





# Completion pancreatectomy or a pancreas-preserving procedure during relaparotomy for pancreatic fistula after pancreatoduodenectomy: a multicentre cohort study and meta-analysis

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## Abstract

**Background:** Despite the fact that primary percutaneous catheter drainage has become standard practice, some patients with pancreatic fistula after pancreatoduodenectomy ultimately undergo a relaparotomy. The aim of this study was to compare completion pancreatectomy with a pancreas-preserving procedure in patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy.

**Methods:** This retrospective cohort study of nine institutions included patients who underwent relaparotomy for pancreatic fistula after pancreatoduodenectomy from 2005–2018. Furthermore, a systematic review and meta-analysis were performed according to the PRISMA guidelines.

**Results:** From 4877 patients undergoing pancreatoduodenectomy, 786 (16 per cent) developed a pancreatic fistula grade B/C and 162 (3 per cent) underwent a relaparotomy for pancreatic fistula. Of these patients, 36 (22 per cent) underwent a completion pancreatectomy and 126 (78 per cent) a pancreas-preserving procedure. Mortality was higher after completion pancreatectomy (20 (56 per cent) versus 40 patients (32 per cent);  $P = 0.009$ ), which remained after adjusting for sex, age, BMI, ASA score, previous reintervention, and organ failure in the 24 h before relaparotomy (adjusted odds ratio 2.55, 95 per cent c.i. 1.07 to 6.08). The proportion of additional reinterventions was not different between groups (23 (64 per cent) versus 84 patients (67 per cent);  $P = 0.756$ ). The meta-analysis including 33 studies evaluating 745 patients, confirmed the association between completion pancreatectomy and mortality (Mantel–Haenszel random-effects model: odds ratio 1.99, 95 per cent c.i. 1.03 to 3.84).

**Conclusion:** Based on the current data, a pancreas-preserving procedure seems preferable to completion pancreatectomy in patients in whom a relaparotomy is deemed necessary for pancreatic fistula after pancreatoduodenectomy.

## Introduction

Postoperative pancreatic fistula is among the most notorious complications after pancreatoduodenectomy as it is associated with a high morbidity and mortality rate<sup>1</sup>. Primary percutaneous catheter drainage has become standard practice in the management of a clinically relevant pancreatic fistula. However, percutaneous catheter drainage is not successful in all patients and a small subset ultimately undergo a relaparotomy<sup>2</sup>. An international survey

showed good agreement between surgeons on the indication for relaparotomy when image-guided percutaneous catheter drainage of fluid collections is not technically feasible<sup>3</sup>.

During relaparotomy, different strategies are possible: surgical drainage (intra-abdominal lavage and placement of drains); repair or redo of the pancreatic anastomosis; salvage pancreatogastrostomy; and completion pancreatectomy<sup>4</sup>. Completion pancreatectomy is the most aggressive strategy which aims to remove completely the focus

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of intra-abdominal leakage and associated inflammation. Downsides of this procedure are the additional inflammatory stress from the extensive surgical procedure and subsequent possible deterioration of organ failure, technical difficulty resulting in blood loss, risk of damaging other structures and pancreatic exocrine and endocrine insufficiency. On the other hand, pancreas-preserving procedures might not be sufficient and thereby lead to further clinical deterioration including multiple organ failure, more reinterventions and prolonged hospital stay<sup>5,6</sup>. Few studies have been performed on the clinical outcomes of different surgical strategies in patients with pancreatic fistula after pancreatoduodenectomy<sup>4</sup>.

The aim of this study was to evaluate surgical strategies (completion pancreatectomy *versus* a pancreas-preserving procedure) in patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy. Additionally, a systematic review and meta-analysis were performed to summarize the available evidence on this topic.

## Methods

### Study design and patient selection

This was a retrospective multicentre cohort study of the Dutch Pancreatic Cancer Group<sup>7</sup> in which nine institutions participated. The need for informed consent was waived by the Medical Ethics Committee of the Leiden University Medical Centre. This study was performed in accordance with the Declaration of Helsinki and reported according to the STROBE criteria<sup>8</sup>.

All patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy from 2005 to 2018 were included. The indication for relaparotomy was assessed by three independent authors (J.V.G., D.K., J.S.D.M.) and discrepancies were resolved by consensus. Patients were identified using the prospective Dutch Pancreatic Cancer Audit (2013–2018). Participation in the Dutch Pancreatic Cancer Audit is mandatory for all institutions performing pancreatic surgery in the Netherlands<sup>9</sup>. In addition, an existing database<sup>2</sup> containing patients with severe pancreatic fistula after pancreatoduodenectomy (8 institutions, 2005–2013) was evaluated.

### Data collection

Data were extracted from the Dutch Pancreatic Cancer Audit and through systematic evaluation of medical records using a predefined case record form. Variables of interest included: patient-related variables (gender, age, BMI, pathology, preoperative biliary drainage, ASA score); surgery-related variables (type and duration of surgery, pancreatic anastomosis, vascular resection, additional organ resection, blood loss); postoperative variables (postoperative complications, reinterventions, organ failure, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, systemic inflammatory response syndrome (SIRS), duration of admission to the intensive care unit (ICU), Clavien–Dindo classification of surgical complications, removal of abdominal drain, duration of hospital stay, postoperative mortality); and follow-up variables (new-onset postoperative exocrine insufficiency and diabetes mellitus, and adjuvant therapy).

### Definitions

Postoperative pancreatic fistula was defined and classified according to the International Study Group of Pancreatic Surgery criteria<sup>10</sup>. Death was defined as death during the index admission up to 3 months after discharge. Organ failure was defined as one or more of the following: respiratory organ failure (partial

pressure of oxygen less than 60 mmHg despite a fraction of inspired oxygen of 0.3 or need for mechanical ventilation), circulatory organ failure (systolic blood pressure less than 90 mmHg despite adequate fluid resuscitation or need for inotropic support) or renal organ failure (creatinine level greater than 2.0 mg/dl after rehydration or need for haemofiltration or haemodialysis). APACHE II score and SIRS criteria were scored 24 h before and 24 h after initial relaparotomy<sup>11,12</sup>. SIRS was considered in cases of two or more positive criteria<sup>12</sup>. Other pancreatic-specific complications (postpancreatectomy haemorrhage, bile leakage, delayed gastric emptying) were defined and classified according to the International Study Group of Pancreatic Surgery or Liver Surgery definitions<sup>13–15</sup>. Only grade B and C were reported as these are generally considered as clinically relevant. Duration of pancreatic fistula was calculated as time from pancreatoduodenectomy to removal of last abdominal catheter in patients undergoing a pancreas-preserving procedure. New-onset postoperative exocrine pancreatic insufficiency and diabetes mellitus were defined as need for oral pancreatic enzyme supplementation or antidiabetics within 3 months after discharge, not present before pancreatoduodenectomy. All data were collected which were available from the medical charts (from index admission up to 3 months after discharge).

### Outcomes and comparison

The primary outcome was death (defined as death during the index admission up to 3 months after discharge). Secondary outcomes included organ failure and APACHE II score in the 24 h after initial relaparotomy, the number and type of additional reinterventions after initial relaparotomy, duration of ICU stay, duration of hospital stay, new-onset postoperative exocrine pancreatic insufficiency and diabetes mellitus, duration of pancreatic fistula in patients undergoing a pancreas-preserving procedure and proportion of patients with pancreatic cancer receiving adjuvant therapy.

Patients were divided into two groups based on the surgical strategy during the initial relaparotomy for pancreatic fistula: completion pancreatectomy *versus* pancreas-preserving procedure. A sensitivity analysis over time was performed stratified by period (2005–2008, 2009–2012, 2013–2015 and 2016–2018).

### Statistical analysis

Statistical analysis was performed with SPSS Statistics for Windows™, version 23.0 (IBM, Armonk, New York, USA). Continuous variables with a skewed distribution were presented as median (i.q.r.) and compared using the Mann–Whitney *U* test. Categorical variables were presented as numbers (percentages) and compared using  $\chi^2$  or Fisher's Exact tests, as appropriate. Multivariable logistic regression analysis for mortality was conducted to adjust for theoretical confounding factors with sufficient available data (sex, age, BMI, ASA score, reintervention before initial relaparotomy and organ failure in the 24 h before initial relaparotomy). Results are given as odds ratios with 95 per cent confidence intervals. All tests were two-sided and statistical significance was defined as  $P < 0.050$ .

### Systematic review and meta-analysis

A systematic literature search ([Supplementary material](#)) was performed according to the PRISMA guidelines<sup>16</sup>. The databases of PubMed, MEDLINE, Embase, Web of Science and COCHRANE Library were searched for full-text, English-written studies. Titles, abstracts and full-text articles were screened by two independent authors (J.V.G., D.K.) for eligibility. Studies were included

if patients were described who underwent relaparotomy for pancreatic fistula after pancreatoduodenectomy. Literature reviews and case reports were excluded. Data extraction was performed using a standardized form with study characteristics and postoperative outcomes (mortality, duration of hospital stay, ICU admission, organ failure and additional reinterventions). The risk of bias was determined using the ROBINS-I tool for cohort studies<sup>17</sup>. A meta-analysis was performed for death (completion pancreatectomy versus pancreas-preserving procedure) using Review Manager (RevMan version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The  $I^2$  statistic was used to assess heterogeneity between studies. An  $I^2$  value of greater than 50 per cent was considered as substantial heterogeneity. The Mantel-Haenszel random-effects model was used to calculate pooled effects. A fixed-effects model was used for sensitivity analysis.

## Results

### Baseline characteristics

Of the 4877 patients undergoing pancreatoduodenectomy, 786 (16 per cent) developed a pancreatic fistula grade B/C and 162 (3 per cent of all; 21 per cent of those with a pancreatic fistula) underwent a relaparotomy for pancreatic fistula (Fig. 1). During initial relaparotomy for pancreatic fistula, completion pancreatectomy was performed in 36 (22 per cent) patients and a pancreas-preserving procedure in 126 (78 per cent) patients (Table 1). Strategies during an initial pancreas-preserving procedure included 80 patients (63 per cent) who had surgical drainage, 20 patients (16 per cent) with attempt to repair the pancreatic anastomosis, 21 patients (17 per cent) disconnection of the pancreatic anastomosis with preservation of the remnant and five patients (4 per cent) redo of the pancreatic anastomosis. Patients undergoing completion pancreatectomy were older

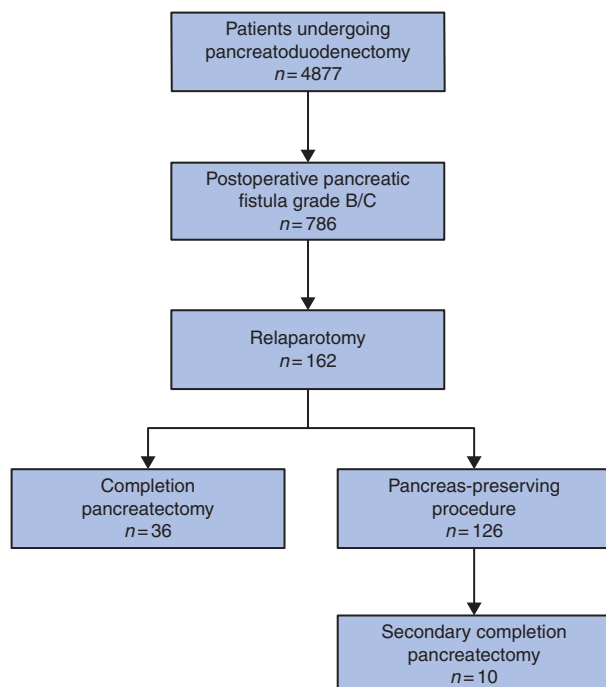


Fig. 1 Flow chart of patient selection

(median 70 (i.q.r. 66–73) versus 64 (i.q.r. 58–71) years;  $P=0.025$ ). In the completion pancreatectomy group, 13 patients (36 per cent) were ASA III–IV compared with 26 (21 per cent) patients in the pancreas-preserving group ( $P=0.055$ ).

Patients undergoing completion pancreatectomy more often had single or multiple organ failure 24 h before the initial relaparotomy ( $P=0.035$ ). The highest APACHE II score within the 24 h before the initial relaparotomy (median 14 (i.q.r. 10–18) versus 12 (i.q.r. 8–15);  $P=0.055$ ), the proportion of reinterventions before the initial relaparotomy (17 patients (47 per cent) versus 57 patients (45 per cent);  $P=0.833$ ) and the proportion of reinterventions for postpancreatectomy haemorrhage before the initial relaparotomy (6 patients (17 per cent) versus 12 patients (10 per cent);  $P=0.229$ ) did not differ significantly between groups. The timing of initial relaparotomy also did not differ (median on postoperative day 10 (i.q.r. 4–14) versus 9 (i.q.r. 6–14);  $P=0.521$ ). Other details regarding baseline characteristics, reinterventions and disease severity before initial relaparotomy are shown in Table S1.

### Main outcomes

Main outcomes are summarized in Table 2. Patients undergoing completion pancreatectomy had a higher mortality rate, compared with patients undergoing a pancreas-preserving procedure (20 patients (56 per cent) versus 40 patients (32 per cent);  $P=0.009$ ). At multivariable analysis, adjusting for sex, age, BMI, ASA score, previous reintervention and organ failure in the 24 h before relaparotomy, completion pancreatectomy was associated with fatal outcome (adjusted odds ratio 2.55, 95 per cent c.i. 1.07 to 6.08; Table 3).

There was no difference in the number of postoperative abdominal catheters after initial relaparotomy between groups (median 2 (i.q.r. 1–2) versus 2 (i.q.r. 2–3);  $P=0.119$ ; 10 per cent missing data). Patients undergoing completion pancreatectomy had higher APACHE II scores within the 24 h after initial relaparotomy (median 18 (i.q.r. 15–23) versus 15 (i.q.r. 11–18);  $P<0.001$ ), whereas single or multiple organ failure ( $P=0.165$ ) did not differ. The proportion of additional reintervention after initial relaparotomy was not different (23 patients (64 per cent) versus 84 patients (67 per cent);  $P=0.756$ ). Out of 126 initial pancreas-preserving procedures, 10 (8 per cent) patients ultimately underwent completion pancreatectomy. The proportion of additional reinterventions for postpancreatectomy haemorrhage after initial relaparotomy did not differ between groups (6 patients (17 per cent) versus 21 patients (17 per cent);  $P>0.999$ ). In surviving patients, duration of hospital stay did not differ (median 55 (i.q.r. 31–70) versus 56 (i.q.r. 40–71) days;  $P=0.592$ ). In surviving patients undergoing a pancreas-preserving procedure, 32 patients (43 per cent) developed new-onset postoperative pancreatic exocrine insufficiency and 19 patients (26 per cent) developed new-onset diabetes mellitus.

### Other outcomes

Median time to resolution of postoperative pancreatic fistula was 47 (i.q.r. 25–69) days in patients undergoing a pancreas-preserving procedure (Table S2). One of five (20 per cent) surviving pancreatic cancer patients who underwent a completion pancreatectomy received adjuvant therapy, compared with one of 25 patients (4 per cent) in the pancreas-preserving group ( $P=0.314$ ). Other details regarding disease severity, reinterventions and other postoperative outcomes after initial relaparotomy are given in Table S2.

**Table 1** Baseline characteristics by surgical strategy for pancreatic fistula

Characteristics	Completion pancreatectomy (n = 36)	Pancreas-preserving procedure (n = 126)	P
<b>Baseline at time of index surgery</b>			
Sex (female)	8 (22)	36 (28.6)	0.450
Age*	70 (66, 73)	64 (58, 71)	0.025
BMI*†	26.8 (24.2, 28.9)	26.1 (23.4, 28.7)	0.447
ASA (III–IV)	13 (36)	26 (20.6)	0.055
Type of resection			0.302
Whipple	11 (31)	28 (22.2)	
PPPD	25 (66)	96 (77.8)	
Vascular resection	4 (11)	7 (5.6)	0.243
Additional organ resection	4 (11)	16 (12.7)	0.789
Pancreatic anastomosis			0.111
Duct-to-mucosa PJ	28 (78)	113 (89.7)	
Duct-to-mucosa PG	0	1 (0.8)	
Dunking PJ	8 (22)	12 (9.5)	
Pathology			0.786
Pancreatic cancer/pancreatitis	12 (33)	39 (31.0)	
Other	24 (67)	87 (69.0)	
<b>Baseline at time of initial relaparotomy</b>			
Previous reintervention	17 (47)	57 (45.2)	0.833
Radiological intervention	15 (42)	52 (41.3)	0.966
Relaparotomy	5 (14)	7 (5.6)	0.092
Previous reintervention for PPH	6 (17)	12 (9.5)	0.229
Radiological intervention for PPH	5 (14)	10 (12.6)	0.277
Relaparotomy for PPH	1 (3)	2 (1.6)	0.640
Organ failure 24 h before†			0.035
No	19 (53)	68 (54.8)	
Single	6 (17)	39 (31.5)	
Multiple	11 (31)	17 (13.7)	
Highest APACHE II score 24 h before*†	14 (10, 18)	12 (8, 15)	0.055
Postoperative day of initial relaparotomy for POPF*	10 (4, 14)	9 (6, 14)	0.521

Continuous variables all compared using the Mann, Whitney U test. Categorical variables all compared using  $\chi^2$ . Except: vascular resection, additional organ resection, previous reintervention for postpancreatectomy haemorrhage (PPH), relaparotomy for PPH, which were compared with Fisher's exact tests. Values in parentheses are percentages unless indicated otherwise \*values are median (i.q.r.). †Missing data: BMI (n = 6), organ failure 24 h before (n = 2), highest Acute Physiology And Chronic Health Evaluation (APACHE) II score 24 h before (n = 14). PPPD, pylorus-preserving pancreatoduodenectomy; PJ, pancreatojejunostomy; PG, pancreatogastrostomy; POPF, postoperative pancreatic fistula.

**Table 2** Main outcomes by surgical strategy for pancreatic fistula

Outcomes	Completion pancreatectomy (n = 36)	Pancreas-preserving procedure (n = 126)	P
Death	20 (56)	40 (31.7)	0.009
Organ failure 24 h after initial relaparotomy†			0.165
No	6 (17)	34 (27.4)	
Single	5 (14)	26 (21.0)	
Multiple	25 (69)	64 (51.6)	
Highest APACHE II score 24 h after initial relaparotomy*†	18 (15, 23)	15 (11, 18)	<0.001
ICU admission	35 (97)	107 (84.9)	0.048
Duration of ICU admission (days)*	13 (3, 32)	7 (2, 17)	0.091
Additional reintervention after initial relaparotomy	23 (64)	84 (66.7)	0.756
Radiological intervention	16 (44)	71 (56.3)	0.206
Relaparotomy	14 (39)	40 (31.7)	0.423
Secondary completion pancreatectomy	–	10 (7.9)	
Additional reintervention for PPH after initial relaparotomy	6 (17)	21 (16.7)	>0.999
Radiological intervention for PPH	2 (6)	12 (9.5)	0.455
Relaparotomy for PPH	4 (11)	10 (7.9)	0.550
Duration of hospital stay (days)*	38 (24, 61)	53 (31, 66)	0.042
Duration of hospital stay in survivors (days)*	55 (31, 70)	56 (40, 71)	0.592
New-onset postoperative pancreatic exocrine insufficiency in survivors†	–	32 (43.2)	–
New-onset postoperative diabetes mellitus in survivors†	–	19 (25.7)	–

Continuous variables all compared using the Mann, Whitney U test. Categorical variables all compared using  $\chi^2$ . Except: additional reintervention for postpancreatectomy haemorrhage (PPH) after initial relaparotomy, radiological intervention for PPH, additional reintervention for PPH after initial relaparotomy, relaparotomy for PPH, which were compared with Fisher's exact tests. Values in parentheses are percentages unless indicated otherwise \*values are median (i.q.r.). †Missing data: organ failure 24 h after (n = 2), highest APACHE II score 24 h after (n = 28), new-onset postoperative pancreatic exocrine insufficiency (n = 14), new-onset postoperative diabetes mellitus (n = 14), APACHE, Acute Physiology And Chronic Health Evaluation; ICU, intensive care unit.

### Sensitivity analysis by period

The sensitivity analysis stratified by period showed a linear decrease in proportion of patients undergoing relaparotomy for pancreatic fistula ( $P < 0.001$ ) and no linear change in proportion of patients undergoing completion pancreatectomy or a

pancreas-preserving procedure ( $P = 0.228$ ) (Fig. 2). The sensitivity analysis stratified by period also showed a higher mortality rate after completion pancreatectomy compared with a pancreas-preserving procedure in all four periods (Table S3).

**Table 3** Multivariable analysis for fatal outcome

Strategy during initial relaparotomy, pancreas-preserving	Odds ratio	P
<b>Completion pancreatectomy</b>	2.55 (1.07, 6.08)	0.035
<b>Sex</b>		
Male	Reference	
Female	1.97 (0.87, 4.44)	0.104
<b>Age</b>	1.08 (1.03, 1.13)	0.002
<b>BMI*</b>	1.02 (0.93, 1.12)	0.702
<b>ASA score</b>		
I-II	Reference	
III-IV	0.89 (0.38, 2.07)	0.785
<b>Previous reintervention</b>		
No	Reference	
Yes	1.12 (0.56, 2.38)	0.707
<b>Organ failure 24 h before*</b>		
No	Reference	
Single organ	1.15 (0.49, 2.69)	0.755
Multiple organ	2.47 (0.91, 6.68)	0.075

Continuous variables all compared using the Mann, Whitney U test. Categorical variables all compared using  $\chi^2$ . Except: additional reintervention for postpancreatectomy haemorrhage (PPH) after initial relaparotomy, radiological intervention for PPH, additional reintervention for PPH after initial relaparotomy, relaparotomy for PPH, which were compared with Fisher's exact tests. Values in parentheses are 95% confidence intervals. \*Missing data: BMI or organ failure 24 h before ( $n = 7$ ).

## Systematic review and meta-analysis

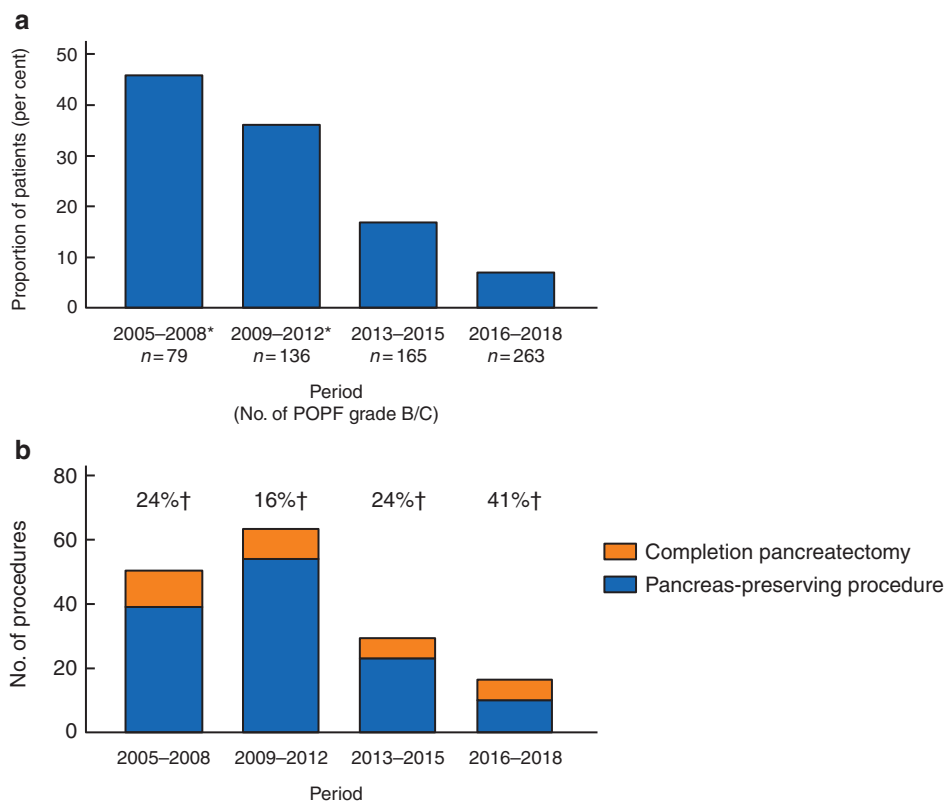
The literature search identified 763 unique studies. After screening titles, abstracts and full texts, 35 studies were included, which reported on patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy (Fig. S1 and Table S4). All included studies, except one, were retrospective in design and the number of included patients ranged from three to 57. Five out of

35 studies were graded as having moderate overall risk of bias, mainly due to confounding and lack of defining outcomes; the remaining studies did not provide sufficient information to determine the risk of bias in one or more domains of the ROBINS-I tool (Table S5). The meta-analysis consisted of 32 studies (583 patients) and the present study, with a total of 745 patients undergoing completion pancreatectomy or a pancreas-preserving procedure for pancreatic fistula. Mortality rate ranged from 0 to 100 per cent and completion pancreatectomy was associated with death (random-effects model, odds ratio 1.99, 95 per cent c.i. 1.03 to 3.84,  $P = 0.040$ ;  $I^2 = 28$  per cent; Fig. 3). The funnel plot showed a symmetrical scatter around the mean (Fig. S2). Sensitivity analysis showed a similar association between completion pancreatectomy and death (fixed-effects model, odds ratio 1.94, 95 per cent c.i. 1.27 to 2.97;  $I^2 = 28$  per cent; Fig. S3).

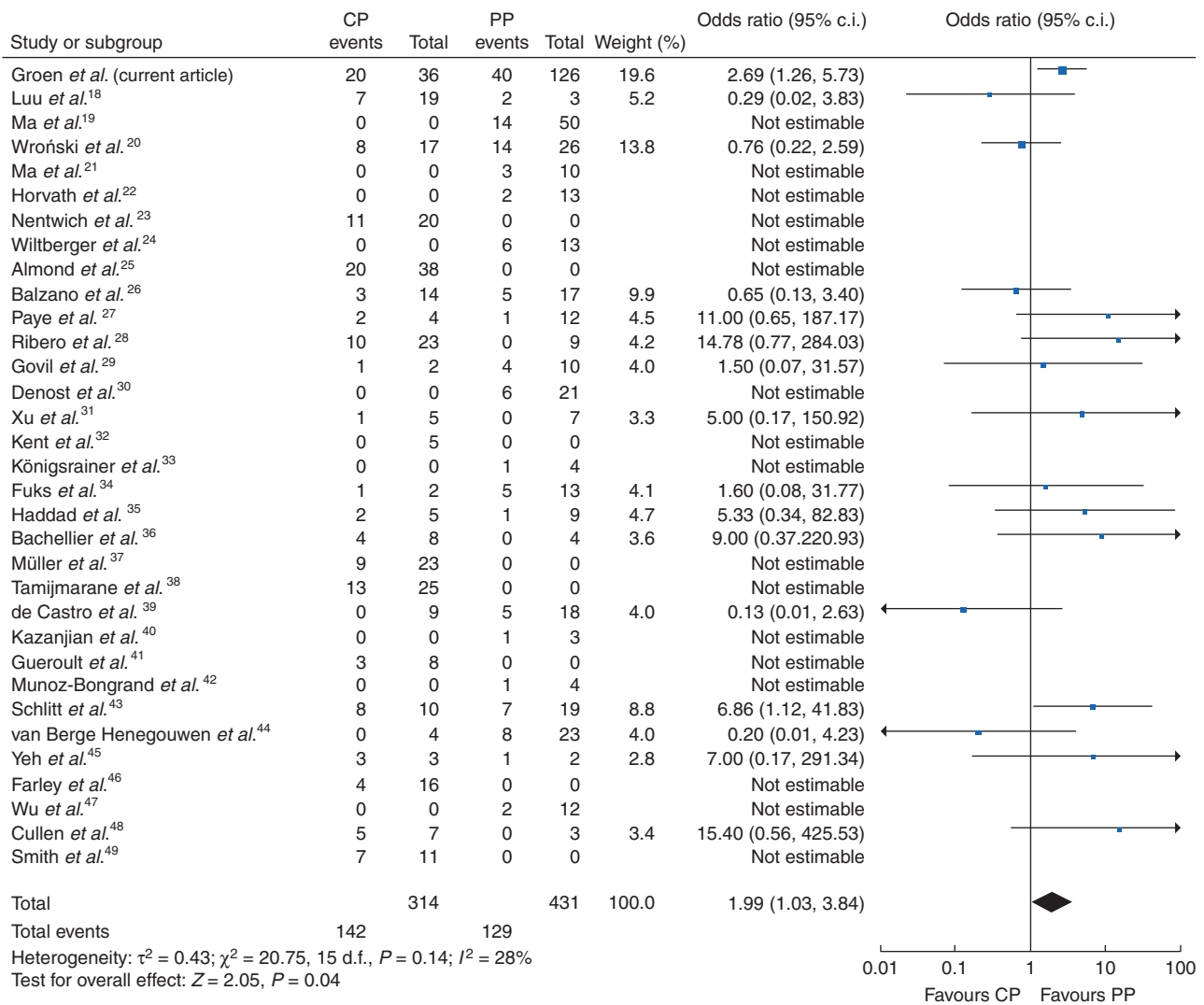
Twenty-two surgical strategies during relaparotomy were described with varying definitions (Table S6). Overall mean/median duration of hospital stay ranged from 15–62 days (23 studies and the present study), ICU admission after relaparotomy ranged from 38–100 per cent (5 studies and the present study), organ failure after relaparotomy ranged from 25–83 per cent (7 studies and the present study) and relaparotomy after relaparotomy ranged from 0–100 per cent (15 studies and the present study).

## Discussion

The present cohort study found that one in five patients with a postoperative pancreatic fistula grade B/C after pancreatoduodenectomy underwent a relaparotomy. Completion pancreatectomy was independently associated with a doubling of mortality rate, compared with a pancreas-preserving

**Fig. 2** Sensitivity analysis

**a** Proportion of patients undergoing relaparotomy for postoperative pancreatic fistula (POPF).  $P < 0.001$  for  $\chi^2$  for linear trend. **b** Proportion of patients undergoing completion pancreatectomy or a pancreas-preserving procedure during relaparotomy for pancreatic fistula.  $P = 0.228$  for  $\chi^2$  for linear trend. \*Data from six of nine institutions; †numbers indicate the percentage of patients undergoing completion pancreatectomy.



**Fig. 3** Forest plot of death after initial relaparotomy by surgical strategy for pancreatic fistula: completion pancreatectomy (CP) versus pancreas-preserving (PP) procedure (random-effects model)<sup>18–49</sup>

procedure. The meta-analysis of 33 cohort studies confirmed this finding. Patients undergoing completion pancreatectomy had a higher APACHE II score within the 24 h after relaparotomy, whereas there was no difference in the proportion of additional reinterventions or duration of hospital stay.

The rate of pancreatic fistula grade B/C in this study was fairly comparable to previous studies (16 versus 9–11 per cent)<sup>1,50</sup>, as was the rate of relaparotomy for pancreatic fistula (21 versus 17–37 per cent)<sup>1,50</sup>. A recent study showed large variation in overall reoperation rate (6–17 per cent) between several pancreatic surgery registries in the USA and Europe<sup>51</sup>. The paradigm shift to percutaneous catheter drainage as primary management of pancreatic fistula and advances in interventional radiology probably explain the linear decrease in proportion of patients undergoing relaparotomy over the study period. The systematic review of studies from 1992–2020 shows that a variety of 22 surgical strategies are used or have been used in clinical practice during relaparotomy for pancreatic fistula. It remains unknown what the exact considerations are and it is likely that personal experience and preference influence the surgeon’s choice. Completion pancreatectomy has been associated with a longer duration of surgery and more blood loss<sup>5,52</sup>, and a higher APACHE II score after

relaparotomy in this study, which suggest that a completion pancreatectomy has a significant impact on the clinical condition of the patient. These factors should be considered when deciding to proceed with a completion pancreatectomy or a pancreas-preserving procedure<sup>53</sup>.

The high mortality rate after completion pancreatectomy may be explained by more severe tissue injury and inflammatory response in already critically ill patients. This effect was seen in a randomized trial in patients with necrotizing pancreatitis and secondary infection in which primary open necrosectomy was compared with a minimally invasive step-up approach<sup>54</sup> and in a matched cohort study in patients with pancreatic fistula in which relaparotomy was compared with catheter drainage as primary treatment<sup>2</sup>. Randomized trials on surgical strategies during relaparotomy for pancreatic fistula after pancreatoduodenectomy are not currently available. Such a trial would be difficult to perform as this critically ill population is increasingly rare, and it seems unlikely that surgeons will accept that the surgical strategy in this population is randomized<sup>55</sup>. Although the systematic review summarized the evidence on this topic, it should be noted that the included studies were all small, observational and heterogeneous. Despite the fact that the indications for

relaparotomy may have varied and changed over time, mortality rates were higher after completion pancreatectomy in all four periods in the sensitivity analysis.

A theoretical advantage of completion pancreatectomy is that it removes the source of inflammation, thereby possibly decreasing the risk of additional reinterventions<sup>5,52</sup>. The present and previous studies<sup>2,54</sup> did not show fewer reinterventions after completion pancreatectomy. Furthermore, the risk of postpancreatectomy haemorrhage after the relaparotomy and required reinterventions was not different between the groups (17 versus 17 per cent). Possibly, the actions applied by the surgeons were usually sufficient to prevent erosion of the peripancreatic vascular structures by leaking pancreatic enzymes<sup>56</sup>. A recent study showed that pancreatic fistula and postpancreatectomy haemorrhage can develop independently and have a major impact on organ failure and mortality<sup>57</sup>. The Dutch Pancreatic Cancer Group is currently analysing the data of the nationwide PORSCHE trial to investigate whether early recognition and a minimally invasive step-up approach for pancreatic fistula after pancreatic resection decreases the risk of postpancreatectomy haemorrhage, organ failure and mortality<sup>58</sup>. Of note, the present study was not designed to promote relaparotomy over percutaneous catheter drainage as primary management of pancreatic fistula and the authors emphasize that a minimally invasive step-up approach should be the preferred strategy.

Little is known about new-onset pancreatic exocrine insufficiency. One study reported a rate of 67 per cent (43 per cent in the present study)<sup>59</sup>. More studies reported on new-onset diabetes mellitus, ranging 26–50 per cent (26 per cent in the present study)<sup>52,59–62</sup>. A recent meta-analysis showed an acceptable rate of diabetes-related morbidity and levels of HbA1c 1 year after elective or emergency total pancreatectomy<sup>63</sup>. Unfortunately, these data were not available for the present study. In the previously mentioned meta-analysis, diarrhoea was the most frequent symptom (24 per cent), which may be caused by pancreatic exocrine insufficiency or autonomic denervation of the bowel due to the extent of the resection<sup>63</sup>. In the Netherlands, initiatives like the PACAP-1 trial are aimed at improving pancreatic enzyme replacement therapy in patients with pancreatic cancer<sup>64</sup>.

The results of the present study should be interpreted in light of some limitations. First, some data were collected retrospectively and this holds the risk of information and classification bias. The data extracted from the prospective Dutch Pancreatic Cancer Audit have been validated previously for data accuracy<sup>9</sup>. Second, due to the observational design of this study, confounding by indication is an important potential bias as the surgeon's decision to perform a completion pancreatectomy or pancreas-preserving procedure is based on the experience and personal preferences of the surgeon and the clinical and surgical context of the patient. For example, patients with completion pancreatectomy were older and more often had multiple organ failure. Inherent differences between patients undergoing completion pancreatectomy compared with a pancreas-preserving procedure may partly explain the observed results. The multivariable analysis was limited by the sample size and could only adjust for a few possible confounders. Also, data of some other possible confounders, for example blood loss and the use of antibiotics<sup>1</sup>, were not sufficiently available. Due to these limitations, residual confounding cannot be ruled out and results should be interpreted with caution. Strengths of this study include the detailed data of disease severity and reinterventions before and after the initial relaparotomy and the systematic review of available evidence.

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## Supplementary material

Supplementary material is available at *BJS* online

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