published.

The mean POPF-related mortality rate remained at about 1% throughout the last quarter century long period (Fig. 2A–C and Table 1) despite the many methods utilized in attempt to decrease or prevent POPF.[1–12] Surprisingly, the overall, all cause PO mortality rate remained relatively low at 2.3% (Table 1) and was still only 2.5% after the 40 studies (6298 patients) with a zero overall PO mortality rate were excluded. The mortality rate of the 14 multicenter studies (14,523 patient) was also similar (mean 2.6%, range 0–9.3%), with 37% to 43% of PO deaths related directly to POPF. These are mean values; the variability in POPF-related mortality outlined in Fig. 2A–C confirms that the mortality rate remained essentially constant over the study period. Furthermore, there was no statistically significant difference in the percentage of studies with zero or some POPF-related mortality rate among centers with lesser or greater experience with PDs (Fig. 2A–C).

Some investigators have suggested that PG be used as an alternative to PJ to decrease the POPF-related mortality rate after PD.[5,6] According to the studies examined here, the POPF-related mortality rate was not statistically different between PJ and PG groups (1.0% vs. 0.8%; P = .856; Table 1), nor did the overall mortality rate differ (2.2% vs. 2.2%; P = .999). The superiority of PG compared with PJ in decreasing the mortality rate was one of the main topics examined in 16 systematic reviews and meta-analyses that have been carried out until now [17–32]; 14 confirmed our findings that there were no differences in the overall PO mortality rate,[18–20,22–32] while 2 reported a lesser overall PO mortality rate for PG with respect to PJ.[17,21] He et al,[21] in particular, found a lesser mortality rate for PG with respect to PJ (2.6% vs. 7.1%, P < .00001) in 22 observational clinical studies examining 3199 patients included in their systematic review and meta-analysis.

While 13 reviews reported that the POPF rate was significantly less in patients who underwent PG with respect to PJ,[17,20–31] 2 reported there was no difference in the 2 groups,[18,19] and 1 did not report any information.[32] Seven reviews reported that there was a lesser incidence of B-C POPF Grades for PG with respect to PJ.[21,24,25,27,29,31,32] The lesser POPF rate after PG was not, however, associated with a lesser overall PO mortality rate, and none of the reviews provided information on the direct POPF-related mortality rate.

The overall morbidity rate was the same for PJ and PG according to the majority of the reviews.[18,21–23,25–32] Only 3 of 16 studies reported a lesser morbidity rate for PG with respect to PJ [17,19,20]; Clerveus et al[24] reported the same overall complication rate but a greater rate of postoperative grade IV complications according to the Clavien–Dindo classification[33,34] for PJ.

It is important to point out that there is only a limited overlap of patients included in the studies examined by us and those included in the 16 previous systematic reviews and meta-analyses, because only 3 studies (579 patients) of the 10 RCTs

(1629 patients) focusing on PG versus PJ included in the meta-analyses were also included in our review; none of the other 7 RCTs (1050 patients) reported the rate of POPF-related mortality. When comparing the 2 types of pancreaticoenterostomy, our findings on the overall rates of PO mortality and morbidity do not justify favoring PG over PJ. Only a lesser POPF rate could justify choosing PG, but it is important to remember that Clerveus et al[24] reported a significantly greater incidence of GI bleeding after PG compared with PJ. In summary, we conclude that the best pancreaticoenteric anastomosis is the one with which the surgeon is most familiar.

Placing a stent into the pancreatic duct was designed to divert pancreatic juice away from the anastomosis as well as to allow more precise placement of sutures, thus protecting the pancreatic duct from suture-related injury and iatrogenic occlusion; this technique may help to decrease the POPF rate and its related mortality.[35,36] Several different types of stents have been proposed: internal or external stents with or without a small knob to prevent the stent from slipping out of the pancreatic duct and externally venting stents to prevent distension of the jejunal loop.[7,37] Internal stents were used in the studies reviewed here in 8154 patients, external stents in 4762, and venting stents in 312. For statistical purposes, the 21,856 anastomoses that were not-stented (Table 1) were used as a reference value to which the series containing stents were compared.

The POPF-related mortality rate was less only for the external stents ($P = .014$) (Table 1). The differences in POPF-related postoperative mortality between internal stents ($P = .238$), venting stents ($P = .999$), non-reported types of stents ($P = .999$), non-specified all-cause PO mortality rate per type of stent ($P = .999$), and variable stenting (.999) were not statistically significant. While the overall PO mortality rate was less for the internal and external stents ($P < .0001$), the difference was not significant for the other types of stents (Table 1).

Ten systematic reviews and meta-analyses have been carried out on the use of stents and their overall complication and mortality rates in POPF patients which are summarized as follow.[38–47]

4.1. Internal stents versus no stents

The majority of reviews comparing patients with and without stents did not report any differences in the POPF rate,[39,41,43,44,47] overall mortality,[39–41,43,44,47] or the morbidity rate.[39–41,43,47] Only Zhou et al[40] in 2012 reported a significantly greater POPF rate in patients with a normal pancreas who underwent internal stenting. In 2013, the same authors[44] also reported a significant increase in overall morbidity in stented patients. These results are quite different from ours, but the patients evaluated by those authors were different from ours, because none of the 724 patients included in the RCTs examined by the meta-analyses were among the 8154 patients eligible for our review. It is important to remember that internal stents are at risk of migration[48–50] with a reported incidence of 16.8% (135 of 802), and 32 subclinical and 8 clinically relevant, stent-induced complications have also been reported.[48]

4.2. External stents versus no stents

Seven reviews reported a significant decrease in the POPF rate in externally stented patients,[38–42,45,47] 4 reviews reported a significant decrease in the rates of Grades B and C POPFs,[38,41,42,45] and 6 reviews also reported a significant decrease in the overall morbidity rate.[38–42,47] Unlike our results, the reviews did not report any differences in the overall mortality rate.[38–42,45,47]

4.3. External versus internal stents

While 4 reviews compared external versus internal stents,[39,41,46,47] none reported differences in the overall morbidity or mortality rates, and 3 reported no differences in the POPF rate.[39,41,47] Only Ke et al[46] reported a lesser POPF rate in patients with a normal pancreas who were managed with external pancreatic stents after a PD.

The differences between the findings of the systematic reviews and meta-analyses and our results may be related in part to the fact that only 3 (608 patients) of the 25 RCTs (2754 patients) included in the systematic reviews and meta-analyses comparing internal and external stents were included in our review, while the other 22 studies (2146 patients) were excluded due to the lack of sufficient data on POPF-related mortality rate. Nevertheless, the results from the large number of patients included in our review seem to favor the use of external stents. The risk-stratified benefits linked to external stents have also been reported by McMillan et al.[51] No conclusion can be drawn for venting stents given the lack of prospective RCTs, the small number of patients studied, and the variety of stents used.

According to our review, the use of fibrin glue to reinforce the pancreatic anastomosis or the use of somatostatin analogues in an attempt to decrease pancreatic secretion have failed to improve the POPF-related mortality rate. A recent systematic review and meta-analysis of 15 RCTs on the use somatostatin analogues compiled the data of 1133 patients (583 in the somatostatin analogues Group and 550 in the control Group).[10] The POPF rate was 16.5% in the former and 18.5% in the latter, with 21 deaths in the former and 13 in the latter. Because the POPF-related mortality rate was not reported by these 15 RCTs, those patients were excluded from our review. The findings outlined here regarding somatostatin analogues has lead us to conclude that this approach is not effective in preventing POPF nor in decreasing the overall mortality rate in patients undergoing PD.

The analysis of the distribution of Grades A, B, and C POPFs according to the ISGPF definition[14] reveal wide differences in the incidence of each Grade ranging from 0 to ≥20% for Grades A and B and from 0 to ≥9% for Grade C (Fig. 3A–C). Furthermore, while most Grade C POPFs were unusual in each series (with an incidence of 0–6% in 88% of the series and an incidence of 0–3% in 50%), a similar percentage of Grade A POPFs occurred with an incidence of between 0% and 18% and Grade B POPFs of between 0% and 15%. In contrast the mortality rate of Grade C POPFs varied greatly across the different series and ranged from 0% to 100%. These findings may be explained by the fact that the severity of a POPF is classified on the basis of its final result and not on its characteristics at the time of diagnosis [52]; another possible explanation is because the management of POPF remains controversial. In fact, as stated by Melloul et al[53] "it seems that each center adopts its own policy for the management of POPF regardless of the definition used. As there is no consensus on the optimal management of POPF and no standardized treatment, interpretations of the definitions of POPF proposed by ISGPF vary considerably according to the treatment adopted to manage this issue." Unfortunately, few efforts have been made to organize prospective RCTs to define the severity of POPF at diagnosis and to set treatment guidelines based on the severity.

In spite of everyone's efforts over the last quarter century, POPF continues to be a major complication, and some authors have proposed evaluating its risk using a risk score based on preoperative variables[54–56] or on the preoperative radiologic

characteristics of the pancreas and peripancreatic area.[57,58] Because a POPF is responsible for much of the morbidity and mortality after PD, a global assessment of the preoperative clinical status in an individual patient could facilitate identifying the risk for POPF in that specific patient; this assessment is a particularly important consideration with regard to frail patients undergoing this major operation.[55] In the setting of a pancreatic neoplasm where resection is the only potentially curative procedure, we must accept the unavoidability of a certain number of POPFs after PD.

Below is a list of variables (both preoperatively and postoperatively) that several authors consider as contributing to development of POPF:

1. Age[59]
2. Sex[60]
3. Smoking history[59]
4. Nutritional factors: Preoperative serum albumin level, nutritional status[61]
5. Body mass index[55,62,63]
6. Weight loss[59]
7. Intra-abdominal fat thickness >65 mm on CT[60]
8. History of chronic pancreatitis[59]
9. Away from portal vein on CT[60]
10. Type of pancreatic disease[54,55,59,60,64,65]
11. Pancreatic texture[54,55,59,60,64,65]
12. Diameter of main pancreatic duct[54,55,60,64,65]
13. Intraoperative blood loss[54,64,65]
14. Injury of the cut surface which could result in pancreatic autolysis[61]
15. Intraoperative pancreatic injury without an early management[61]
16. Blood supply to the anastomosis[66]
17. "High pressure within the enteric lumen of the limb draining the pancreatic juice and bile remain around the anastomotic stoma to corrode itself".[61]

Although little can be done to modify many of these factors, in the early postoperative period it appears that the pancreaticoenteric anastomosis is not watertight in most cases, because abnormal levels of amylase have been measured in the peripancreatic abdominal drains during the first 24 to 72 hours postoperatively. Efforts have been made to predict the severity of a POPF based on the drain fluid-amylase (DFA) level. The median DFA (U/L) on Postop Day 1 (POD 1) reported by Sutcliffe et al[67] in patients with a POPF (6205; range 357–23,391) was significantly greater than that in patients without a POPF (69; range 5–5,180). In their systematic review and meta-analysis, Yang et al[68] reported a better sensitivity and specificity for predicting development of a POPF at DFA POD 1 (81% and 87%, respectively) when compared with POD 3 (56% and 79%, respectively). Furthermore, Palani Velu et al[69] found that the threshold value of POD 0 serum amylase for identifying a clinically important POPF was ≥130 IU/L, while a serum amylase of <130 IU/L had a negative predictive value of 89% for the development of a clinically important POPF. Interestingly, Yang et al[70] evaluated the results of an air insufflation test in patients subjected to a pancreaticoenteric anastomosis. If bubbles were present along the suture line during the insufflation test, the area of the anastomosis was oversewn; if bubbles continued to be present, the entire reanastomosis was redone until no bubbles occurred. Leakage of bubbles was found in 10 of the 46 patients studied, and immediate repair or reanastomosis was performed. The rate of a Grade B and C POPF was less (3/46 vs. 15/65, P = .02) in the air insufflation group.

Because the pancreaticoenteric anastomosis is not watertight in many patients, and the relative amounts of "leakage" may vary greatly among patients, it would be important to know what factors determines the severity of a POPF. For a fluid to pass from one viscous cavity to another, a pressure differential is necessary, either because of the effects of gravity or related to peristaltic activity. Unfortunately, we have no data on the pressure postoperatively within the pancreatic duct, the draining jejunal limb, the stomach, or the perianastomotic area, but we do know that the volume of pancreatic juice secreted is greater in patients with relatively normal pancreatic parenchyma versus those with a hard parenchyma.[71] Hashimoto et al[72] monitored the amount of pancreatic juice draining from an external stent after PD and the amylase level in the drainage fluid. The pancreatic parenchyma in the remnant gland was graded as normal, intermediate, or hard consistency (Group 1, 2, and 3, respectively). Ten days PO pancreatic juice secretion after PD of Group 1 was 24,446 ± 27 mL, and was greater (P < .01) than that of Group 2 (846 ± 14 mL) and 3 (460 ± 8 mL). Interestingly, the output of pancreatic juice was fluctuated in patients who developed leakage, and an abrupt decrease in the amount of externally draining pancreatic juice was noted in those who developed a POPF. The presence of a soft texture of the parenchyma and a small diameter pancreatic duct is indicative of preservation of exocrine function which leads to increased secretion of pancreatic juice and, possibly, a greater pressure within the pancreaticoenteric lumen. As suggested by Yu et al,[61] this greater pressure of activated pancreatic enzymes (proteases, phosphatases, etc.) within the enteric lumen at the pancreaticoenteric anastomosis might augment leakage through a non-watertight anastomosis with possible further autodigestion of the new anastomosis with progression of the anastomotic leakage. A perianastomotic suction drain will decrease the pressure in the perianastomotic area as maximal negative pressures (−71 to −175 mm Hg) have been generated with the reservoirs empty of fluid[73]; whether this effect decreases either the progression of the anastomotic breakdown or the consequences of any leakage is still controversial.

Within this context, typical peripancreatic drainage is unable to evacuate all escaped pancreatic juice and thereby prevent, in some patients, the development of a severe, Grade C POPF, abscess, and/or hemorrhage with the subsequent possible mortality. To prevent this possibility, Horiuchi et al[74] proposed diluting and inactivating the escaped pancreatic juice by the use a continuous lavage of the perianastomotic area with gabexate mesilate, an protease inhibitor, a procedure they evaluated in 27 patients after a PD. A POPF was diagnosed in 8 of these 27 patients, 3 with Grade A, 5 with Grade B, and none with a Grade C POPF. Zhang et al,[75] proposed inactivating the pancreatic juice with an intravenous administration of ulinastatin (a potent trypsin inhibitor) immediately preoperatively and once daily for the first 5 days postoperatively. The number of B–C Grade POPF was significantly less in the ulinastatin Group (7% vs. 24%; P = .045).

Decreasing both the amount of pancreatic juice, and the pressure, within the jejunal limb draining the anastomosis through external drainage of the pancreatobiliary secretions, may explain why external stents were successful in decreasing POPF-related mortality (P = .014, Table 1). While our review showed that these "venting stents" failed to attain a statistically significant decrease in the POPF-related mortality (Table 1), only 312 such patients have been reported, and there was only a 0.3% rate of POPF-related mortality.

In theory, use of somatostatin analogues to decrease the volume of pancreatic secretion in conjunction with a venting external drainage system with the potential for lavage of the peripancreatic area with protease inhibitors such as gabexate mesilate[74] or ulinastatin[75] could combine these concepts of decreasing the luminal pressure in the anastomotic area and evacuating and/or inhibiting the autodigestive properties of any pancreatic anastomotic leakage. Adequate prospective randomized studies are needed to examine this hypothesis. An additional use of a venting catheter can be used to check the anastomosis intraoperatively for leakage via the insufflation technique and postoperatively radiologically by a contrast study before removing the perianastomotic drains.

5. Conclusion

Our analysis has shown that the 1% rate of the POPF-related mortality has remained unchanged for the past quarter century in spite of the multiple efforts to decrease pancreatoenteric anastomotic leaks. Multiple studies have confirmed that prophylactic somatostatin analogues and fibrin glue are not effective in decreasing POPF and mortality rates; similarly there were no differences in the POPF-related and overall mortality rates related to PG and to PJ. By decreasing the amount of pancreatic juice (and possibly the intraluminal pressure) in the region of the pancreaticoenteric anastomosis, external stents were able to significantly decrease the POPF-related mortality rate ($P = .014$; Table 1), while both internal and external stents significantly reduced the overall mortality rate ($P < .0001$; Table 1). Despite decreasing the POPF-related mortality rate, POPF-related deaths still occur. We suggest that adequate externally venting intraluminal drains within the jejunal limb draining the pancreaticoenteric anastomosis may remove efficiently pancreatobiliary secretions, may allow for intraluminal infusion of protease inhibitors, may allow for intraoperative evaluation of whether the pancreaticoenteric anastomosis is watertight, and may allow postoperative evaluation of the integrity of the anastomosis before removal of the drain, thereby further decreasing POPF-related mortality. Such well designed RCTs may give the answer.

Acknowledgments

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