Pancreatic Surgery: Improving Postoperative Outcomes

Francina Jasmijn Smits

PANCREATIC SURGERY

IMPROVING POSTOPERATIVE OUTCOMES

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Pancreatic surgery: improving postoperative outcomes
PhD thesis, Utrecht University, the Netherlands

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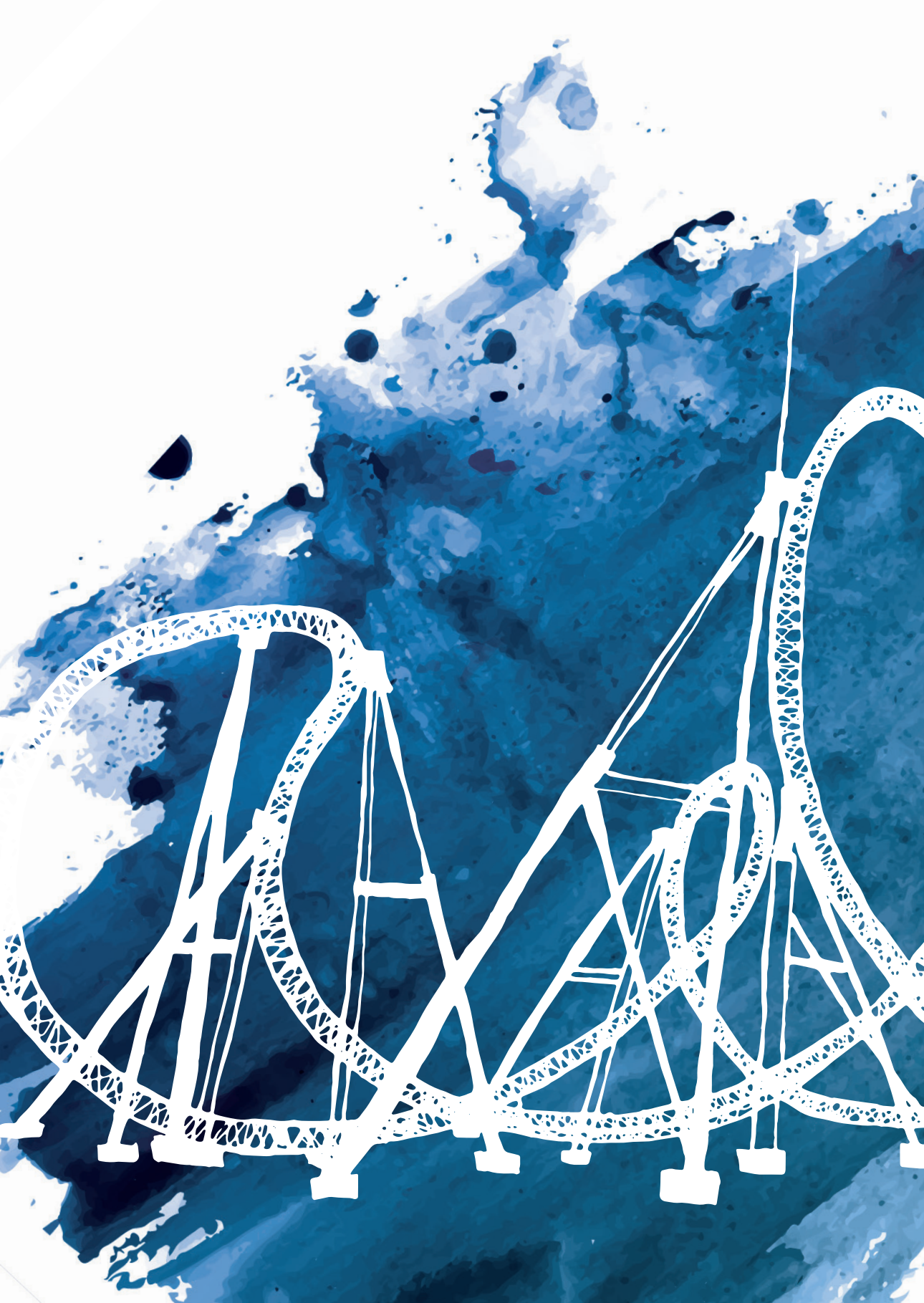
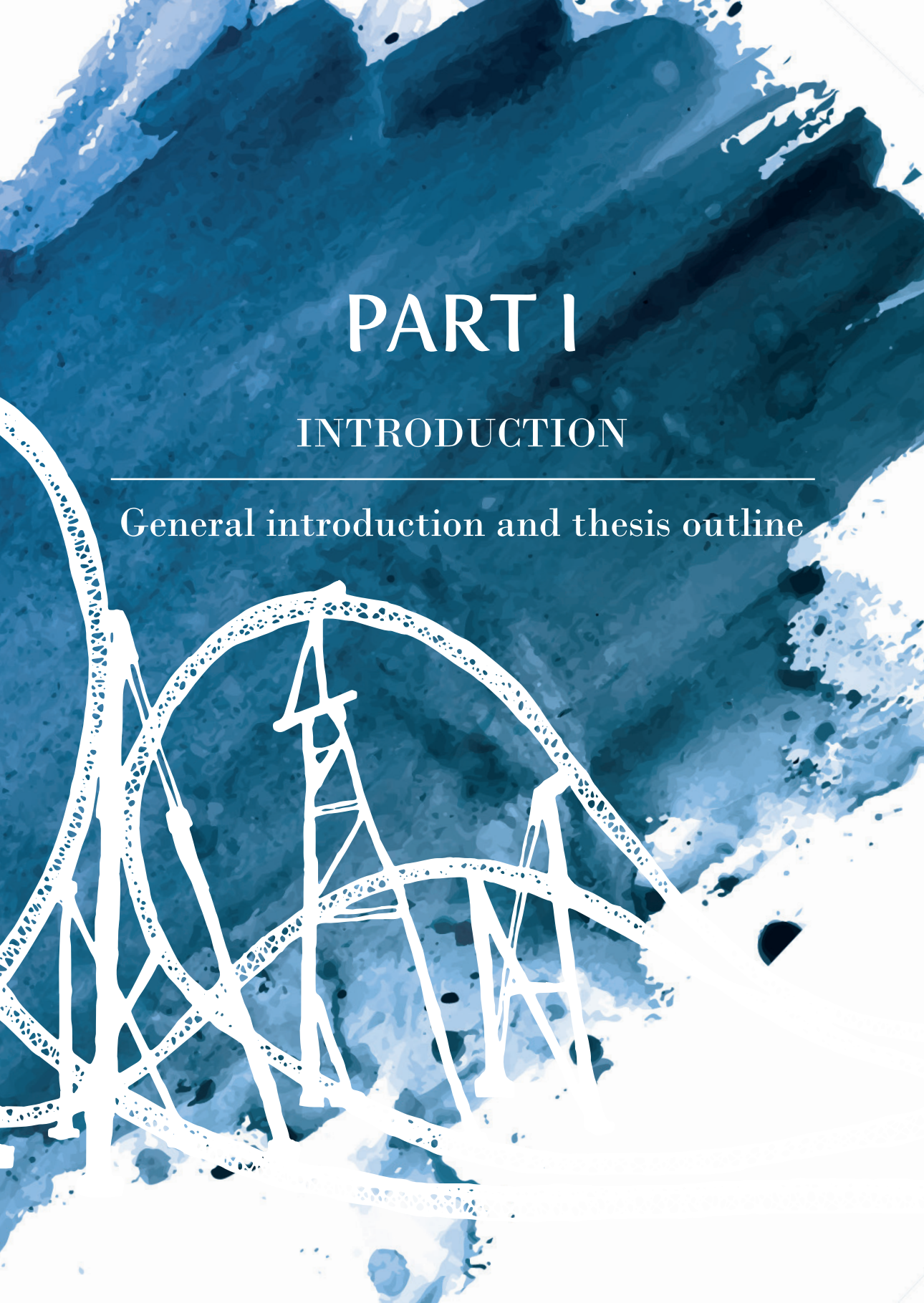


PART I

INTRODUCTION

General introduction and thesis outline



General introduction

The Latin word *chirurgia* derives from the Greek *cheiros* (hand) and *ergon* (work). A well-known description of the work of a surgeon was recorded in the sixteenth-century by Ambroise Paré: "*There are five duties in surgery: to remove what is superfluous, to restore what has been dislocated, to separate what has grown together, to reunite what has been divided and to redress the defects of nature*. "[1] One of the most basic concepts in surgery involves the treatment of abcesses or other fluid collections. Even our distant ancestors understood the necessity of draining collections: Native Americans sharpened hollow feather-quills that were placed in the collection to allow free outlet of fluid or pus.[2]

During the early 19th century, surgical interventions were simple and fast because of the extraordinary pain. They were often seen as a last resort, as postoperative infections led to high mortality. Due to the discovery of anesthesia in the 1840's, procedures became both more extensive and sophisticated, as the limitations imposed by patient discomfort disappeared. In that time, however, the germ theory was not widely accepted and therefore neither the instruments or the hands were cleaned, which resulted in an impressive postoperative mortality of 50%.[3]

Today, even with continuous improvements in a healthcare, postoperative complications are still not always preventable.[5] Postoperative complications occur in around 20% of patients and have a great impact on health care utilization and costs.[4] Some therefore suggest that the focus on improving outcomes should include early recognition and management of complications.[6,7] Recognizing the first signs of complications before they lead to clinical deterioration is, however, challenging. Noticing subtle changes in vital signs, biochemical tests and radiologic features requires a well trained and experienced multidisciplinary medical team.[8] Improving the 'failure to rescue' rate (i.e. mortality in patients with major complications) has emerged as a main target for quality improvement by the international surgical community.[5,6] There is a clear need for studies to develop effective interventions that can be broadly implemented to improve failure to rescue rates worldwide.[5]

Pancreatic surgery

In 1898 the first pancreatoduodenectomy was performed by Alessandro Codivilla. He *en bloc* resected the pancreatic head, distal stomach, proximal duodenum, distal common bile duct and gall bladder and reconstructed gastrointestinal continuity using a Roux-en-Y gastrostomy. It is assumed that he did not perform a pancreatic anastomosis, but left the pancreatic stump ligated. The patient developed continuous drainage of serous fluid from the surgical wound, which is suggestive for leakage of pancreatic juices (i.e. pancreatic fistula). The patient died within weeks after the resection.[9] In the years after, different steps of the pancreatoduodenectomy were published, including the "Kocher maneuver". This led to the first successful pancreatoduodenectomy in 1909 by Walther Kausch.[10] In the two decades after, only two successful pancreatoduodenectomies were

reported. It was only in 1935 that Allen Whipple published his landmark manuscript on the pancreatoduodenectomy.[11]

Pancreatoduodenectomy is a complex procedure. A graphic overview is provided in figure 1. The pancreas lies in the back of the abdomen, behind the stomach in the retroperitoneal plane and it has, especially near the head of the pancreas, a close relation with major abdominal vessels. To recreate gastrointestinal continuity, three anastomoses have to be performed: gastrojejunostomy, hepaticojejunostomy and a pancreatojejunostomy or pancreatogastrostomy.[12] The pancreas itself has a sponge-like structure, which makes it technically difficult to obtain perfect traction on sutures in the pancreatic anastomosis. Pancreatic resection is therefore an example of a complex operation with a high risk of postoperative complications (30 to 73%).[13,14]

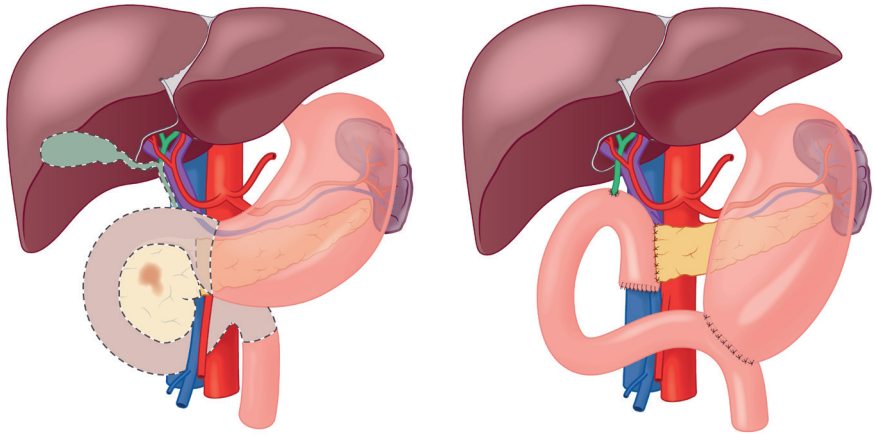


Figure 1. Schematic overview of pancreatoduodenectomy (left: the to be resected parts; right: after reconstruction).

Postoperative Pancreatic Fistula

The most feared postoperative complication is pancreatic fistula. Intra-abdominal leakage of amylase-rich fluid may lead to a potentially fatal cascade of erosion of (major) vessels, systemic inflammation, sepsis and organ failure leading to prolonged hospital stay and increased costs.[15-17] Postoperative pancreatic fistula can be divided into three groups, according to the International Study Group on Pancreatic Surgery definition. Patients with a biochemical leak do have increased amylase levels in drain fluid, but do not require a change in postoperative management. Patients who do require one or more interventions, suffer from clinically relevant postoperative pancreatic fistula which can be divided into grade B (i.e. requiring antibiotic treatment or minimally invasive

drainage) and grade C (i.e. requiring relaparotomy or resulting in organ failure or death)[15]. Mortality in patients with clinically relevant pancreatic fistula is 12 to 18%.[18-20]

Many interventions have been studied to prevent the development of postoperative pancreatic fistula. One of the most studied interventions might be the use of somatostatin analogues, which has shown mixed results so far.[21] A recent large randomized trial showed a decrease in clinically relevant pancreatic fistula (8% vs 17%, P=0.02).[14] However, this concerned a single center study in one of the top centers worldwide, so the results might not be reproducible for others. As it remains the Achilles heel of pancreatic surgery, other preventive interventions focus on pancreatic anastomosis. Fibrin sealants have been proven to be effective in controlling bleeding in cardiovascular and liver surgery and show favorable results in anastomotic sealing after pulmonary lobectomy.[22,23] The sealing capacity may also strengthen the anastomosis, hereby improving anastomotic healing and, hence, may lead to a decrease in incidence and severity of postoperative pancreatic fistula. Besides strengthening the anastomosis by adding sealants, many other different pancreatic anastomotic techniques have been reported. A complete, easily accessible illustrated overview of all different techniques was missing and is provided as part of this thesis. Even with all proposed techniqual improvements to the pancreatic anastomosis, it appears pancreatic fistula cannot be prevented completely as a postoperative risk of 12% remains.[24]

As with all patients with septic complications, early identification and adequate management increases the chances of a good outcome.[25,26] Early signs of postoperative pancreatic fistula, however, are often subtle, which makes it difficult to distinguish a biochemical leak from the potentially life threatening subtype of pancreatic fistula.[27,28] Especially in centers where only a few patients with clinically relevant pancreatic fistula are encountered each year, early signs of pancreatic fistula might remain unrecognized.[29] Inflammatory biomarkers such as C-reactive protein (CRP) and white blood cell count (WBC) might be suitable for early detection of complications.[28]

For decades, postoperative pancreatic fistula was treated through direct relaparotomy. Primary catheter drainage, however, is a less invasive alternative to relaparotomy: it reduces both the tissue damage and the systemic inflammatory response that would otherwise be induced by surgical stress in these already critically ill patients.[30,31] Minimally invasive catheter drainage appears to be successful in the majority of patients and relaparotomy might only be needed in a small selection of these patients.[32-34] During relaparotomy, different strategies are possible: surgical drainage (i.e. intra-abdominal lavage and placement of drains), repair or redo of the pancreatic anastomosis, salvage pancreaticogastrostomy, and completion pancreatectomy.[35] Completion pancreatectomy is the most aggressive strategy which aims to completely remove the focus of intra-abdominal leakage and associated inflammation, but it leads to brittle diabetes.[36] Only few studies have been performed on the clinical outcomes of different surgical strategies in patients with pancreatic fistula after pancreatoduodenectomy.

Postpancreatectomy Hemorrhage

Where early postpancreatectomy hemorrhage (i.e. occurring <24 hours after index pancreatic resection) is often due to inadequate hemostasis or an underlying coagulopathy, late postpancreatectomy hemorrhage is often the result of a multifactorial pathophysiological mechanism, including vessel erosion due to postoperative pancreatic fistula.[37] Severe postpancreatectomy hemorrhage requires a fast and effective management. The management of early postpancreatectomy hemorrhage is mostly carried out through relaparotomy, whereas the management of late postpancreatectomy hemorrhage is more complex.[38,39] The general assumption is that an endovascular approach currently offers the best treatment available through embolization or covered stenting.[40-41] However, the incidence of postpancreatectomy hemorrhage is low and literature on postpancreatectomy hemorrhage mostly consists of retrospective cohorts and small case series. Therefore, a complete overview of the literature might provide more insight in the best treatment strategy of this potentially lethal complication.

Best practice after pancreatic resection

Outcomes following pancreatic resection have improved through centralization in high-volume centers, due to a focus on technical aspects of the surgery, process measures and institutional factors.[42,43] Nevertheless, even in high-volume centers, complications after pancreatic resection remain a serious problem.[44,45] Moreover, most patients in the world still undergo surgery in low-volume or mid-volume centers.[46,47] Nationwide, 90-day mortality rates range from 7 to 12%.[47-49] Improving failure to rescue has therefore also been prioritized in pancreatic surgery.[29,50-52] In this thesis efforts made to decrease failure to rescue and to improve outcomes for patients undergoing pancreatic resection are described.

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Summary of study questions addressed in this thesis

Chapter

1. What is the impact of individual complications on mortality, organ failure, hospital stay and readmission after pancreatoduodenectomy?

2. Do matrix-bound sealants prevent or ameliorate the course of post-operative pancreatic fistula after a pancreatic resection according to available literature?

3. What pancreatic anastomosis techniques have been described in peer-reviewed articles on patients undergoing pancreatoduodenectomy and is one technique superior to others in terms of the incidence of clinically relevant postoperative pancreatic fistula when all randomized controlled trials are evaluated?

4. What is the accuracy of postoperative clinical, biochemical and radiologic variables for early recognition of clinically relevant pancreatic fistula after pancreatic resection as described in available literature?

5. Is C-reactive protein (CRP) superior to white blood cell count in the detection of major complications in the first seven days after pancreatoduodenectomy?

6. Are clinical outcomes of patients undergoing catheter drainage superior to those undergoing relaparotomy as the primary treatment for severe pancreatic fistula after pancreatoduodenectomy?

7. What predictors can be identified for successful minimally invasive catheter drainage as first invasive intervention in the treatment of postoperative pancreatic fistula after pancreatoduodenectomy?

8. When performing relaparotomy for pancreatic fistula after pancreatoduodenectomy, is completion pancreatectomy superior to pancreas-preserving procedures when evaluating both Dutch data and available literature in terms of clinical outcomes?

9. What is the available evidence on the incidence, detection, management and clinical outcomes of treatment strategies for late postpancreatectomy hemorrhage?

10. Can major complications and death be prevented by the nationwide implementation of an algorithm for early recognition and minimally invasive management of complications in patients undergoing pancreatic resection as compared to usual care?

11. What procedures have to be performed to obtain both medical ethical and local approval before the start of the PORSCH trial, and what are the differences between participating centers?

Chapter I

Impact of Complications After Pancreatoduodenectomy on Mortality, Organ Failure, Hospital Stay, and Readmission: Analysis of a Nationwide Audit

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Annals of Surgery, Volume 275(1), January 2022

Abstract

Background
An initial complication may provoke a sequence of adverse events potentially leading to mortality after pancreatoduodenectomy. This study was conducted to aid prioritization of quality improvement initiatives. The objective of this study was to quantify the impact of individual complications on mortality, organ failure, hospital stay, and readmission after pancreatoduodenectomy.

Methods
Data from consecutive patients undergoing pancreatoduodenectomy (2014-2017) were extracted from the Dutch Pancreatic Cancer Audit. Population attributable fractions (PAF) were calculated for the association of each complication (ie, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, wound infection, and pneumonia) with each unfavorable outcome [ie, in-hospital mortality, organ failure, prolonged hospital stay (>75th percentile), and unplanned readmission), whereas adjusting for confounders and other complications. The PAF represents the proportion of an outcome that could be prevented if a complication would be eliminated completely.

Results
Overall, 2620 patients were analyzed. In-hospital mortality occurred in 95 patients (3.6%), organ failure in 198 patients (7.6%), and readmission in 427 patients (16.2%). Postoperative pancreatic fistula and postpancreatectomy hemorrhage had the greatest independent impact on mortality [PAF 25.7% (95% CI 13.4-37.9) and 32.8% (21.9-43.8), respectively] and organ failure [PAF 21.8% (95% CI 12.9-30.6) and 22.1% (15.0-29.1), respectively]. Delayed gastric emptying had the greatest independent impact on prolonged hospital stay [PAF 27.6% (95% CI 23.5-31.8)]. The impact of individual complications on unplanned readmission was smaller than 11%.

Conclusion
Interventions focusing on postoperative pancreatic fistula and postpancreatectomy hemorrhage may have the greatest impact on in-hospital mortality and organ failure. To prevent prolonged hospital stay, initiatives should in addition focus on delayed gastric emptying.

Introduction

Resection combined with (neo)adjuvant chemotherapy provides the best chance of long term survival in patients with pancreatic ductal adenocarcinoma.[1-3] Pancreatoduodenectomy, however, remains associated with a 40%-60% risk of postoperative complications and subsequent 2%-5% risk of in-hospital mortality, even in high-volume centers.[4-6]

It is well recognized that individual complications may lead to a sequence of other complications and unfavorable outcomes (ie, mortality, organ failure, prolonged hospital stay, and readmission).[7,8] To improve quality of care and decrease costs after pancreatoduodenectomy, initiatives focus on the prevention, and optimal treatment of complications. To allocate healthcare and research resources most efficiently, initiatives should target those complications that have the greatest impact on reducing these unfavorable outcomes. Several studies have described the incidence of complications and outcomes after pancreatic resection.[9-11] However, simple data on the frequency are not sufficient to estimate the impact of a complication on the population undergoing pancreatoduodenectomy.

In this context, the population attributable fraction (PAF) is a useful measure as it represents the fraction of all patients with a specific unfavorable outcome (eg, mortality) that can be attributed to a specific exposure (eg, postoperative pancreatic fistula).[12-14] A specific strength of the PAF is that it incorporates both the frequency of an exposure and the likelihood that an outcome will occur in the presence of this exposure. Consequently, previous studies that utilized the PAF in surgery have identified several complications with a larger impact on a population level, than previously assumed.[15-19] This provided new insights and therewith facilitated more targeted quality improvement programs, which may be of considerable interest in the field of pancreatic surgery.

The aim of this study was to quantify the impact of individual complications (ie, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, wound infection, and pneumonia) on mortality, organ failure, hospital stay, and readmission after pancreatoduodenectomy in a national, prospective cohort.

Methods

All consecutive patients who underwent a pancreatoduodenectomy for a presumed pancreatic, periampullary or duodenal (pre)malignancy or pancreatitis from January 2014 to December 2017 in the Netherlands as registered in the Dutch Pancreatic Cancer Audit (DPCA) were analyzed. All patients were prospectively registered in the DPCA. Participation in the DPCA is mandatory for all pancreatic surgery centers in the Netherlands, each performing a minimum of 20 pancreatoduodenectomies annually.[20] Patients were excluded if they received preoperative chemo(radio)therapy, for this was

only administered within (randomized) trials in The Netherlands (n = 136), or in case of essential missing data on postoperative complications (n = 28). The Medical Research Ethics Committee of the University Medical Center Utrecht reviewed the study and waived the need for informed consent. The study was conducted according to the declaration of Helsinki and according to STROBE guidelines.[21]

Data Extraction and Outcome Measures

Data extracted from the DPCA included patient and treatment-related characteristics (ie, age, sex, body mass index, weight loss, Eastern Cooperative Oncology Group performance score, American Society of Anesthesiologists classification, comorbidity to calculate the Charlson Comorbidity Index (ie, history of diabetes, liver disease, malignancy, infectious diseases, kidney disease, cardiovascular disease, pulmonary disease, neurologic disease, connective tissue disease, and gastrointestinal disease), surgical approach (open or minimally invasive), additional venous, arterial or visceral resection(s), diameter of the pancreatic duct, pancreatic texture and tumor histology). Furthermore, pancreatectomy specific complications (ie, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, chyle leakage, and delayed gastric emptying), general complications (ie, wound infection and pneumonia), and outcomes (ie, mortality, organ failure, length of hospital stay, and unplanned readmission rate) were extracted from the DPCA. Pancreatectomy specific complications were defined in accordance to International Study Group on Pancreatic Surgery (ISGPS)/International Study Group on Liver Surgery (ISGLS) definitions. Only clinically relevant grade B/C complications were included in the analysis.[22-26] Diagnosis of wound infection, pneumonia and organ failure was based on clinical features; no predefined diagnosis was adapted in the DPCA. Data were registered up to 30 days after pancreatic resection or - if length of admission exceeded 30 days - during entire hospital admission.

Unfavorable outcomes were in-hospital mortality, organ failure, prolonged hospital stay, and unplanned readmissions. Prolonged hospital stay was defined as a duration exceeding the 75th percentile in this cohort (ie, >18 days).

Statistical Analysis

We evaluated the association between each complication (ie, postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, wound infection, and pneumonia) and each study outcome (ie, in-hospital mortality, organ failure, prolonged hospital stay, and unplanned readmission rate).

The association of each complication-outcome pair was analyzed with adjustment for confounders. Potential confounding pathways between complications and study unfavorable outcomes were visualized in a Directed Acyclic Graph (dagitty.net/mIrLv6X; supplementary appendix Fig. S1, http://links.lww.com/SLA/C13).[27] The pathways were based on previously published studies and, whenever substantial evidence was lacking, on expert consensus.[23,24,26,28-32] The identified minimal sufficient set of confounders included:

sex, age, body mass index, Eastern Cooperative Oncology Group performance score, American Society of Anesthesiologists classification, Charlson Comorbidity Index, surgical approach (open vs. minimally invasive), additional arterial, venous or visceral resection, tumor histology (malignant vs benign/premalignant) and hospital volume (=50 pancreatic resections annually, based on the median annual volume in Dutch centers).

A complete set of baseline characteristics was created by multiple imputation using 10 iterations. All baseline and outcome variables were included as predictors for imputation.[33] The relation between each complication-outcome pair represented by the adjusted risk ratio (aRR) was evaluated using a modified Poisson regression analysis robust with standard error variance and adjustment for the minimal sufficient set of confounders as mentioned before and the presence of other complications.[34] The risk adjusted population attributed fraction (PAF) was calculated for each significantly associated complication-outcome pair. The PAF represents the proportion of an unfavorable outcome that would be prevented when the given complication could be eliminated entirely.[12-14,35] Two sensitivity analyses were performed. First, for hemorrhage could be caused by postoperative pancreatic fistula (ie, mediation instead of confounding), the effect of postoperative pancreatic fistula on in-hospital mortality was also evaluated without adjustment for postpancreatectomy hemorrhage. Second, for textbook outcomes define prolonged hospital stay as longer than the 50th percentile (ie, >12 days), a sensitivity analysis was performed to evaluate the impact of complication this outcome.[36]

Because we did not have data on the onset date of complications, we assumed that all complications were present before the unfavorable outcome. Because grade B/C delayed gastric emptying by definition occurs 8-14 days after pancreatic resection, including patients who died within this time period might cause an underestimation of the effect due to immortal time bias. Therefore, patients who died on or before postoperative day 14 were excluded from all analyses on delayed gastric emptying.[37] Wound infection and pneumonia were only registered in 2016 and 2017 and; therefore, analysis of the impact of these complications was limited to those years in which these complications were registered. Chyle leakage was only registered in 2017, and was; therefore, not included in the analysis.[25] Hospital stay and unplanned readmission were analyzed only in patients surviving the index hospitalization.

Statistical analysis was performed in IBM SPSS Statistics 25 and in R (version 3.5.1) using R-language "Feather Spray" (version 0.3.3) and the "mice" (version 3.3.0), "sandwich" (version 2.5-0) and "AF" (version 0.1.4) packages. Binary variables were presented as count with percentage. Normally distributed continuous data were presented as mean with standard deviation; variables with a skewed distribution were presented as median with interquartile range (IQR). A 2-sided P-value was considered statistically significant.

Results

A total of 2620 patients undergoing pancreatoduodenectomy were eligible for analysis. Median age was 68 years (IQR 60-74) and 1474 patients (56.1%) were male. Pancreatoduodenectomy was performed for a presumed malignancy in 2017 patients (79.1%). Baseline characteristics are presented in Table 1.

Table 1: Baseline characteristics

	Pancreatoduodenectomy	Missing values
	n=2620	
Age (years)†	68 (60-74)	0 (0.0)
Sex ratio (M:F)	1474 (56.1) : 1146 (43.9)	0 (0.0)
BMI (kg/m2)†	25 (22-27)	120 (4.6)
Weight loss ‡	1150 (52.9)	448 (17.1)
ECOG performance status		223 (8.6)
0	1160 (48.3)	
1	989 (41.2)	
≥2	248 (10.3)	
ASA classification		0 (0.0)
I	369 (14.1)	
II	1647 (62.8)	
III	596 (22.7)	
IV	8 (0.0)	
Charlson comorbidity index		31 (1.2)
0-1	453 (17.4)	
2-3	1330 (51.4)	
4-5	672 (26.0)	
≥6	134 (5.2)	
Surgical approach		49 (1.9)
Open procedure	2204 (85.7)	
Minimally invasive	367 (14.3)	
Additional resections		
Arterial	38 (1.5)	23 (0.8)
Venous ¶	136 (5.2)	25 (1.0)
Visceral	220 (8.9)	139 (5.3)
Diameter pancreatic duct†	4 (2-7)	1114 (42.5)
Soft texture pancreas	1476 (61.6)	255 (8.6)
Tumor histology		69 (2.6)
Pancreatic ductal adenocarcinoma	1082 (42.4)	
Distal cholangiocarcinoma	380 (14.9)	
Ampullary carcinoma	338 (13.2)	
Duodenal carcinoma	187 (7.3)	
IPMN	184 (7.2)	
Neuroendocrine neoplasm	127 (5.0)	
Chronic pancreatitis	80 (3.1)	
Other	173 (6.8)	
Operated in high volume center*	1457 (55.6)	0 (0.0)

M, male; F, female; BMI, body mass index; kg, kilogram; m2, square meter; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists; IPMN, intraductal papillary mucinous neoplasm; values in parenthesis are percentages unless indicated otherwise; † median with inter quartile range; ‡ >5% of original weight; ¶ Wedge or segment of portal vein or superior mesenteric vein; *performing >50 pancreatic resections annually

Data on postoperative complications and study outcomes are presented in Table 2. Overall, 1672 patients experienced at least one complication (63.8%). Most common complications were delayed gastric emptying (488 patients, 18.6%) and postoperative pancreatic fistula (379 patients, 14.5%). In-hospital mortality occurred in 95 patients (3.6%) and organ failure in 198 patients (7.9%). Median time to death was 12 days (IQR 7-26 days); 50/95 patients died on or before postoperative day 14 and were excluded from all analyses concerning delayed gastric emptying. Median length of hospital stay was 12 days (IQR 8-18). A total of 427 patients (16.6%) were readmitted after initial discharge from the hospital.

Table 2: Postoperative complications

	Pancreatoduodenectomy	**Missing values**
	n=2620	
Postoperative complications		
Postoperative pancreatic fistula¶		0 (0.0)
Grade B	278 (10.6)	
Grade C	101 (3.8)	
Postpancreatectomy hemorrhage		0 (0.0)
Grade B	99 (3.8)	
Grade C	115 (4.4)	
Postoperative bile leakage		0 (0.0)
Grade B	99 (3.7)	
Grade C	38 (1.5)	
Delayed gastric emptying		0 (0.0)
Grade B	269 (10.2)	
Grade C	219 (8.3)	
Postoperative chyle leakage ‡		1933 (73.8)
Grade B	54 (7.9)	
Grade C	2 (0.0)	
Wound infection‡	127 (10.2)	1375 (52.4)
Pneumonia‡	93 (7.5)	1379 (52.6)
Study outcomes		
Mortality	95 (3.6)	0
Organ failure		109 (4.2)
Single organ failure	110 (4.4)	
Multi organ failure	88 (3.5)	
Hospital stay †	12 (8-18)	37 (1.4)
Prolonged hospital stay*	621 (24.0)	37 (1.4)
Unplanned readmission	427 (16.6)	41 (1.6)

Values in parenthesis are percentages unless indicated otherwise; ¶ 2005 definition; ‡ only registered for year 2017 (chyle leakage) and years 2016 and 2017 (wound infection and pneumonia); † calculated over survivors; median with inter quartile range; *extending stay of 75% of patients in this cohort (*i.e.* >18 days)

aRR's for each complication-outcome pair are presented in (Tables 3-6). Postoperative pancreatic fistula [aRR 2.86 (95% CI 1.76-4.65)] and postpancreatectomy hemorrhage [aRR 6.09 (95% CI 3.80-9.76)] were associated with in-hospital mortality. All evaluated complications except bile leakage showed an association with organ failure, of which postpancreatectomy hemorrhage had the strongest association [aRR 3.14 (2.27-4.34)]. All complications were associated with prolonged hospital stay, however, the strongest association was with delayed gastric emptying [aRR 2.99 (95% CI 2.60-3.44)]. Postoperative pancreatic fistula, postpancreatectomy hemorrhage, bile leakage, and delayed gastric emptying were associated with unplanned readmission (Table 6).

The risk-adjusted PAF's for each complication-outcome pair are given in (Tables 3-6), and visualized in Fig. 1. Postoperative pancreatic fistula and postpancreatectomy hemorrhage had the greatest impact on in-hospital mortality. Complete elimination of these complications in the current cohort would result in an anticipated 25.7% (95% CI 13.4-37.9) and 32.8% (95% CI 21.9-43.8) decrease in in-hospital mortality, respectively. Additionally, postoperative pancreatic fistula and postpancreatectomy hemorrhage had the highest impact on organ failure [PAF 21.8% (95% CI 12.9-30.6), PAF 22.1% (95% CI 15.0-29.1), respectively]. Wound infection and pneumonia also affected organ failure considerably [PAF 18.0% (95% CI 8.2-27.8), PAF 18.9% (95% CI 9.4-28.4), respectively]. Delayed gastric emptying had the highest impact on prolonged hospital stay [PAF 27.6% (95% CI 23.5-31.8)]. All PAF's for readmission rate were relatively small, with postoperative pancreatic fistula having the greatest impact [PAF 10.6 (95% CI 6.0-15.1)]. The impact of all other complications on the unfavorable outcomes was relatively small.

In addition, a sensitivity analysis was performed to evaluate the role of postoperative pancreatic fistula as a mediator to postpancreatectomy hemorrhage. Overall, 86/214 patients with postpancreatectomy hemorrhage also suffered from postoperative pancreatic fistula (40.2%) showing an aRR of 3.94 (95% CI 2.52-6.17) of postoperative pancreatic fistula on mortality without adjustment for postpancreatectomy hemorrhage; the PAF was 29.9% (95% CI 18.4-41.4). The sensitivity analysis on length of hospital stay exceeding the 50th percentile (ie, >12 days) were similar to the outcomes presented in the manuscript (ie, >18 days) and presented in the Supplementary Appendix, http://links.lww.com/SLA/C13.

Table 3: Adjusted attributions of complications to in-hospital mortality

Postoperative complication	Proportion who died*	Adjusted relative risk†	P	Adjusted PAF (%)†	P
Postoperative pancreatic fistula	38 of 379 (10.0)	2.86 (1.76-4.65)	<0.001	25.7 (13.4-37.9)	<0.001
Postpancreatectomy hemorrhage	38 of 214 (17.7)	6.09 (3.80-9.76)	<0.001	32.8 (21.9-43.8)	<0.001
Bile leakage	10 of 137 (7.3)	1.40 (0.74-2.61)	0.30	-	-
Delayed gastric emptying‡	-	-	-	-	-
Wound infection¶	2 of 127 (1.6)	0.28 (0.06-1.22)	0.09	-	-
Pneumonia¶	4 of 93 (4.3)	1.60 (0.58-4.45)	0.81	-	-

Values in parenthesis are *percentages and †95% confidence intervals. PAF, population attributable fraction. ‡Not calculated, for 50/95 patients were excluded in this analysis; ¶Calculated over years 2016-2017

Table 4: Adjusted attributions of complications to organ failure

Postoperative complication	Proportion with organ failure*	Adjusted relative risk†	P	Adjusted PAF (%)†	P
Postoperative pancreatic fistula	84 of 362 (23.2)	2.29 (1.72-3.32)	<0.001	21.8 (12.9-30.6)	<0.001
Postpancreatectomy hemorrhage	67 of 210 (31.9)	3.14 (2.27-4.34)	<0.001	22.1 (15.0-29.1)	<0.001
Bile leakage	27 of 129 (20.9)	1.47 (0.99-2.19)	0.06	-	-
Delayed gastric emptying‡	66 of 449 (14.7)	1.46 (1.01-2.10)	0.04	11.4 (0.6-22.2)	0.04
Wound infection¶	23 of 125 (18.4)	2.46 (1.59-3.82)	<0.001	18.0 (8.2-27.8)	<0.001
Pneumonia¶	25 of 90 (27.7)	2.79 (1.69-4.59)	<0.001	18.9 (9.4-28.4)	0.002

Values in parenthesis are *percentages and †95% confidence intervals. PAF, population attributable fraction. ‡ Calculated over 2570 patients surviving to postoperative day 14 with overall mortality of 45 (1,7%); ¶Calculated over years 2016-2017

Table 5: Adjusted attributions of complications to prolonged hospital stay ‡

Postoperative complication	Proportion with prolonged stay*	Adjusted relative risk†	P	Adjusted PAF (%)†	P
Postoperative pancreatic fistula	232 of 334 (69.4)	2.09 (1.81-2.41)	<0.001	15.5 (12.3-18.7)	<0.001
Postpancreatectomy hemorrhage	110 of 169 (65.1)	1.33 (1.11-1.60)	0.002	4.9 (2.8-7.0)	<0.001
Bile leakage	100 of 124 (80.6)	2.09 (1.73-2.52)	<0.001	7.1 (5.1-9.1)	<0.001
Delayed gastric emptying	322 of 461 (69.8)	2.99 (2.60-3.44)	<0.001	27.6 (23.5-31.8)	<0.001
Wound infection¶	52 of 121 (43.0)	1.27 (1.01-1.58)	0.04	3.3 (0.0-6.4)	0.04
Pneumonia¶	51 of 85 (60.0)	1.51 (1.20-1.89)	<0.001	5.1 (2.2-8.0)	<0.001

‡Calculated over survivors; prolonged stay >18 days. Values in parenthesis are *percentages and †95% confidence intervals. PAF, population attributable fraction. ¶Calculated over years 2016-2017

Table 6: Adjusted attributions of complications to unplanned readmission ‡

Postoperative complication	Proportion readmitted*	Adjusted relative risk†	P	Adjusted PAF (%)†	P
Postoperative pancreatic fistula	107 of 328 (32.6)	1.78 (1.42-2.24)	<0.001	10.6 (6.0 -15.1)	<0.001
Postpancreatectomy hemorrhage	55 of 173 (31.7)	1.64 (1.12-1.91)	0.005	4.0 (0.9-7.1)	0.01
Bile leakage	40 of 126 (31.7)	1.54 (1.14-2.09)	0.005	3.3 (0.7-5.9)	0.01
Delayed gastric emptying	121 of 456 (26.5)	1.35 (1.09-1.67)	0.005	7.1 (1.9-12.1)	0.007
Wound infection¶	25 of 124 (20.2)	0.94 (0.64-1.38)	0.72	-	-
Pneumonia¶	18 of 86 (20.9)	0.83 (0.53-1.31)	0.42	-	-

‡Calculated over survivors. Values in parenthesis are *percentages and †95% confidence intervals. PAF, population attributable fraction. ¶Calculated over years 2016-2017

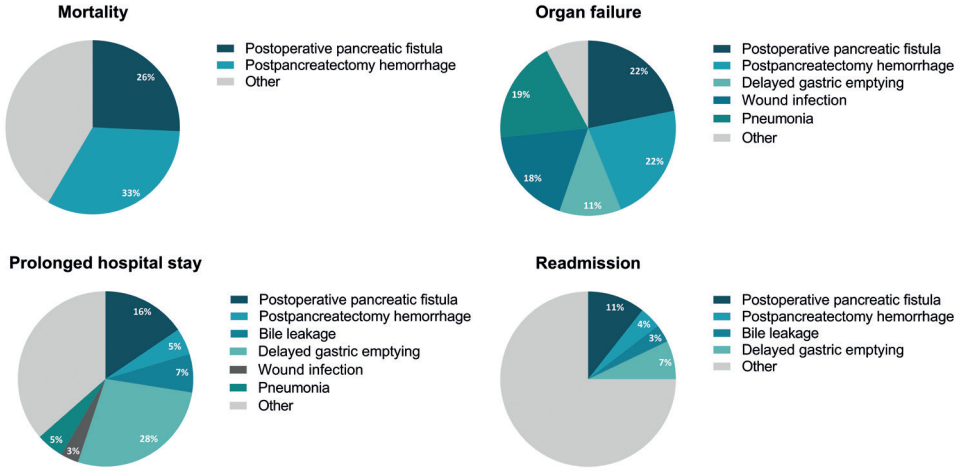

Figure 1. Risk-adjusted population attributed fractions for each complication–outcome pair showing a significant association.

Discussion

This study identified the complications after pancreatoduodenectomy with the greatest attributable risk to unfavorable outcomes (ie, mortality, organ failure, hospital stay, and readmission). Postoperative pancreatic fistula and postpancreatectomy hemorrhage attributed considerable to all unfavorable outcomes and accounted for 25.7% and 32.8% of the total in-hospital mortality, respectively. Delayed gastric emptying had the greatest impact on prolonged hospital stay. The impact of evaluated complications on readmission was relatively small (maximum risk adjusted attribution of 10.6%).

Although the reported incidence of postpancreatectomy hemorrhage is relatively low (ca. 8%), it had the highest impact on in-hospital mortality and organ failure in this study.[38-40] Postoperative pancreatic fistula had the second largest impact on mortality and organ failure. Postoperative pancreatic fistula may lead to bleeding, and thereby to unfavorable outcomes such as organ failure, and death.[39,41-43] If bleeding is a mediator rather than a confounder in the association between postoperative pancreatic fistula and unfavorable outcomes, it is incorrect to adjust for the impact of postpancreatectomy hemorrhage whereas evaluating the impact of postoperative pancreatic fistula on unfavorable outcomes. Therefore, an additional sensitivity analysis was performed to evaluate the impact of postoperative pancreatic fistula on in-hospital mortality without adjusting for postpancreatectomy hemorrhage, demonstrating a slightly increased impact of fistula on mortality; from 25.7% to 29.9%.

Complications in general are associated with prolonged hospital stay after surgery.[44] In this study, a strong association between delayed gastric emptying and prolonged hospital stay was identified (estimated PAF 27.6%). A plausible explanation is that adequate oral intake is generally accepted as a criterion before hospital discharge. Recent analyses showed that unplanned readmissions were mainly related to infectious complications, dehydration, and malnutrition.[45,46] Unfortunately, factors associated with the latter two were not registered in the DPCA. This might explain why in the current analysis 75% of the readmissions could not be attributed to a specific complication.

An advantage of calculating the PAF compared to other measures of impact is that it enables determination of the burden of complications on a population level. As a result, our analysis may be used to guide quality improvement initiatives to specifically target those complications that have the greatest clinical and/or economic impact.[7,18] PAF calculations were recently conducted in other surgical fields.[15-19] Goense et al evaluated the impact of complications after esophagectomy and found pulmonary complications and anastomotic leakage to have the greatest overall impact on in-hospital mortality, prolonged hospital stay, reoperations and unplanned readmissions.[19] Scarborough et al concluded that anastomotic leakage has a large impact on in-hospital mortality and resource use after colonic resection, which was concerning because current quality improvement programs focus on other complications showing estimated PAF's of less than 10%.[18] The impact of complications after pancreatic resection on the entire population undergoing pancreatoduodenectomy has, to the best of our knowledge, not yet been evaluated.

Strengths of this study include the population-based, nationwide design; the prospective mandatory data collection and large sample size.[20] Calculation of risk-adjusted PAF's provides a simple but comprehensive overview of the overall impact of a complication on outcomes on a population level. Analysis was not only adjusted for patient and treatment related confounders, but also for all other complications, as some patients developed more than one complication. There were also several limitations. It was assumed that

the unfavorable outcomes were at least partially caused by the complications, although the likelihood of developing complications can be influenced by the study unfavorable outcomes. For example, the risk of pneumonia might increase when length of hospital stay is prolonged, causing an overestimation of the effect due to reversed causality. Another example is probably the association between wound infection and organ failure. Unfortunately, the DPCA does not include data on sequence of complications and unfavorable outcomes. Conversely, an underestimation of the impact can be caused by immortal time bias, for example, induced by early mortality.[37] To minimize this effect, patients who died within 14 days after pancreatoduodenectomy were excluded from the delayed gastric emptying analysis. However, as a result, the PAF estimates for delayed gastric emptying are only applicable for patients surviving the first 14 days after resection. Another limitation was that no uniform definitions for organ failure, pneumonia and wound infection were adopted in the DPCA. Consequently, reporting bias might be introduced. For example, pneumonia is more likely to be reported when it leads to organ failure or even death, which might lead to an overestimated impact. Additionally, we assumed that our directed acyclic graph included all potential confounding pathways. Nevertheless, the risk of unregistered or unknown confounders remains. Also, patients who underwent neoadjuvant (radio)chemotherapy were excluded from our analysis, because this is currently not considered standard practice in The Netherlands and was only administered in (randomized) trials. This potentially leads to participation and performance bias, resulting in better outcomes of these patients as compared to a nationwide cohort. We believe this limits the generalizability to centers where neoadjuvant treatment is standard of care. To create a homogeneous patient group, these patients were excluded from this analysis. Lastly, results of this study might not be generalizable to all hospitals individually or outside the Netherlands, as local postoperative monitoring and complication management might lead to different outcomes. To address this potential source of bias, we have adjusted the analyses by hospital volume for pancreatic resections.

Postoperative pancreatic fistula and associated postpancreatectomy hemorrhage had the greatest attribution to in-hospital mortality in this study. In addition, a recent analysis showed these complications were strongly associated with both the risk of not receiving adjuvant chemotherapy and time to commence adjuvant chemotherapy, which are likely to influence survival.[47] Despite many initiatives to prevent postoperative pancreatic fistula, the incidence of this potentially fatal complication remains as high as 15%.[48-50] We hypothesize that early recognition and adequate drainage of postoperative pancreatic fistula might mitigate the risk of subsequent postpancreatectomy hemorrhage, organ failure, and mortality.[51] To investigate this hypothesis, we are currently conducting the nationwide PORSCH trial (NCT03400280), a quality improvement program to evaluate the implementation of a standardized best practice algorithm for postoperative care in the 17 centers of the Dutch Pancreatic Cancer Group (ie, all centers performing pancreatic surgery in The Netherlands).

In conclusion, quality improvement programs to reduce mortality after pancreatoduodenectomy should primarily focus on prevention and adequate management of postoperative pancreatic fistula and postpancreatectomy hemorrhage. To reduce hospital stay, the focus should be on delayed gastric emptying.

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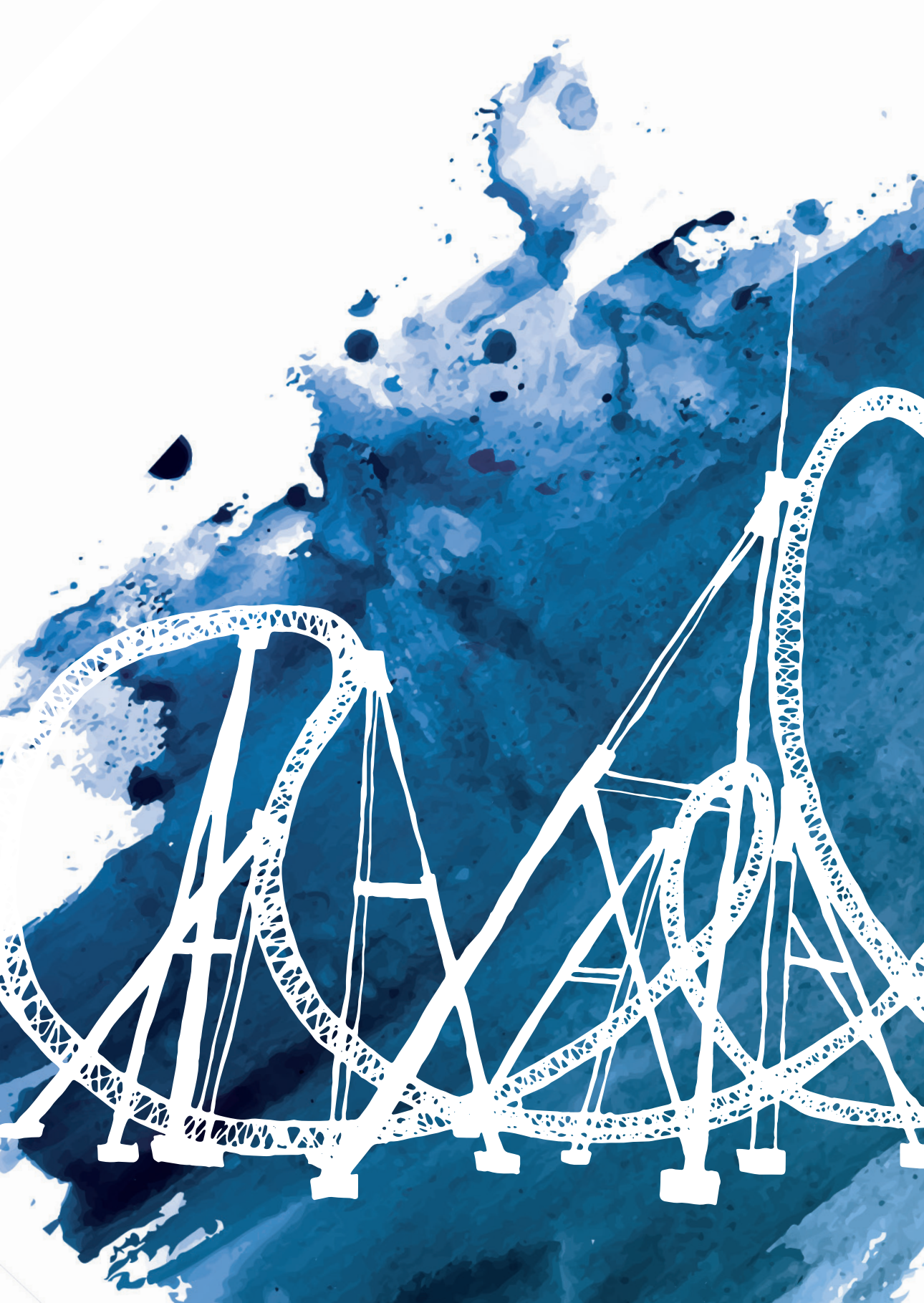
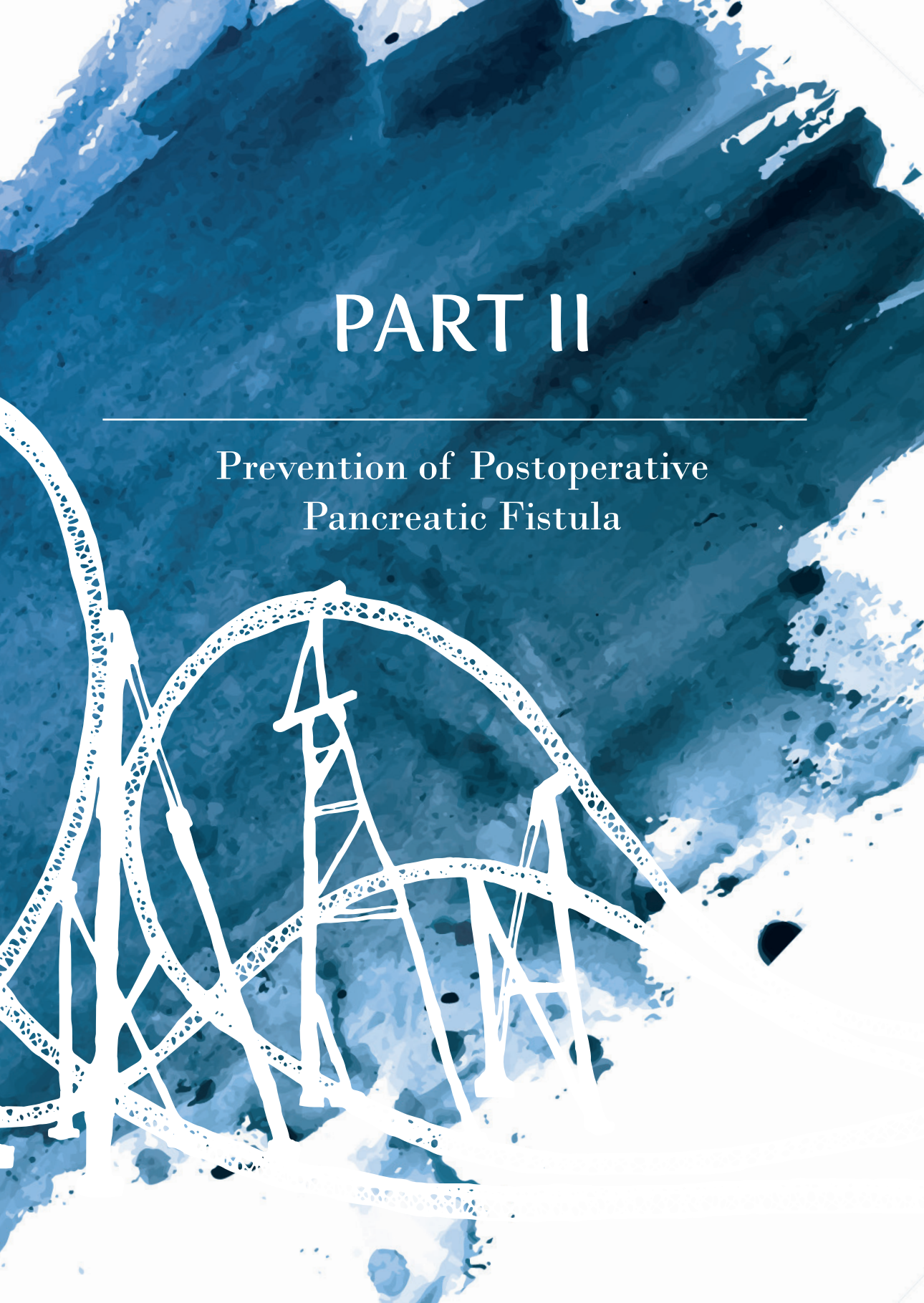


PART II

Prevention of Postoperative Pancreatic Fistula



Chapter 2

Systematic Review On The Use Of Matrix-Bound Sealants In Pancreatic Surgery

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HPB (Oxford). 2015;17(11):1033-1039

Abstract

Background
Pancreatic fistula is a potentially life-threatening complication after a pancreatic resection. The aim of this systematic review was to evaluate the role of matrix-bound sealants after a pancreatic resection in terms of preventing or ameliorating the course of a post-operative pancreatic fistula.

Methods
A systematic search was performed in the literature from May 2005 to April 2015. Included were clinical studies using matrix-bound sealants after a pancreatic resection, reporting a post-operative pancreatic fistula (POPF) according to the International Study Group on Pancreatic Fistula classification, in which grade B and C fistulae were considered clinically relevant.

Results
Two were studies on patients undergoing pancreatoduodenectomy (sealants n = 67, controls n = 27) and four studies on a distal pancreatectomy (sealants n = 258, controls n = 178). After a pancreatoduodenectomy, 13% of patients treated with sealants versus 11% of patients without sealants developed a POPF (P = 0.76), of which 4% versus 4% were clinically relevant (P = 0.87). After a distal pancreatectomy, 42% of patients treated with sealants versus 52% of patients without sealants developed a POPF (P = 0.03). Of these, 9% versus 12% were clinically relevant (P = 0.19).

Conclusions
The present data do not support the routine use of matrix-bound sealants after a pancreatic resection, as there was no effect on clinically relevant POPF. Larger, well-designed studies are needed to determine the efficacy of sealants in preventing POPF after a pancreatoduodenectomy.

Introduction

A pancreatic fistula is a potentially life-threatening complication after pancreatic resection as it is associated with intra-abdominal abscesses, sepsis and major hemorrhage[1-5]. Even though over the past decades outcome has improved due to better surgical technique and centralization of pancreatic surgery[6], postoperative pancreatic fistula (POPF) still occurs in up to 28% of patients undergoing pancreatic resection[7].

In 2005, the International Study Group on Pancreatic Fistula (ISGPF) defined POPF as an amylase level in any amount of measurable drain fluid of at least three times the upper level of normal serum amylase on or after the third postoperative day. POPF is graded A, B or C, in which grade B and C are clinically relevant, as they require a change in treatment strategy[8]. This standardized definition has been widely used in the literature ever since.

Several strategies have been proposed to decrease the incidence of POPF but only a few are potentially successful. This includes pancreatogastric anastomosis[9-15], external drainage of the pancreatic anastomosis[16], preoperative administration of pasireotide (Novartis Oncology, Basel)®[17]. Nevertheless, even in the intervention arms of these successful studies the incidence of POPF was still as high as 10% and further improvements are therefore wanted.

Over the past years various types of fibrin sealants have found their way into surgical practice. Some studies suggest that fibrin glue is effective in preventing POPF, whereas others show no clinically relevant benefit[18]. Because fibrin glue is liquid and may therefore be easily washed away, fibrin sealants combined with a collagen patch could be useful in preventing POPF. Fibrin sealants have been proven to be effective in controlling bleeding in cardiovascular and liver surgery[19] and show favorable results in anastomotic sealing after pulmonary lobectomy[20]. The sealing capacity may also strengthen the anastomosis hereby improving anastomotic healing and, hence, may lead to a decrease in incidence and severity of POPF. This beneficial effect might lead to a reduction in major morbidity and even mortality after pancreatic resection, with subsequent improvement of patient's quality of life and reduction in health care costs[21].

The aim of this systematic review is to evaluate the role of matrix-bound sealants after pancreatic resection in terms of preventing or ameliorating the course of postoperative pancreatic fistula.

Methods

Study selection

A systematic search of the literature from May 2005 to April 2015 in PubMed, Embase and Cochrane Library was performed in adherence to the PRISMA (Preferred Reporting

Items for Systematic Reviews and Meta-Analyses) guidelines[22]. The search was limited to this interval because the first uniform ISGPF definitions for POPF were published in May 2005[8].

PubMed, Embase and Cochrane Library search terms were: '(sealant OR sealing OR TachoSil OR TachoComb OR patch) AND (pancreatoduodenectomy OR pancreaticoduodenectomy OR PPPD OR Whipple OR pancreatic)'. All titles and abstracts were screened. Full text papers were reviewed by two authors before inclusion. Reference lists were crosschecked for potentially relevant studies.

Eligibility criteria

Included were all clinical studies written in English reporting on the use of fibrin sealant patches after pancreatic resection. Excluded were studies using a sealants in liquid form (i.e. glue), studies not reporting fistula or mortality, studies not using the ISGPF definition on POPF and animal studies. When multiple papers were identified from one group it was checked whether study population overlapped. If so, the study with the largest number of patients was included.

Assessment of methodological quality

All studies were graded for methodological quality. Randomized controlled trials were graded according to the Cochrane Collaboration's tool[23], cohort studies in accordance to the Newcastle-Ottawa quality assessment scale (NOS)[24].

Data extraction

The following data were extracted from the individual studies: study design, patient characteristics, number of patients undergoing pancreatic resection, specifics on the used fibrin sealant patch, incidence and severity of POPF and 30-day mortality. When available, data on underlying disease, performed procedure, use of internal or external stent in pancreatic duct, postoperative abdominal drain, type of anastomosis, additional pharmacological therapy, incidence and severity of post pancreatectomy hemorrhage and delayed gastric emptying, time to abdominal drain removal, total morbidity and length of hospital stay and follow-up were also collected. Corresponding authors of studies were contacted if any of these data were not reported.

Statistical analysis

The primary outcomes were incidence and grade of POPF. Patients treated with fibrin sealants were compared to the control group, consisting of patients who were not treated with sealants. Separate analyses were performed for patients undergoing pancreatoduodenectomy versus distal pancreatectomy. Dichotomous data evaluated using the chi-square test. For all continuous data, mean (s.d.) and median (range) values were extracted or obtained from authors when not available in the manuscripts. Using the mean (s.d.) values, the weighted mean (s.d.) values were calculated, or calculated from median (range) values, using the method reported by Hozo et al[25]. A P-value

of <0.05 was considered statistically significant. Statistical analyses were performed in SPSS version 20.0 (SPSS, Chicago, III, USA).

Results

The literature search identified 1132 papers for additional screening. Most of these studies were excluded after title and abstract screening. A total of 19 studies were screened on full text, 13 studies were excluded based on the reasons listed in figure 1. Six studies were included in the present systematic review. Two of these regarded patients undergoing pancreatoduodenectomy[26,27] and 4 studies regarding distal pancreatectomy[28-31]. In three studies the use of fibrin sealant after pancreatic resection was compared to the same procedure without using fibrin patch[26,29,30]. The remaining three studies were non-comparative, using fibrin patch in all patients[27,28,31]. Characteristics of all studies are summarized in table 1.

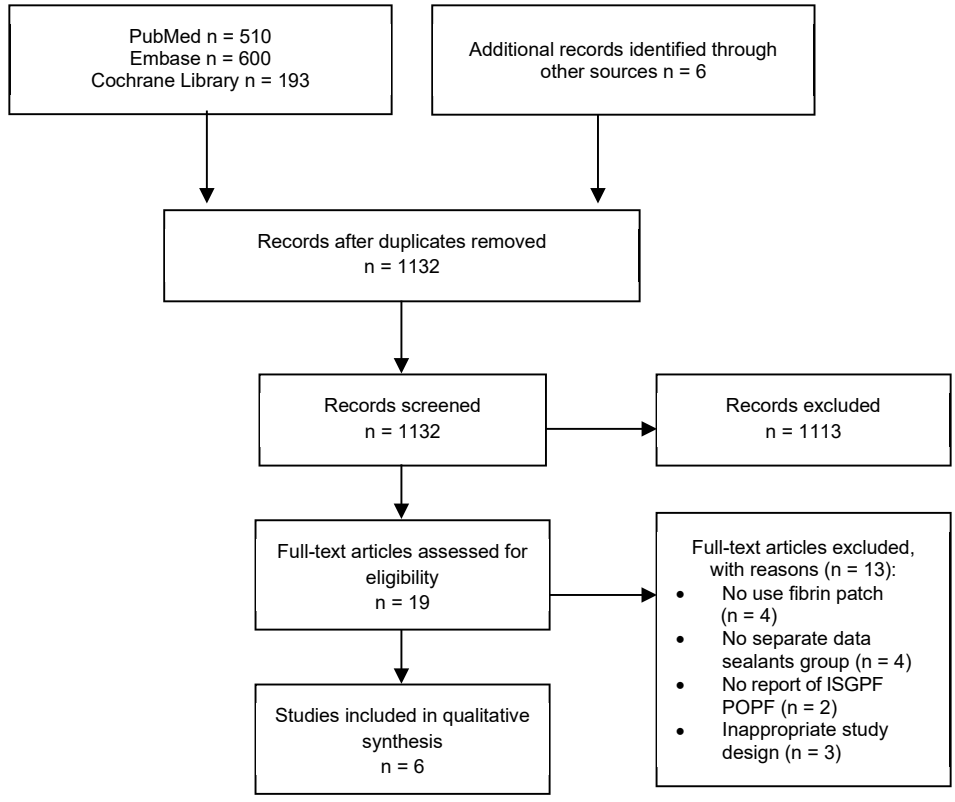

Figure 1. Flowchart of study selection in systematic review

Table 1: Characteristics of included studies*

Study	Year	Country	Study design	Study interval	Sample size (n)	Procedure	Study groups	Type of sealants and application	Follow-up
Chirletti	2009	Italy	Prospective cohort	January 1995 – December 2008	54	Whipple	Tachosil ® (n=27) vs. Control (n=27)	TachoSil ® placed around pancreatojejunostomy	60 days
Mita	2011	Japan	Retrospective cohort	January 2005 – November 2009	40	Whipple (n=21), PPPD (n=19)	Tachocomb ®	Tachocomb ® around pancreatojejunostomy, 1 minute compression	NR
Marangos	2011	Norway	Retrospective cohort	March 1997 – December 2010	121	Laparoscopic distal pancreatectomy	Tachosil ® (n=73) vs. Control (n=48)	Tachosil ® placed over staple line	NR
Mita	2011	Japan	Retrospective cohort	January 2005 – October 2009	25	Distal pancreatectomy	Tachocomb ®	Tachocomb ® application before transection with stapler	NR
Katagiri	2012	Japan	Retrospective cohort	March 2003 – January 2010	15	Laparoscopic distal pancreatectomy	Tachocomb ®	Tachocomb ® over staple line, 30 seconds compression	NR
Montorsi	2012	Italy	randomized controlled trial	January 2009 – May 2011	275	Distal pancreatectomy	Tachosil ® (n=145) vs. Control (n=130)	Tachosil ® over staple- or suture line, 3 minutes compression	2 months

*PPPD, pylorus preserving pancreatoduodenectomy; NR, not reported

Methodological quality

Details of the assessment of methodological quality are summarized in table 2. Only one randomized controlled trial was included (Oxford level of evidence 1b)[29]. In this study the participants or study personnel were not blinded for intervention or outcome. All other studies were cohort studies, one was prospective[26] and four studies were retrospective[27,28,30,31] (all Oxford level of evidence 2b). All patients were selected in a consecutive fashion from a fixed time frame. One study did not report any data on baseline characteristics[26]. All studies used the ISGPF definition for POPF. However, all studies but one[29] did not report measurement of amylase levels regularly or following a protocol, causing a high risk of measurement bias. Follow-up was poorly reported in included studies. In the randomized trial there was a statistically significant imbalance between study groups with regard to sex and procedure with or without splenectomy[29]. Most studies did not report on risk factors for POPF, such as texture of the pancreas, diameter of pancreatic duct or the use of somatostatin analogues. Over all, many data used to measure methodological quality are not reported in the included studies, causing an uncertain risk of bias.

Table 2: Assessment of methodological quality

		Newcastle – Ottawa quality assessment Scale for cohort studies							The Cochrane Collaboration's tool for randomized controlled trials					
		Selection bias				Measurement bias			Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
Reference	Oxford level of evidence	Representative recruitment	Selection of controls	Ascertainment of exposure	Comparable groups	Outcome assessment	Follow-up duration	Follow-up complete	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Chirletti 2009	2b	●	●	●	●	○	●	●	-	-	-	-	-	-
Mita 2011	2b	●	-	●	-	○	●	●	-	-	-	-	-	-
Marangos 2011	2b	●	●	●	○	○	●	●	-	-	-	-	-	-
Mita 2011	2b	●	-	●	-	○	●	●	-	-	-	-	-	-
Katagiri 2012	2b	●	-	●	-	○	●	●	-	-	-	-	-	-
Montorsi 2012	1b	-	-	-	-	-	-	-	●	○	●	●	●	●

●, Consistent with criteria, low risk of bias; ●, partly consistent with criteria, unknown risk of bias; ○, not consistent with criteria, high risk of bias; –, not applicable.

Patient characteristics

Out of the 6 studies included, 94 patients underwent pancreatoduodenectomy and 436 patients underwent distal pancreatectomy. The number of patients per study varied from 15 to 275. From the 94 pancreatoduodenectomies, 64 patients (68%) received a fibrin patch to cover the pancreatojejunostomy. After distal pancreatectomy, the staple- or suture line on the pancreatic stump was covered with a sealant patch in 243 patients (55%). Only one study on pancreatoduodenectomy reported the age (67.9 ± 8.4 years) of the included patients[27]. In the studies on distal pancreatectomy, the weighted mean age was 63 ± 10.4 years in the sealants group and 62 ± 13.8 years in the control group. One study reported the American Society of Anesthesiologist (ASA) class (median 2 (1-3) for both groups)[30]. The study performed by Montorsi et al.[29] reported a pancreatic duct diameter of ≥3 mm in 15 patients (12%) in the control group and 17 patients (12%) in the sealants group (P=0.69). In this study the pancreas was found to be firm in 16 patients (12%) in the control group and 23 patients (16%) in the sealants group (P=0.40). Due to the difference in definition on soft pancreas, these data were not pooled.

Pancreatoduodenectomy

Two studies on the use of fibrin patches in pancreatoduodenectomy were included. Both used external drainage of the pancreatic duct in their pancreaticojejunostomy. The products applied were TachoSil (Takeda Pharmaceutical Company, Japan)®[26] and TachoComb (Takeda Pharmaceutical Company, Japan)®[27], which were placed around the pancreatic anastomoses. In one study patients received additional Octreotide® for 6 days postoperative[26]. Details of the procedures are summarized in table 1.

Table 3 shows the outcomes reported in the included studies. After pancreatoduodenectomy 9 out of 67 patients (13%) treated with sealants and 3 of 27 patients (11%) who did not receive sealants developed POPF (P=0.76). These were grade A POPF in 6 (9%) and 2 patients (7%) respectively (P=0.81) and 3 (4%) versus 1 (4%) were clinically relevant POPF respectively (P=0.87). The incidence of post pancreatectomy hemorrhage after pancreatoduodenectomy was only reported in one study: there were 4 grade B post pancreatectomy hemorrhage (15%) and no separate data were reported for the sealants and the control groups[26]. Total morbidity (n=14 (35%)), time to drain removal (mean 9 ± 4 days) and hospital stay (mean 33 ± 9 days) after pancreatoduodenectomy were only reported in one study[27]. Mortality after pancreatoduodenectomy was 2 out of 94 patients (2%, both in one study), one from a myocardial infarction and one from sepsis due to pancreatitis[26].

Distal pancreatectomy

In four studies patients underwent distal pancreatectomy[28-31]. In two studies distal pancreatectomy was performed laparoscopically[30,31], in one study all distal pancreatectomies were open procedures[28] and in one study both open and laparoscopic distal pancreatectomies were included[29]. In most patients the pancreas was closed using a stapling device, only in one study in some patients the pancreatic stump was hand sewn[29]. TachoSil (Takeda

Pharmaceutical Company, Japan)® was used in two studies[29, 30], TachoComb (Takeda Pharmaceutical Company, Japan)® was the product of use to cover the pancreatic stump in the two remaining studies[28,31]. In one study the fibrin sealant was firmly adhered to the pancreas before dividing it using a stapler[28] (table 1).

Table 3 shows the outcomes. After distal pancreatectomy there was a statistically significant decrease in POPF: 108 out of 258 patients (42%) treated with sealants versus 93 out of 178 patients (52%) who did not receive fibrin sealants developed POPF (P=0.03). These fistulas were grade A in 86 patients in the sealants group (33%) versus 71 (40%) in the control group (p=0.16). There was no significant difference in clinically relevant fistula (grade B/C): 22 in the sealants group (9%) versus 22 in the control group (12%) (P=0.19). The incidence of post pancreatectomy hemorrhage after distal pancreatectomy was reported in two studies[29,30]: 4 patients (2%) in the sealants group and 7 patients (4%) in the control group (p=0.81). Data on delayed gastric emptying were only reported (0%) in one study[31]. The number of patients with one or more complications (total morbidity) after distal pancreatectomy was similar in both groups: 76 (35%) in the sealants group versus 64 (36%) in the control group (p=0.85). The mean duration of drainage (mean ± s.d.) was 7 ± 13 days in the sealants group and 7 ± 19 days in the control group (data extracted from two studies[28,29]). One study reported all drains were removed on postoperative day 1 to 4 31. The pooled mean duration of hospital stay (mean ± s.d.) was 10 ± 6 days in the sealants group and 9 ± 7 days in the control groups. There was no mortality reported in the studies on distal pancreatectomy.

Table 3: Outcomes*

Reference	n	POPF	PPH	DGE	Total morbidity	Duration fistula (days) †	Hospital stay (days) †
Chirletti	C: n=27 S: n=27	C: Grade A n=2; Grade B n=1 S: Grade A n=1	Grade B n=4	Grade A n=8; Grade C n=1	NR	NR	NR
Mita.	S: n=40	S: Grade A n=5; Grade B n=3;	NR	n=4	n=14	9 ± 4	33 ± 9
Marangos	C: n=48 S: n=73	C: Grade B n=4 S: Grade A n=1; Grade B n=6; Grade C n=3	C: Grade B/C n=3 S: Grade B/C n=2§	NR	C: n=15 S: n=21	NR	C: 5 (2-16) S: 5.5 (2-35)
Mita	S: n=25	S: Grade A n=4; Grade B n=1	NR	NR	n=7	8 ± 2	22 ± 10
Katagiri	S: n=15	S: Grade A n=3	n=0	n=0	NR	(1-4) ‡	S: 7 (4-15)
Montorsi	C: n=130 S: n=145	C: Grade A n=71; Grade B n=13; Grade C n=5 S: Grade A n=78; Grade B n=11; Grade C n=1	C: n=4 S: n=2	NR	C: 49 S: 55	C: 7 (3-119) S: 7 (2-88)	C: 10 (6-55) S: 10 (6-33)

* POPF, postoperative pancreatic fistula; PPH, post pancreatectomy hemorrhage; DGE, delayed gastric emptying; All grades not shown n=0; C, control group; S, sealants group; NR, not reported; †, median (range) or mean ± s.d; § No differentiation can be made between grade B and C PPH based on the presented data; ‡ median not reported;

Discussion

The pooled data in this systematic review do not show an advantage of the use of sealants after pancreatic resection, for there was no statistically significant decrease in the incidence of clinically relevant fistula (i.e. ISGPF POPF grade B/C). With regard to the other postoperative complications, time to drain removal, hospital stay and mortality, no major differences between the sealants and control group were found.

Another recent study[32](1996-2012) on the use of fibrin sealants in patients undergoing a pancreatic resection evaluated randomized controlled trials investigating the use of all types of fibrin sealants. The pooled data in this review showed also no significant decrease in POPF by using fibrin sealants. This review did not select the studies based on the use of the ISGPF definition. Before this definition was introduced in 2005, no uniform criteria for POPF were available. In contrast to the current study, this previous review also included studies on liquid sealants as well as sealants combined with matrix. In the current review, only studies reporting on the effect of matrix-bound sealants on POPF according to the ISGPF were included. Therefore there was only one study included in both the study by Orci et al. and the current systematic review[29].

Possibly, there is a different pathophysiology for the development of POPF after pancreatoduodenectomy versus distal pancreatectomy and therefor a different rationale for the use of sealants. The inadequate healing of the pancreatic anastomosis causes fistula after pancreatoduodenectomy, leading to leakage of activated pancreatic juices into the abdominal cavity. POPF after distal pancreatectomy is the result of failure of the staple or suture line over the distal pancreatic duct. The sphincter of Oddi is still functioning, preventing activation of pancreatic juice. Once the closure of the distal pancreatic duct fails, the fistula will be the way of lowest resistance when the sphincter closes. For this reason, data on pancreatoduodenectomy and distal pancreatectomy were presented separately. Matrix bound sealants might be used to seal the pancreatic anastomosis after pancreatoduodenectomy or to cover the closure line on the pancreatic stump after distal pancreatectomy. Liquid sealants are easily washed away and might not have this sealing capacity. For this reason only studies using fibrin sealant combined with collagen matrix, such as TachoSil (Takeda Pharmaceutical Company, Japan)® or TachoComb (Takeda Pharmaceutical Company, Japan)® were included in this review.

There were differences in application of fibrin sealants in studies included in this review. In one study, the fibrin patch was adhered around the pancreas before it was transected using a stapling device[28]. Using this method, the cut surface of the pancreas is not covered with the patch. This study included 25 patients undergoing distal pancreatectomy with addition of sealant patch. Of these 5 patients (20%) developed POPF, of which 1 was clinically relevant (grade B, 4%). The rate of clinically relevant POPF was low in this study. Total morbidity (28%) and time to drain removal (mean 8 ± 2 days) was similar to other studies and previously published data on POPF after distal pancreatectomy[28-31].

Hospital stay was somewhat long (mean 22 ± 10 days), for which no explanation could be extracted from the manuscript.

A limitation of this review is that most studies were small and retrospective. Only one randomized controlled trial could be included and all other included studies were observational cohort studies of which only one was prospectively performed. These cohort studies had relatively small sample sizes, especially the studies concerning pancreatoduodenectomy. Also, the included studies were heterogeneous. A pancreatojejunostomy was performed in all 94 patients undergoing pancreatoduodenectomy, while after distal pancreatectomy the pancreatic stump was either closed using staples or sutures. The effect of matrix-bound sealants in pancreatoduodenectomy presented in this systematic review is based on little evidence. Another important limitation of this study is the lack of information reported on risk factors for POPF. (e.g. texture of pancreas, diameter of pancreatic duct and the use of somatostatin analogues,). Therefore, there could be a significant difference in distribution of these known risk factors for POPF between study groups. The effectiveness of sealants in distal pancreatectomy to prevent POPF was unlikely, mostly due to the results from the randomized controlled trial performed by Montorsi et al.[29]

In conclusion, the current literature does not support the routine use of sealants after pancreatic resection, because there was no effect on clinically relevant fistula. Larger well-designed studies are needed to determine the efficacy of local matrix-bound sealants in preventing pancreatic fistula after pancreatoduodenectomy.

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Chapter 3

A web-based overview, systematic review and meta-analysis of pancreatic anastomosis techniques following pancreatoduodenectomy

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Abstract

Background
Many pancreatic anastomoses have been proposed to reduce the incidence of postoperative pancreatic fistula (POPF) after pancreatoduodenectomy, but a complete overview is lacking. This systematic review and meta-analysis aims to provide an online overview of all pancreatic anastomosis techniques and to evaluate the incidence of clinically relevant POPF in randomized controlled trials (RCTs).

Methods
A literature search was performed to December 2017. Included were studies giving a detailed description of the pancreatic anastomosis after open pancreatoduodenectomy and RCTs comparing techniques for the incidence of POPF (International Study Group of Pancreatic Surgery [ISGPS] Grade B/C). Meta-analyses were performed using a random-effects model.

Results
A total of 61 different anastomoses were found and summarized in 19 subgroups (www.pancreatic-anastomosis.com). In 6 RCTs, the POPF rate was 12% after pancreaticogastrostomy (n = 69/555) versus 20% after pancreaticojejunostomy (n = 106/531) (RR0.59; 95%CI 0.35–1.01, P = 0.05). Six RCTs comparing subtypes of pancreaticojejunostomy showed a pooled POPF rate of 10% (n = 109/1057). Duct-to-mucosa and invagination pancreaticojejunostomy showed similar results, respectively 14% (n = 39/278) versus 10% (n = 27/278) (RR1.40, 95%CI 0.47–4.15, P = 0.54).

Conclusion
The proposed online overview can be used as an interactive platform, for uniformity in reporting anastomotic techniques and for educational purposes. The meta-analysis showed no significant difference in POPF rate between pancreatic anastomosis techniques.

Introduction

Pancreatoduodenectomy offers the best chances for long-term survival to patients with pancreatic and periampullary malignancy.[1] Due to an increased incidence of (pre-)malignant lesions, improved neoadjuvant therapies and extended criteria for resectability, the number of patients undergoing pancreatic resection is increasing.[2-4] However, pancreatoduodenectomy is a technically challenging procedure, especially regarding the pancreatic anastomosis. Through centralization, refinements in techniques and advances in (peri)operative management, mortality has dropped below 5%. Nevertheless, morbidity remains 30–50%, with failure of the pancreatic anastomosis as the most feared complication.[5-8]

Anastomotic failure results in postoperative pancreatic fistula (POPF), which is associated with formation of intra-abdominal abscesses, hemorrhage, sepsis and even death, and consequently an increased length of hospital stay and costs.[9-15] The pancreatic anastomosis is therefore considered to be the 'Achilles heel' of pancreatoduodenectomy.[13,16] Using the International Study Group of Pancreatic Surgery (ISGPS) definition, the incidence of POPF is found to be 12% in patients undergoing pancreatoduodenectomy, with a failure to rescue rate of 18%.[17-19]

For a technically successful anastomosis, a tension-free approximation, optimal blood supply and unobstructed flow of pancreatic secretion are essential.[13] Many types of pancreatic anastomoses have been reported, and subtle technical details play an important role in their success. For a more objective comparison of outcomes after pancreatic resection, the ISGPS proposed a classification for recording and reporting of the intraoperative situation and the pancreatic anastomosis.[20] However, a complete, easily accessible overview of all different techniques, supported by photos and short video clips, is missing.

The aim of this systematic review and meta-analysis is to provide an online overview of all pancreatic anastomosis techniques published in peer-reviewed articles and to evaluate the incidence of clinically relevant POPF in randomized controlled trials (RCTs) comparing different pancreatic anastomoses following pancreatoduodenectomy.

Methods

A systematic search of the literature was performed in PubMed, EMBASE and Cochrane Library, identifying relevant articles up to December 1st, 2017. The following search was carried out: ((pancreatojejunostomy OR pancreaticojejunostomy OR pancreatogastrostomy OR pancreaticogastrostomy OR ((pancreas OR pancreatic) AND (anastomosis OR anastomoses OR anastomose))) AND (surgery OR resection

OR pancreatoduodenectomy OR pancreaticoduodenectomy OR Whipple OR PPPD OR technique OR reconstruction)).

Included were all clinical studies in English, describing the technical aspects of the pancreatic anastomosis in open pancreatoduodenectomy for presumed (pre-)malignancy in detail. For formal meta-analysis, randomized controlled trials (RCTs) reporting incidences of clinically relevant POPF, i.e. ISGPS grade B/C, after different pancreatic anastomotic techniques were collected (figure 1). When studies reported on overlapping study populations, the study with the largest number of patients was included. All titles and abstracts were screened, after which full-text articles were read independently by two authors (LAD, FJS) before inclusion. Disagreement on eligibility was addressed by discussion and consensus. References were crosschecked for relevant studies.

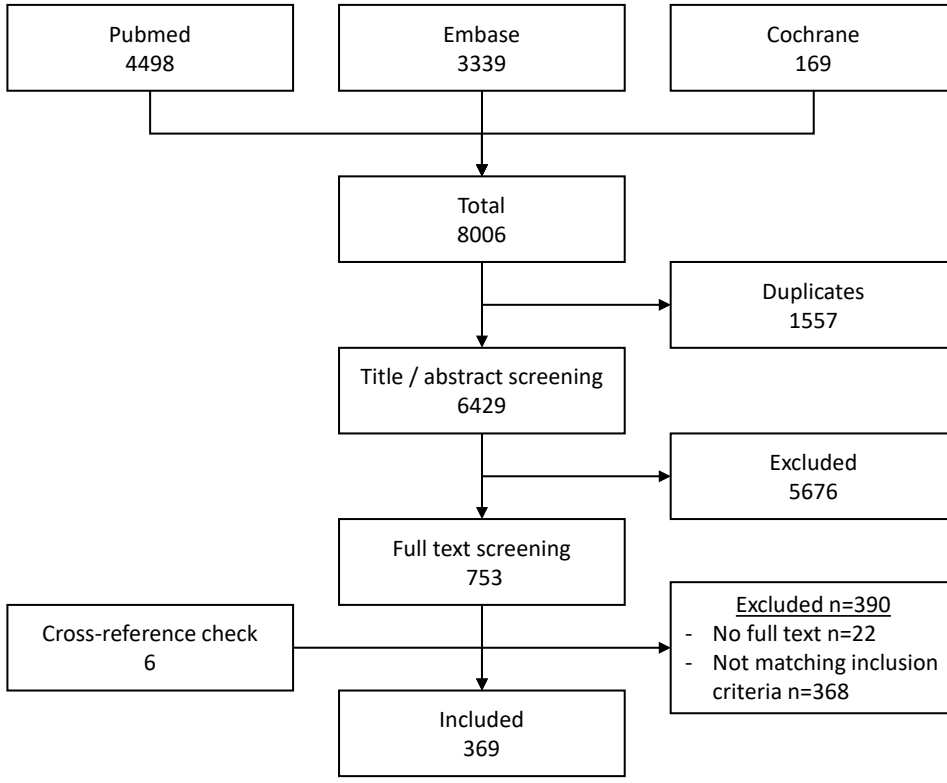

Figure 1. Flow chart of study selection in systematic review

Data extraction and synthesis

The Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines were followed.[21] Methodological quality of RCTs was independently graded by two reviewers, according to the Cochrane Collaboration's tool for assessing risk of bias.[22] The following data were extracted from the included studies: study characteristics (i.e. single- or multicenter design, number of surgeons performing pancreatoduodenectomies in trial, trial arms, number of patients), patient characteristics (i.e. age, gender), technical details of pancreatic anastomosis, pancreatic texture, diameter of the main pancreatic duct, intraoperative blood loss, disease pathology, incidence of POPF and postoperative pancreatic exocrine and endocrine functions.

Main outcomes and measures

Technical details of pancreatic anastomoses were summarized, and different anastomosis techniques were divided into subgroups. Separate statistical analyses were performed for RCTs comparing pancreaticogastrostomy with pancreaticojejunostomy and RCTs comparing different techniques for pancreaticojejunostomy. The primary endpoint was incidence of POPF (i.e. grade B/C). Pooled POPF rates were calculated for pancreatic texture (i.e. firm vs. soft) and trial design (i.e. single-center, two-center and multicenter trials). Results were presented as risk ratios (RR) with 95% confidence intervals (95% CI). Analyses were performed using Review Manager (RevMan) version 5.3, using a random-effects model, and IBM SPSS Statistics, version 23. A two-sided P-value <0.05 was considered statistically significant. Statistical heterogeneity was assessed using the I^2 test, with a value of $I^2 > 50\%$ representing substantial heterogeneity. Secondary endpoints were postoperative pancreatic exocrine and endocrine functions.

Results

Search results

A total of 367 manuscripts were ultimately included: 355 studies reporting the details of pancreatic anastomotic techniques; 6 RCTs comparing pancreaticogastrostomy with pancreaticojejunostomy and 6 RCTs comparing different pancreaticojejunal anastomoses.

Anastomotic techniques

The pancreatic anastomoses were divided into 3 groups: end-to-end pancreaticojejunostomy, end-to-side pancreaticojejunostomy and end-to-side pancreaticogastrostomy. Overall, 61 different types of pancreatic anastomoses were identified in the literature; these techniques were summarized and visualized in 19 subgroups. An overview of all pancreatic anastomotic techniques with illustrations can be found on the website www.pancreatic-anastomosis.com, which was constructed with the results of this study.

Methodological quality

Overall, the methodological quality of the included RCTs was moderate. All studies described a random component in the sequence generation process, and reported data on baseline characteristics. In two studies, allocation was based on the closed envelope method, however, it was not clear whether appropriate safeguards were used.[22,23] Blinding was properly carried out in only one study.[25] Four studies discussed that there was no or partial blinding.[26-29] The remaining seven studies did not mention blinding. In most studies, selective reporting was not an issue. In one study, however, postoperative pathology was included as postoperative variable in the methods section, but not mentioned in the results section. One study did not report regular measurement of amylase levels.[30] The moderate methodological quality of included trials caused a considerable risk of bias.

Pancreatic texture and trial design

Incidence of either firm or soft pancreatic texture was comparable between the randomized studies comparing pancreaticogastrostomy to pancreaticogastrostomy and the RCTs analyzing different types of pancreaticojejunostomy: the pooled incidence for soft pancreatic texture was 55% (n = 594/1072) and 55% (n = 583/1057), respectively. Overall, the pooled incidence of POPF was 17% (n = 113/649), 16% (n = 50/320) and 10% (n = 121/1174) in multicenter-, two-center- and single-center trials, respectively.

Pancreaticojejunostomy versus pancreaticogastrostomy

Six RCTs comparing the incidence of POPF between 555 patients with pancreaticogastrostomy and 531 patients with pancreaticojejunostomy were included. Study characteristics and patient characteristics of each study are shown in Table 1. Formal meta-analysis showed a POPF rate of 12% (n = 69/555) after pancreaticogastrostomy versus 20% (n = 106/531) after pancreaticojejunostomy (RR 0.59, 95% CI 0.35–1.01, P = 0.05). Calculated heterogeneity between studies was 61% (figure 2).

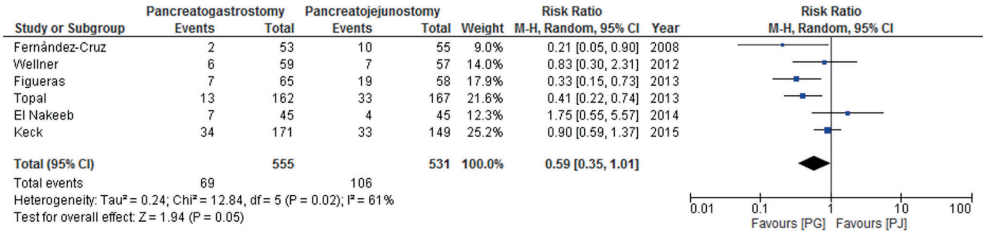

Figure 2. Meta-analysis and forest plot of RCTs comparing POPF rates between PG and PJ

Table 1: Study and patient characteristics of 6 RCTs comparing PG and PJ and 6 RCTs comparing different PJ's

Reference	Trial design	Age (years)	Male gender	Soft pancreatic texture	Diameter of MPD (mm)		Intra-operative blood loss (ml)	Pathology		Trial arms	n	POPF
								PDAC or pancrea-titis	Ampullary, duodenal, cystic, islet cell			
		Median (IQR)	n (%)	n (%)	≤ 3 mm (%)	Median (IQR)	Median (IQR)	n (%)	n (%)			n (%)
Fernàndez-Cruz	Single-center	63 ± 2*	67 (62)	49 (45)		3 ± 1.7*	965 ± 786*	58 (54)	50 (46)	DTM PG after GP	53	2 (4)
							972 ± 725*			DTM PJ	55	10 (18)
Wellner	Single-center (3 surgeons)	66 (23-84)	56 (48)	64 (55)	38		NR	74 (64)	42 (36)	Invagination PG	59	6 (10)
										DTM PJ	57	7 (12)
Figueras	Two-center	66 (35-80)	81 (66)	67 (54)		4 (1-15)	638 (100-4.000)	62 (50)	61 (50)	Invagination PG	65	7 (11)
										DTM PJ	58	19 (33)
Topal	Multicenter (4 center)	67 (59-75)	191 (58)	188 (57)	61		450 (300-700)	205 (62)	124 (38)	Invagination PG	162	13 (8)
							400 (300-600)			E-S invagination PJ	167	33 (20)
El Nakeeb	Single-center (8 surgeons)	56 (12-73)	50 (56)	48 (53)	48		500 (50-3.000)	46 (51)	44 (49)	DTM PG	45	7 (16)
										DTM PJ	45	4 (9)
Keck	Multicenter (14 center)	68 (29-87)	188 (59)	178 (58)	56		500 (0-4.800)	112 (75)	37 (25)	PG	171	34 (20)
										PJ	149	33 (22)
Berger	Two-center (8 surgeons)	68 (32-90)	99 (50)	101 (51)		4 (1-12)	500 (100-2.000)	NR	NR	DTM PJ	100	17 (17)
							450 (100-10.000)			E-S invagination PJ	97	7 (7)
										E-S invagination PJ	54	2 (4)
El Nakeeb	Single-center	54 (12-75)	67 (63)	52 (49)	50		500 (50-3.000)	NR	NR	DTM PJ	53	6 (11)
Xu	Single-center (1 surgeon)	58 ± 11*	166 (54)	**	**	**	601 ± 348*	NR	NR	DTM PJ	153	13 (8)
							560 ± 323*			Papillary-like PJ	155	1 (1)

Reference	Trial design	Age (years)	Male gender	Soft pancreatic texture	Diameter of MPD (mm)		Intra-operative blood loss (ml)	Pathology		Trial arms	n	POPF
								PDAC or pancrea-titis	Ampullary, duodenal, cystic, islet cell			
		Median (IQR)	n (%)	n (%)	≤ 3 mm (%)	Median (IQR)	Median (IQR)	n (%)	n (%)			n (%)
Bai	Single-center (1 surgeon)	63 (21-79)	77 (58)	80 (61)		3 (2-22)	300 (100-2.000)	77 (58)	55 (42)	DTM PJ	64	2 (3)
							300 (100-1.500)			E-S invagination PJ	68	12 (18)
Singh	Single-center (4 surgeons)	53 ± 12*	63 (65)	42 (43)		4 ± 2.1*	NR	18 (9)	175 (91)	DTM PJ	97	16 (16)
		52 ± 14	63 (66)	48 (50)		4 ± 1.5*				E-E invagination PJ	96	13 (14)
Senda	Single-center (4 surgeons)	67 (22-84)	72 (60)	61 (51)	40		530 (60-8040)	68 (57)	52 (43)	DTM PJ	61	14 (23)
										E-S invagination PJ	59	6 (10)

PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; BMI, body mass index; IQR, interquartile range; SD, standard deviation; MPD, main pancreatic duct; NR, not reported; PDAC, pancreatic ductal adenocarcinoma DTM, duct-to-mucosa; GP, gastric partition; E-S, end-to-side; E-E, end-to-end; POPF, postoperative pancreatic fistula; * Mean ± SD; ** Nature of pancreatic remnant: soft texture and nondilated MPD n=199 (65%)

Three trials reported on postoperative pancreatic exocrine and endocrine function.[23,28,31] The RCT of El Nakeeb et al. showed that 21% of patients suffered from severe steatorrhea for which they needed pancreatic enzyme supplements in the pancreaticojejunostomy-group, compared to 44% in the pancreaticogastrostomy-group (P = 0.03). Median albumin one year postoperatively was 3.6 g/dl after pancreaticojejunostomy versus 3.3 g/dl in patients with pancreaticogastrostomy (P ≤ 0.001).[23] Figueras et al. found significant differences in weight loss and stool elastase between pancreaticojejunostomy and pancreaticogastrostomy three months after resection. Weight loss in patients with pancreaticojejunostomy was 7% versus 4.5% with pancreaticogastrostomy (P = 0.03), and stool elastase was 14 ug/g versus 44 ug/g (P = 0.02) in both groups respectively.[31] In the study of Keck et al., 89% versus 72% of patients with pancreaticojejunostomy versus pancreaticogastrostomy used oral enzyme supplements at six months postoperatively (P ≤ 0.001), although this difference no longer existed at 12 months of follow-up.[28] None of the studies found significant differences in endocrine function.

Different techniques for pancreaticojejunostomy

In 6 RCTs, the incidence of POPF was compared in 1057 patients with different subtypes of pancreaticojejunostomy. Study characteristics and patient characteristics of each study are shown in Table 1. The pooled incidence of POPF was 10% (n = 109/1057). Similar results were found for duct-to-mucosa versus invagination pancreaticojejunostomy (respectively 14% (n = 39/278) vs. 10% (n = 27/278), RR 1.40, 95% CI 0.47–4.15, P = 0.54). Statistical heterogeneity between studies was found to be 73% (Figure 3).

Figure 3. Meta-analysis and forest plot of RCTs comparing POPF rates between DTM and end-to-side invagination PJ

Only one study reported on postoperative pancreatic exocrine and endocrine functions. In this study, it was shown that postoperative steatorrhea after one year occurred in 42% (n = 21/50) of patients after duct-to-mucosa pancreaticojejunostomy compared to 22% (n = 11/50) of patients with invagination pancreaticojejunostomy (P = 0.04).[24] Moreover, median albumin concentrations were 3.4 gm% and 3.6 gm% in both groups, respectively (P = 0.03). No differences were found in postoperative pancreatic endocrine function.

Discussion

This systematic review provides a complete overview of 61 major pancreatic anastomotic techniques reported in peer-reviewed publications, summarized on www.pancreatic-anastomosis.com. The meta-analysis of six randomized trials comparing pancreaticogastrostomy with pancreaticojejunostomy demonstrated a clinically relevant POPF rate of 12% versus 20%, respectively. This difference was favorable for pancreaticogastrostomy, although not significant (P = 0.05). Interestingly, the pooled incidence of POPF in six randomized trials comparing different subtypes of pancreaticojejunostomy was only 10%.

To reach a more objective comparison of outcomes after pancreatic surgery, the ISGPS proposed a standardized classification for recording and reporting of the pancreatic anastomosis.[20] This classification effectuates an overall division of the anastomotic technique into pancreaticojejunostomy or pancreaticogastrostomy and duct-to-mucosa or invagination anastomosis. The current overview adheres to the ISGPS classification and provides further details on the different pancreatic anastomotic techniques. Given the large amount of techniques and studies, it is impossible to summarize and compare the outcomes from both large RCTs and smaller observational studies in one clear and compact review. In the modern digital era, the most appropriate way to do so is via a web-based platform.

An international survey of Kennedy et al. showed that pancreaticojejunostomy was the preferred anastomotic method in nearly 90% of 899 respondents from six continents.[32] Most of the formerly published meta-analyses on pancreaticogastrostomy versus pancreaticojejunostomy conclude, however, that pancreaticogastrostomy is associated with a lower rate of POPF.[33-46] The rich blood supply, anatomical apposition, wider lumen and thicker wall of the stomach compared to the jejunum are arguments mentioned in favor of pancreaticogastrostomy.[47-49] This is partially in line with the results, although the current meta-analysis is updated with the latest RCT on this subject, which proves otherwise. This study, carried out by Keck et al., showed that reconstruction by pancreaticogastrostomy, when not restricted to a specific subtype and evaluated in a multicenter setting, does not reduce the incidence of POPF compared to pancreaticojejunostomy.[28] Moreover, the formerly performed meta-analyses are exposed to significant methodological limitations regarding the definition of POPF, since the inclusion of RCTs was not restricted to the most used ISGPS definition. The current results correspond to a Cochrane review on POPF after pancreaticojejunostomy versus pancreaticogastrostomy, in which the same studies were included for a separate analysis on ISGPS clinically relevant pancreatic fistulas was performed. Nevertheless, the authors downgraded the overall quality of evidence to very low due to a high risk of bias.[50] Lastly, in the current meta-analysis, RCTs were included that compared the incidence of POPF between different subtypes of pancreaticojejunostomy. The overall results of the current meta-analysis are in line with the recently published

position statement of the ISGPS, not finding a substantial difference in the incidence of POPF when comparing different anastomosis techniques.[51]

Moreover, some studies suggest that pancreaticogastrostomy is associated with less exocrine insufficiency in the long-term, although impairment of exocrine function following pancreaticogastrostomy is reported by others.[52-57] Accordingly, conflicting results concerning exocrine insufficiency were shown in the current study, and no clear benefit of a certain type of reconstruction with regard to postoperative pancreatic exocrine and endocrine function were found.

As shown in this overview, a large number of different pancreatic anastomosis techniques are being applied by pancreatic surgeons globally. The considerable variety and heterogeneity of anastomotic methods challenges the performance of high quality RCTs in order to properly compare these different reconstruction methods after pancreatoduodenectomy.[12, 58-60] Extensive experience or unfamiliarity with one of the selected anastomotic techniques as well as a learning curve phenomenon may bias the results. Moreover, pancreatic anastomosis techniques are generally described in single-surgeon or single-institution studies often reporting low POPF rates of their preferred pancreatic anastomosis.[11,61,62] This is supported by the current data, showing a higher pooled incidence of POPF in multicenter and two-center trials compared to single-center trials. In the ISGPS position statement, it is stated that experienced surgeons at high-volume centers can decrease the incidence of POPF by performing a variety of techniques in diverse intraoperative situations.[51] For instance a soft texture of the pancreatic parenchyma is known to increase the risk of anastomotic failure.[51, 63-65] In the current review, incidence of pancreatic texture, categorized as firm or soft, was comparable between the randomized studies comparing pancreaticogastrostomy with pancreaticogastrostomy and different types of pancreaticojejunostomy. Therefore, this is not considered to be responsible for the found inconsistency between RCTs. Insight in all different reconstruction methods developed worldwide, however, gives an important contribution to clarify these issues further. Nevertheless, a quantitative comparison of different reconstruction techniques will remain challenging. Besides, non-technical risk factors, such as pancreatic inflammation, seem to play an important role in the incidence of POPF as well. To prevent POPF and improve outcomes after pancreatoduodenectomy, it is therefore important that future research is not narrowly focused on the surgical technique, but also on methods to optimize non-surgical factors.

This review has several limitations. First, comparability of the results for formal meta-analysis should be questioned, since a substantial heterogeneity in methodological design (i.e. single-surgeon, single-center and multicenter trials) and surgical techniques was found between the selected studies. Although this emphasizes the need for more uniformity, a proper comparison of the randomized trials is herewith impeded, and results therefore should be interpreted with caution. Second, the focus was on the anastomotic technique itself and it was not possible to stratify for other factors possibly influencing the rate of POPF, such as use of somatostatin analogues, internal or external stents, fibrin

glue or other sealants, a surgical microscope, omental wrapping or mesh-reinforcement, as these data varied considerably between studies.[66-70] Although it was demonstrated that externalized stents are beneficial in high-risk scenarios, further associations between these factors and the formation of POPF remain controversial.[51,71] In most of the included RCTs, no stents were used to support the anastomoses. Nevertheless, Wellner et al. discussed the use of an external main pancreatic duct stent in pancreaticojejunostomy but not in pancreaticogastrostomy as potential confounder for reducing the incidence of POPF in their control group.[27] Third, current literature unfortunately does not supply sufficient data on risk factors for POPF, in particular non-technical risk factors, to perform risk-stratified analyses. At last, the overall moderate methodological quality of the included trials caused a considerable risk of bias.

As demonstrated by this study, discussing over 350 heterogenetic studies including more than 60 pancreatic anastomosis techniques, even after disregard of other reconstruction methods and technical modifications, the debate on the optimal pancreatic anastomosis technique is not closed. For future research, it is necessary to be aware of the many different techniques for pancreatic anastomoses. This is of great importance, given the fact that much more studies on the ongoing quest for the optimal pancreatic anastomosis will follow. A search on the WHO clinical trial registry, combining 20 worldwide registries, showed 7 ongoing randomized trials evaluating the incidence of POPF after different pancreatic anastomotic techniques. Therefore, an overview of all major pancreatic anastomosis techniques described in the literature is presented on the website www.pancreatic-anastomosis.com, with clarifying illustrations. This website will be used as a platform for pancreatic surgeons to share their personal anastomotic technique with surgeons all over the world and will be continuously updated with new techniques that are published in peer-reviewed articles. It could also be used as a learning tool to give insight into the various possibilities of pancreatic anastomoses after pancreatoduodenectomy, for residents, fellows and surgeons.

In short, a complete, online overview of all pancreatic anastomoses published in peer-reviewed articles is presented on www.pancreatic-anastomosis.com. This unique platform for residents, HPB fellows, young and experienced surgeons will have extensive opportunities for uniformity in reporting anastomosis techniques in future research and for educational purposes.

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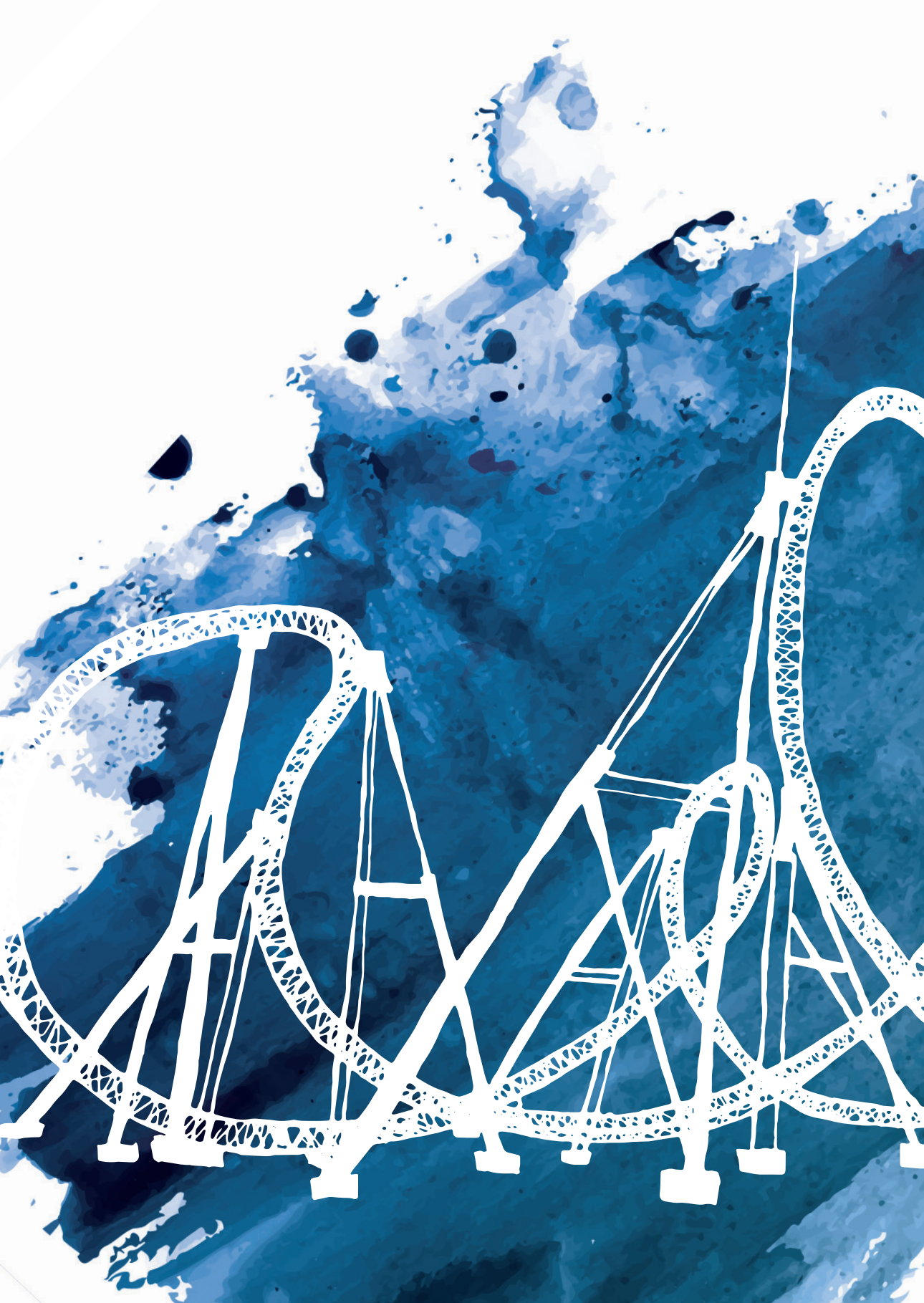
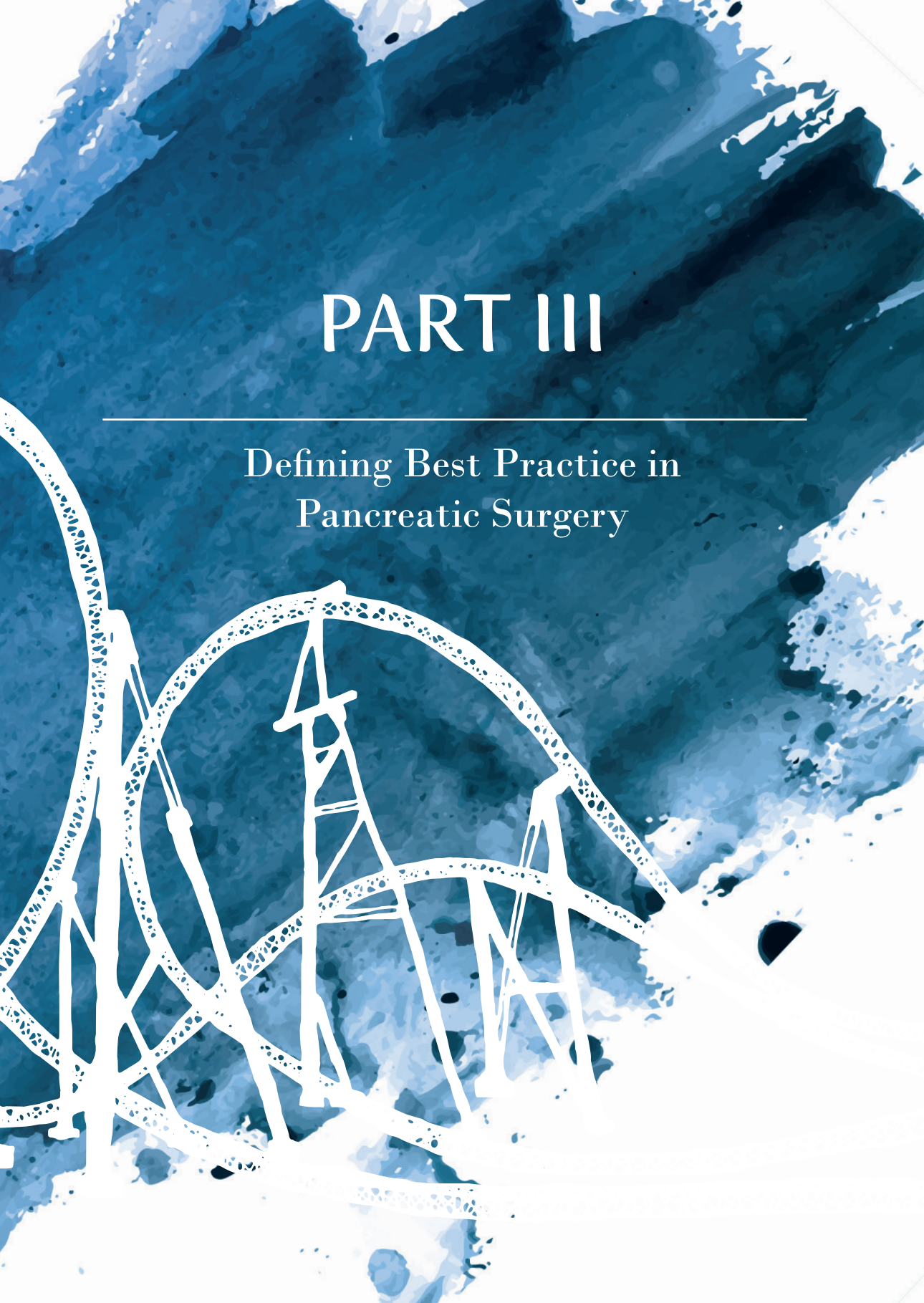


PART III

Defining Best Practice in Pancreatic Surgery



Chapter 4

Early recognition of clinically relevant postoperative pancreatic fistula: a systematic review

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Abstract

Background
Early recognition of postoperative pancreatic fistula might decrease the risk of subsequent life-threatening complications. The aim of this review was to systematically evaluate the accuracy of postoperative clinical, biochemical and radiologic variables for early recognition of clinically relevant postoperative pancreatic fistula.

Methods
A systematic literature search was performed up to August 2018. Clinical studies were included if they report the association between postoperative variables and clinically relevant postoperative pancreatic fistula. Variables were stratified for postoperative day 1-2 (early prediction) versus ≥day 3 (early diagnosis) and had to be reported in at least 2 cohorts.

Results
Overall, 37 included studies reported on diagnostic accuracy of 17 different variables after 8701 pancreatic resections. Clinically relevant postoperative pancreatic fistula occurred in 1532/8701 patients (18%). Early prediction variables included elevated serum and drain amylase (day 1). Identified variables for early diagnosis (≥day 3) were: non-serous drain efflux (day 3); positive drain culture (day 3); elevated temperature (any day); elevated C-Reactive Protein (CRP; day 4); elevated white blood cell count (WBC; day 4) and peripancreatic collections on computed tomography (CT; day 5-10).

Conclusion
This review provides a comprehensive overview of postoperative variables associated with clinically relevant pancreatic fistula. Incorporation of variables in future algorithms could potentially mitigate the clinical impact of postoperative pancreatic fistula.

Introduction

Pancreatic surgery is complex and about 50% of patients will develop postoperative complications[1–3]. One of the most feared complications is postoperative pancreatic fistula, in which there is leakage of pancreatic juice into the abdomen[4,5]. A large meta-analyses showed that clinically relevant postoperative pancreatic fistula occur in 12% of patients after pancreatoduodenectomy[3,6].

As with all patients with sepsis, early identification and adequate management increases the chances of a good outcome[4,5,8,9]. Early signs of postoperative pancreatic fistula, however, are often subtle, making it difficult to distinguish a biochemical leak from the potentially life threatening subtype of pancreatic fistula[10,11]. Especially in centers where only a few patients with clinically relevant pancreatic fistula are encountered each year, early signs of pancreatic fistula might remain unrecognized[12].

Intensified monitoring in the early postoperative phase according to an algorithm might aid early recognition and early management of pancreatic fistula and thereby improve clinical outcome of patients undergoing pancreatic resection. What diagnostic tests are included in such an algorithm should be based on best available evidence on diagnostic accuracy of these tests. This systematic review forms the base of a best practice algorithm incorporating both early diagnosis and minimally invasive management of clinically relevant postoperative pancreatic fistula. Currently, it is evaluated if the implementation of this best practice algorithm in all Dutch centers performing pancreatic surgery will improve clinical outcomes on a nationwide level (PORSCH trial, NTR6905).

The aim of this review was to systematically evaluate the literature on the accuracy of postoperative clinical, biochemical and radiologic variables for early recognition of clinically relevant pancreatic fistula after pancreatic resection.

Methods

Study selection

This study was designed and conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines[13]. A systematic search in PubMed, Embase and Cochrane Library was performed in all literature published to August 2018. Search terms were synonyms for pancreatic resection, pancreatic fistula and diagnostic accuracy (see the supplementary appendix for the complete search string). All titles and abstracts were screened in duple; full-text papers were reviewed by two authors before inclusion. Reference lists of included studies were crosschecked for potentially relevant studies.

Eligibility criteria

Included were clinical studies reporting on postoperative clinical, biochemical and imaging variables in relation to clinically relevant pancreatic fistula (i.e. grade B/C or postoperative pancreatic fistula requiring invasive intervention) after pancreatoduodenectomy or distal pancreatectomy. Studies including a small proportion of other pancreatic resections (i.e. <5% of the study cohort) were also included. Excluded were studies reporting on 5 patients or less with clinically relevant pancreatic fistula, as these studies may be subjective to spectrum bias resulting in overestimation of the accuracy of the test14. Studies not reporting sensitivity and specificity (or sufficient data to calculate these), studies comparing different grades of pancreatic fistula (because they excluded patients without pancreatic fistula), studies reporting exclusively on pancreatic resections for pancreatic trauma and studies in non-English language were also excluded. Although the majority of studies on pancreatic resection use the International Study Group on Pancreatic Surgery (ISGPS, either 2005 or 2016 version) definitions on pancreatic fistula, this was not used as a selection criterion for eligibility.

Quality assessment

The methodological quality of each eligible study was assessed using the quality assessment of diagnostic accuracy studies instrument (QUADAS-2)[15]. Risk of bias and applicability were evaluated across four key domains: patient selection (preferably consecutive cohort), index test (preferably test variable with predefined cut-off value), reference standard (preferably according to ISGPS definition with predefined indications for invasive interventions) and timing of tests (preferably on or after postoperative day 3). The rationale of this cut-off value in postoperative timing was twofold. First, inflammatory parameters rise and remain elevated up to 72 hours after major abdominal surgery[10,11,16–18], resulting in a lower diagnostic accuracy of these tested variables when evaluated before postoperative day 3. Second, this cut-off value in timing is also included in the ISGPS definition. Variables tested before day 3 might therefore have more prognostic than diagnostic value. In the current analysis, diagnostic variables tested on or after postoperative day 3 and that were associated with pancreatic fistula in more than one cohort were considered to be the most reliable. Variables tested before postoperative day 3 in more than one cohort were considered to be the most reliable predictive variables.

Data collection

The following data were extracted from each study using a predefined record form: name of first author, year of publication, study design, total number of included patients, type of index pancreatic resection (i.e. pancreatoduodenectomy or distal pancreatectomy), mean or median age with standard deviation (SD) or inter quartile range (IQR), proportion of male patients, underlying disease, number of patients with clinically relevant pancreatic fistula, reference standard for clinically relevant pancreatic fistula and tested variable(s). On the tested variable, the following data were collected or calculated: chosen or proposed cut-off value(s), timing (i.e. postoperative day), true positives,

true negatives, false positives, false negatives, sensitivity and specificity. Corresponding authors were contacted if any of these items were missing.

Data analysis

For continuous data, the weighted mean (SD) values were calculated using reported mean (SD) values, or calculated from median values with range, using the method reported by Hozo et al.[19]. For each tested diagnostic variable and each cut-off value, sensitivity and specificity were extracted from manuscripts or calculated from 2x2 contingency table. The variety both timing and proposed cut-off values in tested variables caused high heterogeneity, therefore diagnostic indices were not pooled. An overview of the diagnostic indices reported in included studies with 95% confidence intervals was visualized in forest plots[20].

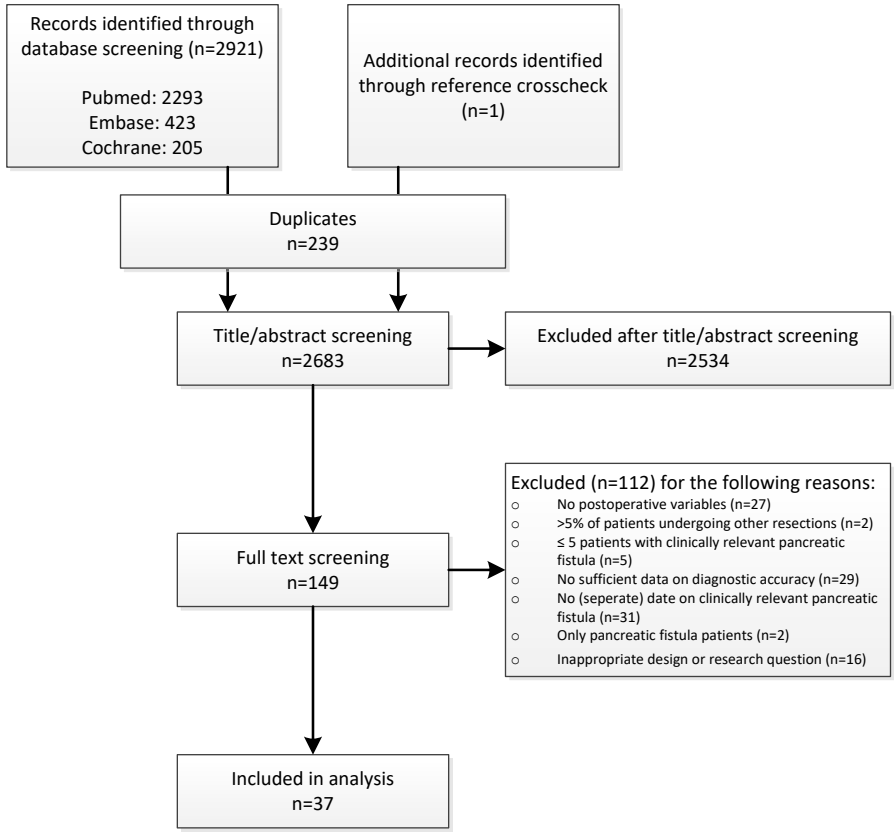

Figure 1. Flow chart of study inclusion

Results

The search identified 2683 unique studies for initial screening. Of these, 149 full text articles were screened after which 112 were excluded for the reasons shown in Figure 1. A total of 37 studies were included in this systematic review[21–57].

Study and patient characteristics

A total of 8701 patients who underwent pancreatic resection were evaluated (median 121 patients per study (range 45-1239)). Included were 8063 pancreatoduodenectomies, 612 distal pancreatectomies and 26 other pancreatic resections. The overall weighted mean age was 65±11 years and 56% of patients (4856/8701) were male. The majority of studies defined clinically relevant pancreatic fistula according to the International Study Group on Pancreatic Surgery definition (ISGPS grade B/C; 2005 definition in 33 studies, 2016 definition in two studies); the two remaining studies used their own definition which was rather similar to the ISGPS definition (Table 1). The incidence of clinically relevant pancreatic fistula ranged from 6% to 56% per study; the overall incidence was 18% (1532/8701 patients), in which pancreatic fistula rate appeared to be slightly lower in high volume studies.

Quality assessment

Methodological quality of included studies according to QUADAS-2 is visualized in Figure 2. In 14 studies, a selection of patients was included in the study or selected from another cohort, causing a high[21–23,28,30,32,33,41,42] or uncertain[37,38,44,48,49] risk of bias. In 14 studies[23–25,29,30,39,41,44,45,47,53,54,56,57] predefined cut-off values were evaluated, causing a high risk of bias concerning the index test in all other studies. Only one study[22] described criteria for performing an invasive intervention for pancreatic fistula, causing an uncertain risk of bias in all other studies. In 14 studies the test variable was tested on or after postoperative day 3, causing a high[21–23,25,27,28,31,32,34–36,41,42,44,45,47,48,52,56] or uncertain[26,30,46,57] risk of bias in all other studies. Concerning applicability, in 8 studies the test variable was only evaluated in subgroup of patients, most often with a high risk of pancreatic fistula and thereby causing a high risk of bias[23,24,32,33,38,39,42,44]. The quality assessment resulted in high quality in 46% and low quality in 14% of included studies (Figure 2).

Table 1: characteristics of included studies and patients*

First author	Year	Study design	Included patients	Type pancreatic resections (n)	Age – mean(SD)	Male sex – n (%)	Low risk pathology – n (%)	Clinically relevant pancreatic fistula – n (%)	Definition reference test	Tested variables
Amico	2018	PC	61	PD	58 (13)	30 (49%)	26 (43%)	20 (33%)	ISGPS B/C	Drain amylase
Ansorge	2014	PC	315	PD	67 (11)	174 (55%)	189 (60%)	59 (19%)	ISGPF B/C	CRP, drain amylase, serum amylase
Bertens‖	2017	RC	216	PD	65 (12)	104 (48%)	115 (53%)	33 (15%)	ISGPF B/C	Drain amylase
Bruno‖	2009	RC	50	PD	58 (16)	23 (46%)	14 (28%)	27 (54%)	Other $	Abdominal CT scan
Casadei	2017	PC	84	PD	68 (13)	43 (51%)	44 (52%)	34 (40%)	ISGPF B/C	Drain amylase
Chen	2018	RC	524	PD	67 (12)	280 (53%)	387 (74%)	46 (9%)	ISGPF B/C	Serum amylase
Dalla Valle	2015	RC	85	PD	67 (nr)	55 (65%)	69 (81%)	12 (14%)	ISGPF B/C	Serum lipase
Dugalic‖	2014	PC	382	PD	60 (9)	231 (61%)	145 (38%)	57 (15%)	ISGPF B/C	Drain amylase
El Nakeeb	2013	RC	471	PD	53 (11)	278 (59%)	392 (83%)	36 (8%)	ISGPF B/C	Drain amylase
Facy	2012	PC	65	PD(43)/DP(21)/ other(1)	62 (10)	34 (52%)	55 (85%)	14 (22%)	ISGPF B/C	Drain amylase, serum lipase
Fujiwara	2013	RC	297	PD(212)/DP(77)/ other(8)	63 (13)	181 (61%)	134 (45%)	166 (56%)	ISGPF B/C	Albumin, CRP
Furukawa‖	2016	RC	46	PD	69 (11)	32 (70%)	13 (28%)	16 (35%)	ISGPF B/C	CRP, pancreatic juice amylase
Giardino‖	2016	PC	84	PD	64 (5)	55 (66%)	62 (74%)	18 (21%)	ISGPF B/C	CRP, procalcitonin
Griffith	2018	PC	68	PD(55)/DP(12)/ other(1)	69 (nr)	33 (49%)	nr	11 (64%)	ISGPF B/C	Drain amylase, drain lipase
Kajiwara	2009	nr	220	PD	nr	125 (57%)	108 (49%)	64 (29%)	ISGPF B/C	Bile infection
Kawai	2011	RC	1239	PD	67 (9)	749 (60%)	619 (50%)	178 (14%)	ISGPF B/C	Drain amylase
Kawaida	2018	PC	75	DP	66 (2)	36 (48%)	30 (40%)	7 (9%)	ISGPF B/C	Drain amylase
Kinaci‖	2016	RC	45	PD	59 (15)	33 (73%)	nr	14 (31%)	ISGPF B/C	Abdominal ultrasound
Kobayashi‖	2013	nr	58	PD	70 (16)	34 (59%)	11 (19%)	29 (50%)	ISGPF B/C	Drain culture, drain amylase
Kosaka	2014	RC	100	PD	70 (2)	64 (64%)	40 (40%)	34 (34%)	ISGPF B/C	CRP, drain amylase, drain aspect, WBC
Kuhlbrey	2016	PC	739	PD(610)/DP(129)	65 (12)	340 (46%)	401 (54%)	160 (22%)	ISGPF B/C	Serum amylase

First author	Year	Study design	Included patients	Type pancreatic resections (n)	Age – mean(SD)	Male sex – n (%)	Low risk pathology – n (%)	Clinically relevant pancreatic fistula – n (%)	Definition reference test	Tested variables
Lee‖	2014	PC	536	PD(380)/DP(140)/ other(16)	63 (13)	262 (49%)	121 (23%)	92 (17%)	Other ¥	Drain amylase
Malya	2018	RC	117	PD	61 (13)	71 (61%)	60 (51%)	9 (8%)	ISGPF B/C	CRP
McMillan‖	2015	PC	106	PD	59 (11)	61 (58%)	60 (57%)	29 (27%)	ISGPF B/C	Drain amylase, serum amylase
McMillan	2017	PC	260	PD	65 (5)	146 (56%)	145 (39%)	29 (11%)	ISGPS B/C	Drain amylase
Moskovic	2010	PC	121	PD	(64 (5)	52 (43%)	75 (62%)	17 (14%)	ISGPF B/C	Temperature
Nagakawa	2013	nr	101	PD	68 (11)	64 (63%)	45 (45%)	13 (13%)	ISGPF B/C	Drain culture
Palani Velu	2014	PC	185	PD	nr	126 (68%)	79 (43%)	43 (23%)	ISGPF B/C	Serum amylase
Palani Velu	2016	RC	230	PD	60 (nr)	151 (66%)	100 (43%)	54 (23%)	ISGPF B/C	CRP
Partelli	2017	RC	463	PD	68 (11)	261 (56%)	nr	64 (14%)	ISGPF B/C	CRP, drain amylase
Solaini	2015	PC	378	PD(305)/DP(73)	64 (5)	183 (48%)	148 (39%)	31 (8%)	ISGPF B/C	CRP
Sutcliffe	2015	PC	130	PD	67 911)	77 (59%)	45 (35%)	20 (15%)	ISGPF B/C	Drain amylase
Tsujie	2012	RC	114	PD	70 (7)	81 (71%)	nr	18 (16%)	ISGPF B/C	Drain amylase
Uchida	2018	RC	85	DP	65 (11)	40 (47%)	nr	29 (34%)	ISGPF B/C	Abdominal CT
Uemura	2014	PC	200	PD	68 (12)	115 (58%)	101 (51%)	15 (8%)	ISGPF B/C	CRP, drain amylase, drain aspect, drain production, temperature, WBC
Ven Fong	2015	PC	369	PD	66 (12)	186 (50%)	205 (56%)	23 (6%)	ISGPF B/C	Drain amylase
Yamashita	2018	RC	82	PD	69 (9)	46 (56%)	30 (37%)	11 (13%)	ISGPF B/C	Drain culture

*Low risk pathology includes both pancreatic ductal adenocarcinoma and chronic pancreatitis; nr: not reported, PC: prospective cohort; RC: retrospective cohort, PD: pancreatoduodenectomy, DP: distal pancreatectomy, CRP: C-reactive protein, CT: computed tomography, WBC: white blood cell count

‖ These studies only included a subset of patients with an increased risk of pancreatic fistula.

$ Definition in study by Bruno et al.: drain output of any measurable volume of fluid on or after postoperative day 3 that had an amylase content greater than three times the serum amylase activity and, second, anastomotic leakage confirmed at reoperation or percutaneous drainage for major complications, such as abdominal bleeding and sepsis.

¥ Definition in study by Lee et al.: persistent drainage (a drain output of any measurable volume of fluid on or after post-operative day (POD) 3) of amylase-rich fluid (an amylase content greater than three times the serum amylase activity) in addition to the following: drain continuation >7 days, percutaneous drainage, or reoperation for a pancreatic fluid collection

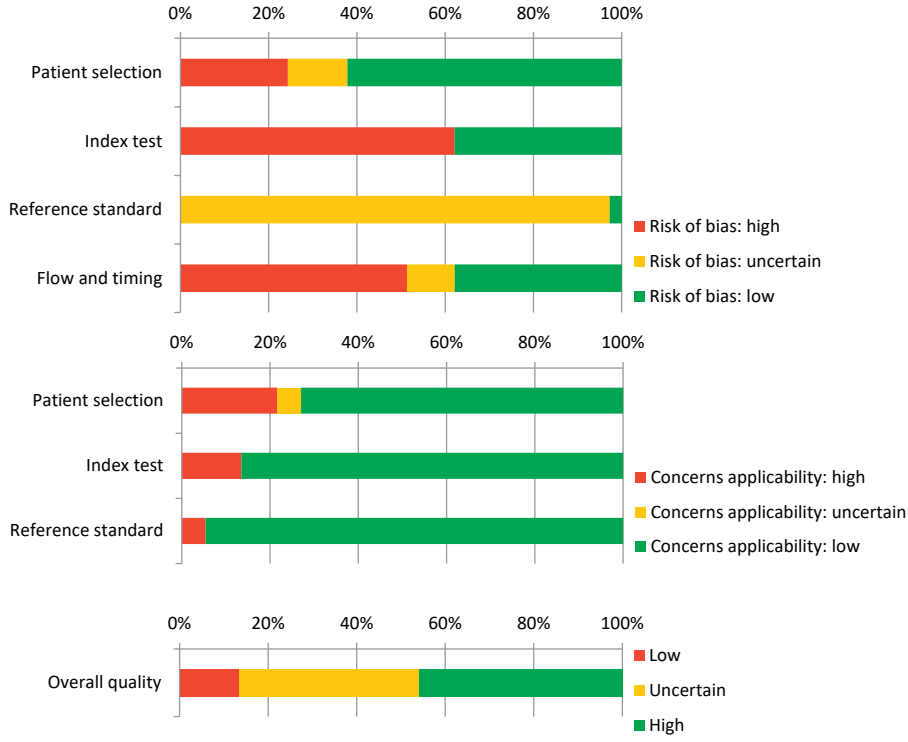

Figure 2. QUADAS-2 quality assessment

Tested variables

In the 37 included studies, a total of 17 different test variables were evaluated. An overview of these clinical, biochemical and imaging variables and their diagnostic indices is provided in Table 2 and Figure 3.

Seven different clinical variables were reported to be associated to clinically relevant postoperative pancreatic fistula. An unusual or non-serous aspect of drain fluid was reported in 2 studies (268 patients) and was measured on weighted mean postoperative day 3[40,55]. A positive drain culture was reported in 3 studies (241 patients) and was measured on weighted mean postoperative day 3[39,47,57]. Elevated temperature was reported in 2 studies (321 patients) and was measured on any postoperative day. Proposed cut-off values ranged from 37,7 to 38,6 °C[46,55]. In addition, a positive bile culture[35] and high drain output[55] were reported pancreatic fistula in a single cohort each.

Nine different biochemical variables were reported to be associated to clinically relevant postoperative pancreatic fistula. Elevated drain amylase level was reported in 16 different studies (3696 patients) and was measured on weighted mean postoperative day 1.

Proposed cut-off values ranged from 90 to 10.000 U/l [21–23,25,28–30,34,36,37,39,40,42,44,45,50,52,53,55,56]. Elevated serum amylase was reported in 5 different studies (1869 patients) was measured on weighted mean postoperative day 1. Proposed optimal cut-off values ranged from 54 to 292 U/l [41,44,48]. Elevated C-reactive protein (CRP) was reported in 10 different studies (2230 patients) and was measured on weighted mean postoperative day 4. Proposed cut-off values ranged from 55 to 272 mg/dl[31–33,40,43,49–51,55]. Elevated drain lipase was reported 2 studies (133 patients). Proposed cut-off values ranged from 180 to 1.000 U/l[30,34]. Elevated white blood cell count (WBC) was reported in 2 studies (300 patients) and was measured on weighted mean postoperative day 3. Proposed cut-off values ranged from 7,4 to 9,8 x109/l[40,55]. Elevated albumin level[31], high amylase level in pancreatic juice[32], elevated lipase level in serum[27] and elevated procaltinonin[33] were all associated with clinically relevant pancreatic fistula in a single cohort each (table 2).

Table 2: Diagnostic accuracy of tested variables*

	Studies (n)	Patients (n)	Cut-off (range)	Postoperative day$	Sensitivity (range)	Specificity (range)
Clinical						
Bile culture	1	220	Positive	1	54 %	77 %
Drain aspect efflux	2	268	Unusual – non-serous	3 (1-4)	20 – 53 %	94 – 98 %
Drain culture	3	241	Positive	3 (1-7 or any day)	50 – 96 %	75 – 97 %
Drain output	1	200	55 – 180 ml / 24h	4 (3-4)	7 – 67 %	75 – 76 %
Temperature	2	321	37,7 – 38,6 °C	Any day	18 – 53 %	88 – 97 %
Biochemical						
Albumin	1	297	26,5 g/l	1	42 %	67 %
Amylase (drain)	16	3696	90 – 10.000 U/l	1 (1-4 or any day)	28 – 98 %	3 – 99 %
Amylase (serum)	5	1869	54 – 292 U/l	1 (0-6)	21 – 90 %	44 – 94 %
Amylase in pancreatic juice	1	46	80% decline from day 1	3	56 %	90 %
CRP	10	2230	55 – 272 mg/l	4 (1-5)	50 – 97 %	27 – 90 %
Lipase (drain)	2	133	180 – 1.000 U/l	nr	91 – 93 %	65 – 76 %
Lipase (serum)	1	85	44,5 U/l	1	92 %	66 %
Procalcitonin	1	84	0,4 mg/dl	1	93 %	43 %
WBC	2	300	7,4 – 9,8 x10^9/l	4 (3-4)	73 – 87 %	63 – 82 %
Abdominal imaging						
CT	2	135	Peripancreatic fluid collection	5 – 10	63 – 90 %	11 – 83 %
Ultrasound	1	45	Peripancreatic fluid collection	3 – 7	36 %	74 %

*CRP: C-reactive protein, WBC: white blood cell count, CT: computed tomography n: number, ml: millilitre, h: hours, g: gram, l: litre, U: Units, mg: milligram, dl: decilitre, nr: not reported
$ Weighted mean (range)

Three studies on abdominal imaging were included in this review. Peripancreatic fluid collections were associated with pancreatic fistula both on abdominal computed

tomography (CT; 2 studies, 135 patients[24,54]) and abdominal ultrasound (US; 1 cohort, 45 patients[38]) obtained on postoperative day 5 to 10 or day 3 to 7, respectively. Specificity was higher for collections >8cm diameter (0,55) and collections with an increased heterogeneity (0,88).

An unusual aspect drain output, positive drain culture, elevated temperature, CRP, WBC and peripancreatic collections on abdominal CT are considered to be the most reliable in early diagnosis of postoperative pancreatic fistula, for they were all associated with clinically relevant pancreatic fistula in more than one cohort and tested on or after weighted mean postoperative day 3. Individual diagnostic indices of these tests are presented in Figure 3. Diagnostic indices of all other tests is presented in Table 2 or (when multiple studies and/or cut-off values were tested) in the supplementary appendix.

Discussion

This systematic review provides a comprehensive overview of the current literature on the diagnostic accuracy of postoperative clinical, biochemical, imaging variables to early diagnose clinically relevant postoperative pancreatic fistula. We found that a non-serous drain output, positive drain culture, elevated temperature or CRP or WBC and peripancreatic collections on abdominal CT scan appear to be the most reliable variables for early detection of clinically relevant pancreatic fistula, although proposed cut-off values and timing varies leading to a wide range in diagnostic indices. Clinical implication is therefore difficult. In addition, it should be noted that early elevation in amylase in serum or drain fluid appears to be an important predictor for the occurrence of clinically relevant pancreatic fistula.

Elevation in CRP, WBC and temperature are all well-known signs of inflammation. Leakage of enzyme rich pancreatic juice, necrosis or ischemia of the pancreatic anastomosis or local pancreatitis probably induces the release of cytokines, stimulating the hepatocellular CRP synthesis. The release of CRP and other acute phase enzymes may lead to clinical signs of inflammation (sepsis) and potentially life-threatening complications. In this cascade, CRP elevation precedes clinical signs of inflammation and is thereby in theory more suitable for early detection of inflammatory complications than clinical parameters[10,11,16–18]. In the current overview, 10 included studies evaluated a total of 18 different cut-off values in CRP for diagnosis of pancreatic fistula (range 55 to 272 mg/l). Not one of the proposed cut-off values was externally validated, making it difficult to determine the accuracy of the different reported cut-off values. There might be substantial heterogeneity in individual CRP levels, and therefore the difference between two CRP levels measured at consecutive postoperative days after the third postoperative day may be more accurate.

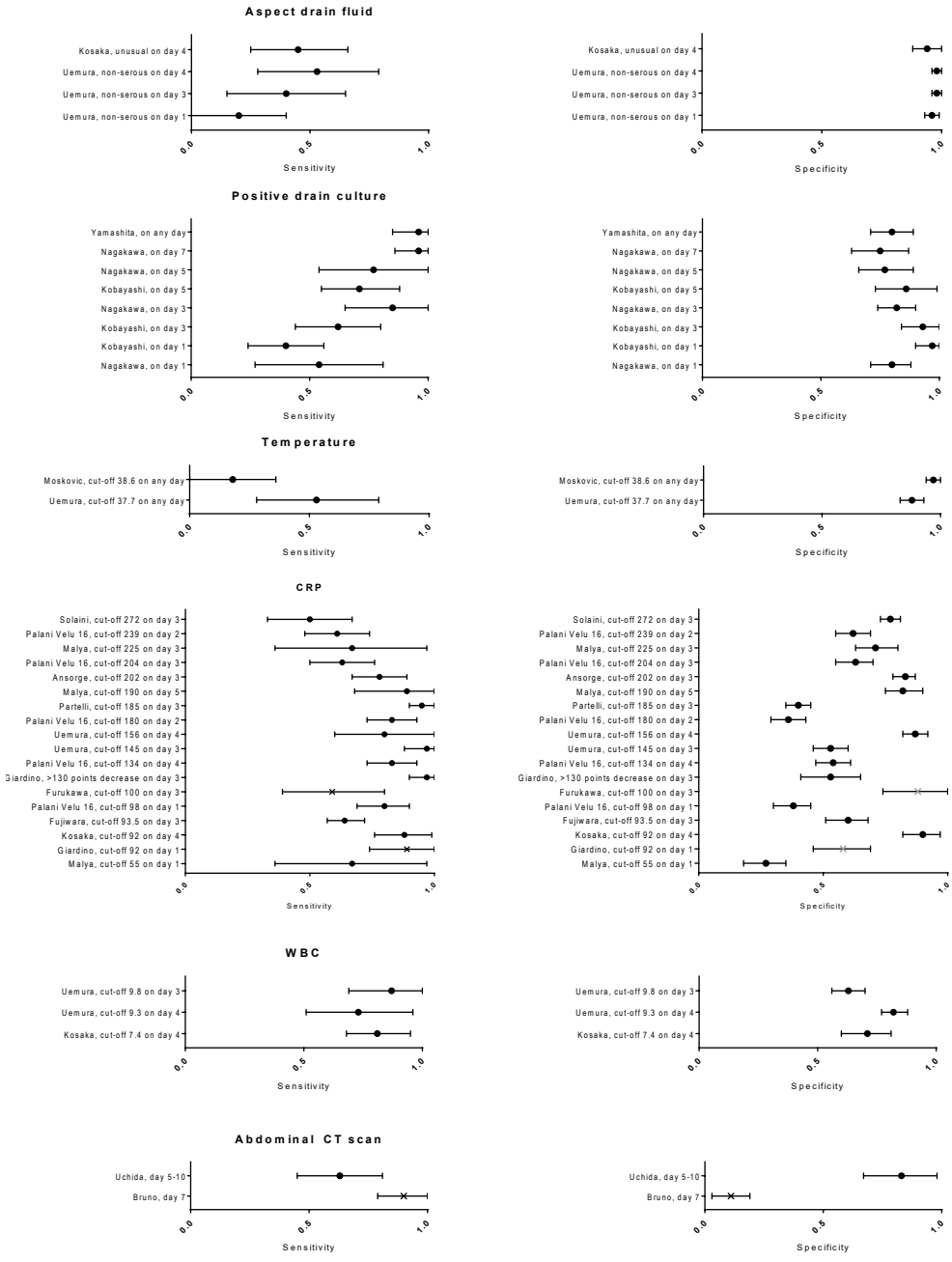

Figure 3. Sensitivity and specificity of different tested variables, at different cut-offs and different time points after pancreatic resection: aspect drain fluid (unusual (i.e. dark-brown, greenish, milky water or clear spring water)or non-serous); positive drain culture; temperature in °C; d) CRP in mg/l; WBC in cells x 10^9/l and abdominal CT scan showing peripancreatic fluid collections. Studies including all patients no matter the risk factors are indicated by a dot; crosses indicate studies only including high risk patients.

This analysis has, to our best knowledge, not yet been reported. An unusual or non-serous aspect of drain output as well as a positive drain culture might be a sign of an infected or dirty leak (i.e. leakage of bile or bowel content) through a dehiscent pancreatic anastomosis, which might be a sign of a more severe postoperative pancreatic fistula6. When the clinical suspicion of pancreatic fistula arises, abdominal imaging should be performed. Abdominal CT scan performs better than abdominal ultrasound in detection of small abdominal collections. Although peripancreatic collections are more frequently seen in patients with postoperative pancreatic fistula, not all peripancreatic collections are amylase rich[58,59]. To our knowledge, there are currently no known radiologic variables with a high accuracy for amylase positive peripancreatic collections.

Several literature overviews have been published on the prediction, rather than diagnosis, of postoperative pancreatic fistula. Different risk scores have been proposed, with the most frequently proposed predictors being pancreatic texture, diameter of the pancreatic duct, underlying pathology and body mass index[60,61]. To our knowledge, an overview of the accuracy of postoperative variables on diagnosing clinically relevant pancreatic fistula is lacking. Results of this overview might be used in addition to the different pre- and intraoperative risk scores.

No less than 16 studies reported on the association between early elevated drain amylase and clinically relevant pancreatic fistula in 3696 patients. There might be a difference between drained- and undrained pancreatic fistula. Undrained pancreatic fistula might be the most dangerous, especially when recognized late. In this type of pancreatic fistula, early diagnosis is mostly based on signs of inflammation. In the current review, we aimed to create a complete overview of all clinical, biochemical and imaging variables measured any time postoperatively. For clinically relevant pancreatic fistula per definition do not manifest until postoperative day 3, we stratified test variables according to their timing (i.e. day 1-2 or ≥day 3)[6]. The emphasis was more on variables measured on or after postoperative day 3, for these early diagnostic variables might be most useful in detection of patients with potentially severe undrained postoperative pancreatic fistula.

This review has several limitations. Ideally, we would have performed a formal meta-analysis in which summary diagnostic indices were provided for all tested variables. This is, however, not possible with the current data, due to heterogeneity between studies. Separate data on different types of pancreatic resections were not reported in this review, for these data were not available for a number of in included studies. A number of studies only included high risk patients (marked with an X in the forest plots), leading to spectrum bias and a slightly above average incidence of postoperative pancreatic fistula. Also, the tested variables might influence the clinical decision whether or not to perform an invasive intervention, and thereby influencing the number of patients grade B/C pancreatic fistula, leading to verification bias. Except for drain amylase levels, none of the proposed cut-off values were externally validated, making it difficult to interpret individual cut-off values. In addition, the number of missing measurements in included

studies cohort may have caused an overestimation of the diagnostic indices. A number of proposed cut-off values were within the normal biochemical range, making it difficult to interpret the value. We do, however, believe this review provides a comprehensive overview of what clinical, biochemical and imaging variables should be used in early recognition of pancreatic fistula.

Future prospective studies should validate the value of the tested variables and proposed timing and cut-off values. To improve clinical outcomes, pancreatic fistula should be recognized in an early stage so the risk of severe associated complications such as bleeding, organ failure and death can be minimized. Results of the current study were used to design a best practice algorithm for early diagnosis and minimally invasive management of postoperative pancreatic fistula, which is currently being evaluated in a nationwide stepped wedge randomized trial (PORSCH, NTR6905) in all 17 centers of the Dutch Pancreatic Cancer Group.

In conclusion, based on the current literature, CRP, WBC and temperature, an unusual aspect of drain output, positive drain culture, and peripancreatic collections on abdominal CT scan appear to be the most reliable test variables for early recognition of postoperative pancreatic fistula. No clear cut-off values could be identified, however, and diagnostic accuracy varies. In addition, early elevation in amylase in serum or drain fluid appears to have the most predictive value for clinically relevant pancreatic fistula. Prospective studies are needed to establish the most accurate combination of test variables and to evaluate the effect of structured implementation in daily clinical practice.

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Chapter 5

C-reactive protein is superior to white blood cell count for early detection of complications after pancreatoduodenectomy: a retrospective multicenter cohort study

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Abstract

Background
Early detection of major complications after pancreatoduodenectomy could improve patient management and decrease the "failure-to-rescue" rate. In this retrospective cohort study, we aimed to compare the value of C-reactive protein (CRP) and white blood cell count (WBC) in the early detection of complications after pancreatoduodenectomy.

Methods
We assessed pancreatoduodenectomies between January 2012 and December 2017. Major complications were defined as grade III or higher according to the Clavien Dindo classification. Postoperative pancreatic fistula (POPF) was a secondary endpoint. ROC-curve and logistic regression analysis were performed for CRP and WBC. Results were validated in an external cohort.

Results
In the development cohort (n = 285), 103 (36.1%) patients experienced a major complication. CRP was superior to WBC in detecting major complications on postoperative day (POD) 3 (AUC:0.74 vs. 0.54, P < 0.001) and POD 5 (AUC:0.77 vs. 0.68, P=0.031), however not on POD 7 (AUC:0.77 vs. 0.76, P=0.773). These results were confirmed in multivariable analysis and in the validation cohort (n = 202). CRP was also superior to WBC in detecting POPF on POD 3 (AUC: 0.78 vs. 0.54, P<0.001) and POD 5 (AUC: 0.83 vs. 0.71, P<0.001).

Conclusion
CRP appears to be superior to WBC in the early detection of major complications and POPF after pancreatoduodenectomy.

Introduction

Pancreatoduodenectomy is the only treatment for tumors of the pancreatic head and periampullary region with curative intent. In high-volume centers, perioperative mortality rates of <3% and morbidity rates of 40–50% are reported.[1-4] As a result of surgical and perioperative improvement in care, mortality rates have dropped significantly over the last decades. However, complication rates remain relatively unchanged.[4,5] Among all, postoperative pancreatic fistula (POPF) is the most threatening complication after pancreatoduodenectomy with an incidence of 10–25%.[1,3,6,7] POPF and intra-abdominal infections can lead to post-pancreatectomy hemorrhage and abdominal sepsis.[8,9] Therefore, early identification of patients at risk might help in decreasing 'failure-to-rescue' rates, which has been identified as an important quality indicator.[10,11] Inflammatory biomarkers such as C-reactive protein (CRP) and white blood cell count (WBC) might be suitable for early detection of complications, as they largely reflect the inflammatory status of a patient. Yet, translation and clinical understanding of CRP and WBC in the early postoperative period remains difficult as these parameters are often elevated due to surgical trauma.[12,13] Furthermore, CRP is predominantly used in Europe, while in non-European countries emphasis lies on WBC. However, recent studies demonstrated that both CRP and WBC are useful in the early detection of complications after pancreatoduodenectomy.[14-20] To our knowledge, no prior study has compared the diagnostic value of CRP and WBC during the early postoperative phase after pancreatoduodenectomy. Therefore, we aimed to determine whether CRP or WBC is superior in the detection of major complications and POPF during the first seven days after pancreatoduodenectomy.

Methods

The Medical Ethical Review Committee of the Erasmus MC in Rotterdam, the Netherlands, approved this study and waived the need for informed consent.

Study population

The cohort for model development included patients who underwent a pancreatoduodenectomy between January 2012 and December 2017 in one academic center in the Netherlands (Erasmus MC). The validation cohort included patients who underwent a pancreatoduodenectomy in one academic (UMC Utrecht) and one non-academic center (Sint Antonius hospital, Nieuwegein) between January 2015 and December 2017. Patients were excluded if they underwent additional concurrent organ resections, such as a hemicolectomy or a liver segment resection, since the height of the postoperative CRP peak is related to the extent of surgical trauma.[21]

Data collection

Demographics, clinical characteristics, operation data and postoperative outcomes were extracted from prospectively maintained databases or collected through systematic reviewed patient's charts. Serum CRP (mg/L) and WBC (x109/L) from POD 1 to POD 7 were collected. CRP and WBC were routinely measured on POD 3, 5 and 7 according to the postoperative protocol from all participating centres. Postoperative complications, including those after initial hospital discharge, were collected up to POD 30. The diameter of the pancreatic duct was measured on preoperative Computed Tomography (CT) scan at the pancreatic neck anterior to the portal vein and subsequently divided in two categories (≤3 mm and >3 mm). Pathological diagnoses were divided into a low risk (pancreatic adenocarcinoma and pancreatitis) and a high-risk group (miscellaneous).[6] Pancreatic texture was determined collected from operation reports of the surgeon (soft/normal or hard).

Definition of complications

The primary endpoint consisted of grade ≥ 3a complications according to the Clavien-Dindo Classification (i.e. requiring surgical, endoscopic or radiological intervention under regional-, general- or local anaesthesia, life threatening complications requiring intensive care management, single organ- or multi-organ failure and patients demise).[22] The secondary endpoint was grade B/C POPF.[23] Other complications were post-pancreatectomy hemorrhage,[25] delayed gastric emptying[26] and bile leakage.[27] Intra-abdominal infections were defined as drained fluid collections with a positive culture or purulent output.

Statistical analysis

Frequency distributions of continuous variables were visually assessed with histograms and potential departures from normality were formally assessed using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are presented as median values ± interquartile range (IQR). Categorical data are shown as counts and percentages.

Missing values of CRP and WBC from POD 1 to 7 were imputed using mixed-effects models. Mixed-effects models assess changes in longitudinal data over time, whilst accounting for intra-individual correlations between measurements and patient characteristics.[28,29] Our models consisted of a fixed-effects part and a random-effects part with a random intercept and a non-linear random slope. The fixed-effect parts included (pre-)operative parameters related to CRP, WBC or outcome (i.e. grade ≥3) ($P < 0.2$). Pancreatic texture was missing in 113 patients (39.6%); therefore it was not included in the mixed-effects models and multivariable models. All further analyses were performed on the dataset with complete longitudinal data, but were limited to POD 3, 5 and 7 as it had most available actual measurements. CRP and WBC measurements drawn after the incidence of a major complication were excluded from further analyses.

Differences in CRP and WBC between complication groups were tested using the Mann–Whitney U test (non-parametric). We constructed scatterplots for CRP and WBC with the associated Pearson's correlation coefficient. Additionally, receiver-operating characteristic (ROC) curves for CRP and WBC were constructed and area-under-the-curve (AUC) values were determined to assess discriminatory capabilities. Cut-off values were established for CRP and WBC based on the trade-off between sensitivity and specificity using ROC-curve analysis. The diagnostic value of delta CRP and delta WBC was examined in similar fashion. Next, we performed multivariable logistic regression analyses including CRP and WBC, adjusted for age, sex and variables univariably associated with the primary endpoint ($P < 0.2$). Bivariable logistic regression models (including only CRP and WBC) were also constructed, and their discrimination and calibration was assessed in the development and validation cohort.

R statistical software (version 3.4.3.; www.r-project.org) was used for all statistical analyses. Two-sided P-values < 0.05 were considered statistically significant.

Results

Study population

In the development cohort, a total of 306 pancreatoduodenectomies were performed. Overall, 21 patients were excluded due to additional concurrent resections, resulting in the final cohort of 285 patients. The validation cohort consisted of 202 patients after exclusion of 14 patients due to additional concurrent resections. Table 1 lists patient characteristics of both cohorts. In the development cohort 103 patients (36.1%) developed a major complication, with a median time of reintervention on POD 8 (interquartile range (IQR) 6–15 days). Furthermore, 51 patients (17.9%) developed POPF in the development cohort. For the validation cohort, 88 patients (40.1%) developed a major complication, with the median time of reintervention on POD 5 (IQR 3–9.5 days). Thirty-five patients (17.3%) developed POPF in the validation cohort. A detailed complication profile of both cohorts is shown in Appendix 1.

Table 1: Patient characteristics of the development and validation cohort.

	Development cohort (N = 285)	Validation cohort (N=202)	P-value
Age in years, median (interquartile range)	68 (58 – 73)	68 (59 – 74)	0.288
Male gender, no. (%)	176 (61.8)	110 (54.5)	0.129
Body mass index, median (interquartile range)	24.6 (22.4 – 27.1)	25.1 (22.7-27.8)	0.173
ASA status 3 – 4, no. (%)	64 (22.5)	49 (24.2)	0.716
Diabetes Mellitus , no. (%)	71 (24.9)	36 (17.8)	0.080
Smoker, no. (%)	61 (21.4)	28 (13.9)	0.234
Preoperative biliary drainage, no. (%)	180 (63.1)		
Diameter pancreatic duct, median (interquartile range)	4 (2 -6)	3 (1-6)	0.218
Soft/normal pancreatic texture, no. (%)	90 (52.3)	92 (71.3)	0.001
Pathological diagnoses, no. (%)			
High risk pathology *	176 (61.8)	111 (55.0)	0.158
Malignant pathology	219 (76.8)	158 (78.2)	0.804
Pancreatic adenocarcinoma	96 (33.7)	84 (41.6)	0.092
Ampullary carcinoma	45 (15.8)	12 (5.9)	0.001
Cholangiocarcinoma	38 (13.3)	30 (14.8)	0.731
Intraductal papillary mucinous neoplasm (IPMN)	29 (10.1)	20 (10.0)	1
Duodenal carcinoma	19 (6.6)	8 (4.0)	0.278
Pancreatic Neuroendocrine Tumor (pNET)	10 (3.5)	20 (9.9)	0.006
Other pathological diagnoses	48 (16.8)	28 (13.8)	0.401
Classic Whipple procedure, no. (%)	207 (72.6)	88 (43.6)	<0.001
Robot-assisted, no. (%)	27 (9.5)	16 (7.9)	0.665
Blood loss, median (interquartile range)	800 (500 – 1500)	500 (300 - 100)	<0.001
Length of hospital stay, median (interquartile range)	13.5 (9.0 - 25.0)	14.0 (9.0 – 21.8)	0.607
Readmissions, no. (%)	21 (7.3)		
Time to major complication, median (interquartile range)	8 (6 – 15)	5 (3.0 – 9.5)	0.003
30-day complications conform Clavien-Dindo, no. (%)			
Grade 0	88 (30.8)	66 (32.7)	0.675
Grade 1-2	119 (42.2)	57 (28.3)	0.002
Grade 3a	61 (21.4)	36 (17.8)	0.390
Grade 3b	10 (3.5)	3 (1.5)	0.280
Grade 4	22 (7.7)	34 (16.8)	0.003
Grade 5	10 (3.5)	6 (3.0)	0.742
Pancreatic fistula, no. (%) †	51 (17.9)	35 (17.3)	0.872
Post pancreatectomy haemorrhage, no. (%) §	20 (7.0)	18 (8.9)	0.443
Delayed gastric emptying, no. (%) ¥	75 (26.3)	58 (28.7)	0.556
Bile leakage, no. (%) ||	23 (8.1)	15 (7.4)	0.794
Intra-abdominal infection, no. (%) ‡	78 (27.4)		

* High risk pathology was defined as any pathological diagnosis other than pancreatic adenocarcinoma and chronic pancreatitis.
† Grade B/C fistula according to International Study Group for Pancreatic Surgery criteria.
§ Grade B/C post pancreatectomy haemorrhage according to International Study Group for Pancreatic Surgery criteria.
¥ Grade B/C post delayed gastric emptying according to International Study Group for Pancreatic Surgery criteria.
|| Grade B/C bile leakage according to the International Study Group for Liver Surgery criteria.
‡ Intra-abdominal infection was defined as the drainage of pus or a drained fluid collection with a positive culture.

CRP and WBC in the development cohort

Patients had a median of 3.5 CRP measurements (IQR: 3–4) and a median of 4 WBC measurements (IQR: 3–5) during the first 7 days after surgery. Before imputation, CRP measurements were available in 83% (POD 3), 58% (POD 5) and 60% (POD 7) of the patients. WBC measurements were available in 83% (POD 3), 60% (POD 5) and 59% (POD 7) of the patients.

Median CRP values were significantly higher in patients who developed major complications on POD 3, POD 5 and POD 7 (all $P < 0.001$), see Fig. 1a. No significant difference in WBC between complication groups was observed on POD 3 ($P = 0.299$). Median WBC was significantly higher in patients who developed major complications on POD 5 and POD 7 (both $P < 0.001$), see Fig. 1b. The positive correlation between CRP and WBC increased from POD 3 towards POD 7, see Fig. 2.

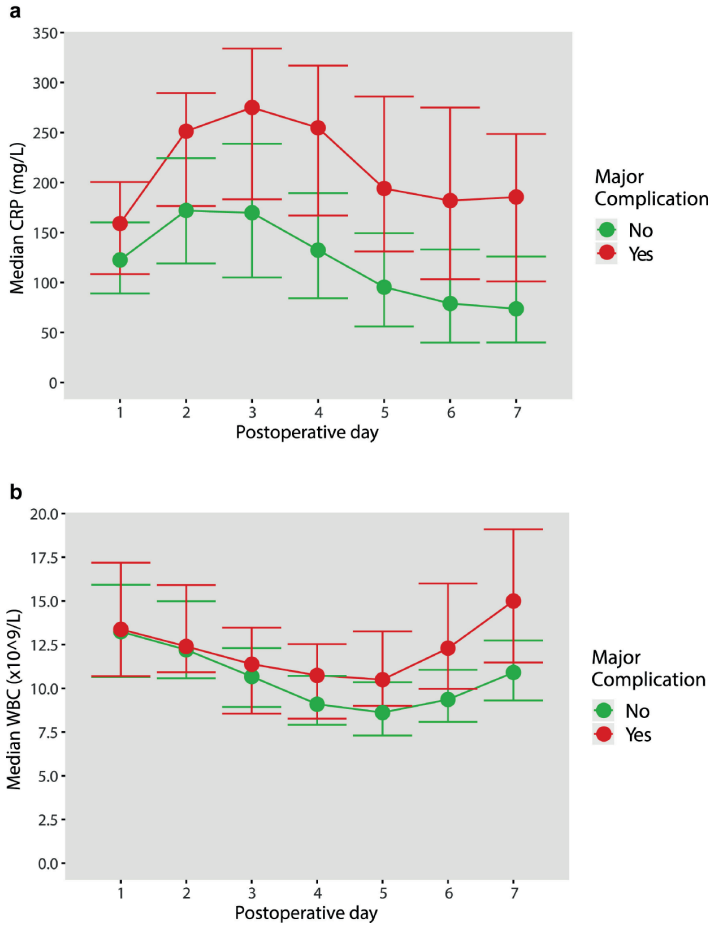

Figure 1. a: The median CRP evolution stratified by complications group. **b:** The median WBC evolution stratified by complication group. The median is indicated with the corresponding interquartile range

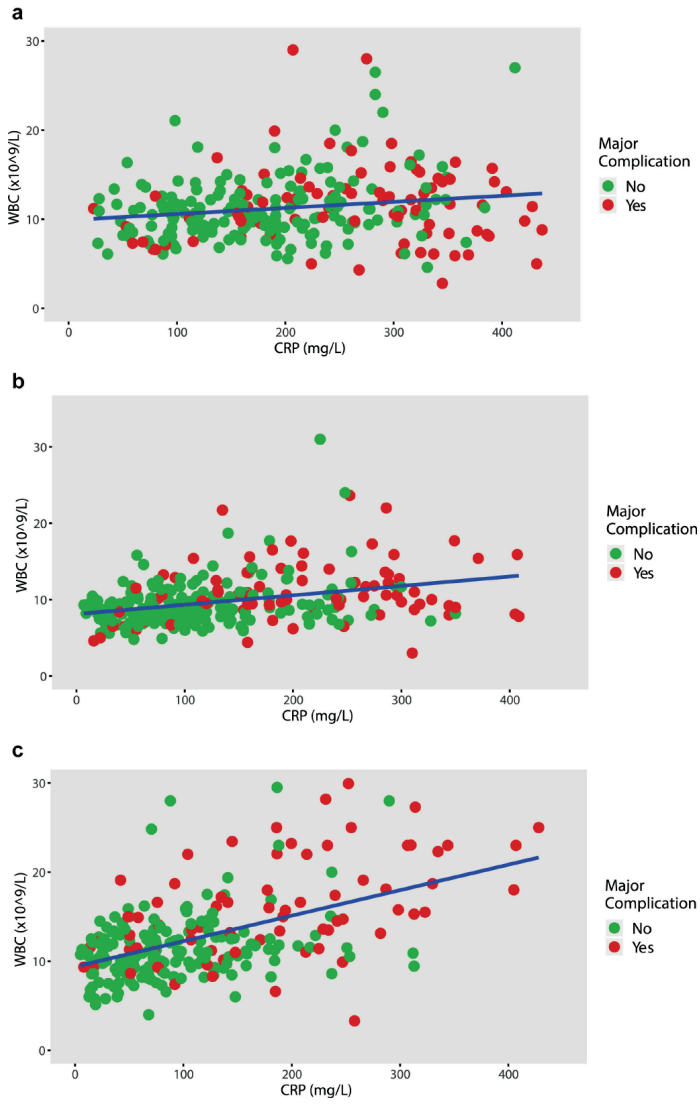

Figure 2. a: CRP versus WBC on postoperative day 3. **b:** CRP versus WBC on postoperative day 5. **c:** CRP versus WBC on postoperative day 7

Patients who developed POPF also had significantly higher CRP levels on POD 3 (307 vs. 181 mg/L, P < 0.001), POD 5 (240 vs. 101 mg/L, P < 0.001) and POD 7 (214 vs. 77 mg/L, P < 0.001). No difference was observed for WBC on POD 3 (11.9 vs. 10.7 × 10^9/L, P = 0.166). While, WBC was significantly higher in patients who developed POPF on POD 5 (10.9 vs. 8.9 × 10^9/L, P < 0.001) and POD 7 (16.6 vs. 11.2 × 10^9/L, P < 0.001).

ROC-curve analysis (Table 2) demonstrated that AUCs of CRP were significantly higher on POD 3 and POD 5 compared to WBC for major complications (P < 0.001 and P = 0.032, respectively) and POPF (both P < 0.001). On POD 7, CRP had a similar AUC as WBC for major complications (P = 0.773) and POPF (P = 0.158). Table 3 displays the diagnostic indices of CRP and WBC for detecting major complications at different cut-off values. Delta CRP and WBC demonstrated to have inferior diagnostic qualities compared to the absolute value of CRP and WBC (Appendix 2).

Table 2: Accuracy of CRP and WBC on POD 3, 5 and 7 in detecting major complications and postoperative pancreatic fistula in the development and validation cohort.

	The development cohort				The validation cohort			
	Major complications		POPF		Major complications		POPF	
	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI
POD 3								
CRP	0.74	0.67-0.80	0.78	0.71-0.85	0.75	0.67-0.83	0.84	0.77-0.92
WBC	0.54	0.46-0.62	0.56	0.47-0.66	0.56	0.46-0.65	0.54	0.41-0.68
POD 5								
CRP	0.77	0.70-0.83	0.83	0.77-0.89	0.81	0.72-0.90	0.90	0.83-0.96
WBC	0.68	0.60-0.75	0.71	0.63-0.80	0.65	0.54-0.75	0.68	0.54-0.82
POD 7								
CRP	0.77	0.70-0.84	0.85	0.79-0.91	0.79	0.69-0.90	0.85	0.75-0.96
WBC	0.76	0.68-0.83	0.78	0.70-0.87	0.76	0.66-0.85	0.77	0.61-0.93

Abbreviations: POPF = postoperative pancreatic fistula, POD = postoperative day, CRP = c-reactive protein, WBC = white blood cell count, AUC = area-under-the-curve, CI = confidence interval.

Multivariable analysis in the development cohort

Univariable analysis demonstrated that BMI, pancreatic duct diameter, soft pancreatic texture and blood loss >1000 ml were associated with major postoperative complications (Appendix 3). The multivariable models (Appendix 4) showed that, CRP was the only independent predictor of major complications on POD 3 and 5 (P < 0.001). On POD 7, both CRP and WBC were independently associated with major complications (P < 0.001 and P = 0.002, respectively). The same was demonstrated in models only containing WBC and CRP, these bivariables models had an AUC of 0.74 on POD 3 (95% CI: 0.67–0.80), 0.78 on POD5 (95% CI: 0.71–0.84), and 0.79 on POD 7 (95% CI: 0.73–0.86).

Calibration and discrimination in the validation cohort

In the validation cohort, AUCs of CRP and WBC were comparable to the development cohort (Table 2). Discrimination of the bivariable models in the validation data proved adequate, with AUCs of 0.75 on POD 3 (95% CI: 0.67–0.82), 0.79 on POD 5 (95% CI: 0.70–0.88) and 0.81 on POD 7 (95%: 0.71–0.90). Calibration of the bivariable models proved adequate in both cohorts (Appendix 5).

Table 3: Diagnostic accuracy of CRP and WBC for detecting major complications at different cut-off values*

	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	No. of positive patients (%)
POD 3						
CRP	150	0.87	0.42	0.42	0.88	181 (67%)
CRP	200	0.72	0.62	0.47	0.82	132 (49%)
CRP	250	0.57	0.81	0.59	0.80	86 (32%)
POD 5						
CRP	100	0.81	0.52	0.43	0.87	153 (58%)
CRP	150	0.71	0.75	0.56	0.86	104 (40%)
CRP	200	0.47	0.86	0.60	0.79	64 (24%)
WBC	8.0	0.81	0.36	0.36	0.81	184 (70%)
WBC	11	0.40	0.81	0.48	0.75	70 (27%)
WBC	13	0.26	0.93	0.61	0.74	34 (13%)
POD 7						
CRP	100	0.75	0.64	0.47	0.86	116 (47%)
CRP	130	0.65	0.78	0.55	0.84	86 (32%)
CRP	175	0.53	0.88	0.65	0.82	60 (24%)
WBC	10	0.85	0.36	0.36	0.85	173 (70%)
WBC	13	0.66	0.77	0.55	0.85	87 (35%)
WBC	15	0.49	0.90	0.66	0.81	55 (22%)

* CRP; C-reactive protein, WBC; White blood cell count

Discussion

In this study, we found that CRP and WBC are both useful in the early detection of complications after pancreatoduodenectomy. However, CRP appears to be superior to WBC in the early postoperative phase (i.e. postoperative day 3 and 5). Patients with continuous elevation of CRP levels were consistently at a higher risk of developing major complications and POPF. While, WBC only demonstrated to have a similar diagnostic value on postoperative day 7. Therefore, focus should lie on CRP follow-up rather than WBC when using a biomarker to evaluate the patient's postoperative condition during the first five days after pancreatoduodenectomy.

Biological markers such as CRP are mostly known and used for their value of detecting inflammation.[30] The usefulness of CRP as an early marker of complications has recently been shown during the first 4 days after pancreatoduodenectomy.[14-20] However, in major abdominal surgery, the accuracy of CRP has been shown to significantly increase per day after surgery.[31] Generally, 48–72 h after a single stimulus (e.g. surgical tissue damage) the serum CRP concentration peaks, after which it decreases with a plasma half-life of 19 h if no other stimuli occur.[32] Our observations are in line with this temporal peak. The higher CRP peak observed on POD 3 in patients with major complications suggests that early inflammatory processes, leading to the activation of CRP, precede the clinical manifestation of complications.

In addition, recent studies suggest that CRP, besides being a product of inflammation, also aids in bridging the innate and adaptive immune system, by suppressing pro-bacterial processes.[33] Previous studies have shown that major surgeries tend to have transient immunosuppressive effects on the white blood cells, which could account for the delayed immune activation and subsequently less discriminatory ability in the early postoperative phase.[34,35] Our findings are substantiated by previous work in patients after colorectal surgery, which demonstrated no additional value of WBC compared to CRP up to POD 5 in detection inflammatory complications.[36,37] Also, a recent study demonstrated no difference in WBC relating to POPF between POD 1 to POD 5 in 176 patients after pancreatoduodenectomy.[15] From a historical perspective, although CRP being first discovered in the United States, there was great skepticism initially regarding the clinical utility of CRP. With the discovery that CRP strongly predicts cardiovascular disease in the mid-1990s, it became more widely accepted for this purpose.[30] Yet, in postoperative practice, CRP is still not used much outside of Europe. Interestingly, no cost-effectiveness studies comparing CRP and WBC exist to our knowledge. In the Netherlands, the costs of a CRP measurement is approximately €4.00 compared to €2.00 for a WBC measurement.

Prior studies examining CRP or WBC after pancreatoduodenectomy are mainly limited to POPF.[14,17,38,39] Focus on all major complications may be desired as POPF makes up a mere 50% of total morbidity in our cohort. Additionally, Prat et al. demonstrated that a considerable proportion of POPFs have a latent character and might not be characterized as POPF.[40] Despite the use of broader complication criteria in our study, we found comparable indices of accuracy compared to studies focusing on POPF. Since POPF is a strong driver of most complications it was separately analyzed. We found similar results as those reported in the literature. Recently, Partelli et al. found an AUC of 0.80 for CRP on POD 3 in 463 patients after pancreatoduodenectomy.[17] Palani Velu et al. demonstrated an AUC of 0.69 for CRP on POD 3 in 230 patients after pancreatoduodenectomy.[14]

"Failure-to-rescue" is an important determinant of mortality after pancreatoduodenectomy, relating to the ineffective management of patients who develop major complications.[10,11] Currently, most complications after pancreaotoduodenectomy are managed with non-operative procedures, such as the administration of antibiotics or the percutaneous drainage of fluid collections.[41] Easily accessible and cheap makers such as CRP and WBC could be useful tools to identify risk groups, especially in case of ambiguity concerning the clinical status of a patient. Vigilance with respect to the development of complications warrants a CRP cut-off with a high sensitivity. Notably, the number of false positive results should also be minimized to avoid unnecessary CT-scans. Based on our data, we consider a sensitivity of approximately 70% appropriate. For a patient on POD 5 this is a CRP cut-off of 150 mg/L. Above this threshold, patients have a risk of 56% on major complications, which justifies additional CT-

scan examination. This allows for early percutaneous drainage and more liberal administration of antibiotic treatment in case of peri-pancreatic fluid collections.

Noteworthy, reinterventions occurred earlier in the validation cohort than in the development cohort (median POD 8 vs. POD 5, P = 0.003). The incidence and timing of major complications is influenced by the clinical practice, which likely explains the observed difference. Yet, the similar discrimination in both cohorts supports the generalizability of our results despite the difference in clinical practice.

Our study has certain limitations. First, due to the retrospective design we had missing data. However, longitudinal CRP and WBC values could be imputed using a mixed-effects model under the missing-at-random assumption, which is a reliable and established method.[42] An advantage of using a mixed-effects model is that missing longitudinal data can be inferred based on intra-individual measurements and the natural course of a biomarker. Furthermore, pancreatic texture was missing in 40% of the patients. Imputation of this variable was deemed infeasible due to probable violation of the missing-at-random assumption (texture was less likely to be reported if normal/soft). This issue was handled by including postoperative pathology in the multivariable analysis, which serves as an objective, surrogate indicator of pancreatic texture. Second, the occurrence of major complications in this study is related to the clinical practice, which is possibly influenced by CRP and WBC leading to potential verification bias. This could only be circumvented by prospectively blinding clinicians for CRP and WBC values, which is deemed unethical. However, we believe our results are still reliable since the decision to intervene is not solely based on the level of CRP or WBC, rather on the clinical status of the patients in combination with findings on postoperative imaging.

In clinical practice, bedside judgement is an important determinant in postoperative patient management. Therefore, basing decisions solely on CRP or WBC is unlikely, and this also yields substantive groups of patients with an intermediate risk on major complications (Appendix 5). The combination of clinical parameters and CRP or WBC may lead to a more effective risk stratification. Future research will require the development of elaborate models to assess their combined potential. In addition, the effect of early detection and management of complications after pancreatic resection on severe morbidity (relaparotomy, ICU admittance and death) is still unknown. This is currently being investigated in a nationwide stepped-wedge, cluster randomized, superiority trial in the Netherlands (PORSCH trial).

CRP appears to be superior to WBC in the early detection of major complications and postoperative pancreatic fistula after pancreatoduodenectomy. These findings emphasize the clinical value of CRP follow-up during the first days after surgery and the role it may have in decision making.

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Chapter 6

Management of Severe Pancreatic Fistula after Pancreatoduodenectomy: a Multicenter Propensity Matched Cohort Study

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Abstract

Background
Postoperative pancreatic fistula is a potentially life-threatening complication after pancreatoduodenectomy. Evidence for best management is lacking. The objective of this study was to evaluate the clinical outcome of patients undergoing catheter drainage compared with relaparotomy as primary treatment for pancreatic fistula after pancreatoduodenectomy.

Methods
A multicenter, retrospective, propensity-matched cohort study was conducted in 9 centers of the Dutch Pancreatic Cancer Group from January 1, 2005, to September 30, 2013. From a cohort of 2196 consecutive patients who underwent pancreatoduodenectomy, 309 patients with severe pancreatic fistula were included. Propensity score matching (based on sex, age, comorbidity, disease severity, and previous reinterventions) was used to minimize selection bias. Data analysis was performed from January to July 2016. The exposure was first intervention for pancreatic fistula: catheter drainage or relaparotomy. Primary end point was in-hospital mortality; secondary end points included new-onset organ failure.

Results
Of the 309 patients included in the analysis, 209 (67.6%) were men, and mean (SD) age was 64.6 (10.1) years. Overall in-hospital mortality was 17.8% (55 patients): 227 patients (73.5%) underwent primary catheter drainage and 82 patients (26.5%) underwent primary relaparotomy. Primary catheter drainage was successful (ie, survival without relaparotomy) in 175 patients (77.1%). With propensity score matching, 64 patients undergoing primary relaparotomy were matched to 64 patients undergoing primary catheter drainage. Mortality was lower after catheter drainage (14.1% vs 35.9%; P = .007; risk ratio, 0.39; 95% CI, 0.20-0.76). The rate of new-onset single-organ failure (4.7% vs 20.3%; P = .007; risk ratio, 0.15; 95% CI, 0.03-0.60) and new-onset multiple-organ failure (15.6% vs 39.1%; P = .008; risk ratio, 0.40; 95% CI, 0.20-0.77) were also lower after primary catheter drainage.

Conclusions
In this propensity-matched cohort, catheter drainage as first intervention for severe pancreatic fistula after pancreatoduodenectomy was associated with a better clinical outcome, including lower mortality, compared with primary relaparotomy.

Introduction

Postoperative pancreatic fistula is a common and dreaded complication after pancreatoduodenectomy.[1-3] This complication, as defined by the International Study Group for Pancreatic Fistula (ISGPF), can be divided into 2 major groups: biochemical, clinically irrelevant fistula (ie, grade A) and clinically relevant pancreatic fistula requiring a change in postoperative management (ie, grades B and C).[4] In a recent systematic review of 40 studies reporting ISGPF-defined pancreatic fistula, clinically relevant pancreatic fistula occurred in 12% of patients after pancreatoduodenectomy and was associated with a mortality up to 39%.[5] Major causes for mortality in these patients are multiple-organ failure and postpancreatectomy hemorrhage as a direct result of the pancreatic fistula.[6]

Consensus on the optimal treatment strategy of clinically relevant pancreatic fistula is lacking.[7-9] For decades, treatment was through direct relaparotomy. With this approach, surgical lavage and drainage and, if necessary, a completion pancreatectomy to entirely remove the source of sepsis can be performed. This invasive procedure is associated with high mortality.[6,10,11] However, other studies have shown that completion pancreatectomy can be performed with a relatively good outcome (ie, low mortality), and the investigators argue that, in patients needing relaparotomy, the operation should be performed as soon as possible.[3,8,12,13] Primary catheter drainage is a less invasive alternative to relaparotomy; it reduces tissue damage and the systemic inflammatory response otherwise induced by surgical stress in these already critically ill patients.[3,14] In another group of critically ill patients with pancreatic disease (infected necrotizing pancreatitis), standard treatment is now a minimally invasive step-up approach consisting of percutaneous catheter drainage as a first step to be followed by surgical intervention if patients do not improve clinically.[15] Several studies have shown a wide range (15%-50%) in the percentage of patients with pancreatic fistula treated with relaparotomy[6,16-21]; however, relaparotomy might be needed in only a small selection of these patients.[2,22,23] The aim of the present study was to evaluate the clinical outcome of patients undergoing catheter drainage compared with relaparotomy as the primary treatment for severe pancreatic fistula after pancreatoduodenectomy in 9 centers of the Dutch Pancreatic Cancer Group.

Methods

Design and Study Population

This was a multicenter, retrospective cohort study. All consecutive patients undergoing pancreatoduodenectomy for presumed cancer or precancerous condition ([pre-] malignancy) from January 1, 2005, to September 30, 2013, in 5 academic medical centers and 4 major teaching hospitals of the Dutch Pancreatic Cancer Group were evaluated. Included were patients with pancreatic fistula according to the ISGPF who underwent an invasive intervention to manage pancreatic fistula (ie, patients who were discharged

with an intraoperatively placed drain in place and patients requiring additional catheter drainage or relaparotomy, defined as severe pancreatic fistula). We aimed to create an adequate sample of patients in whom pancreatic fistula could have been primarily managed through both relaparotomy and catheter drainage. Therefore, we excluded all patients with pancreatic fistula that was primarily managed with relaparotomy that was indicated by a complication that could not have been managed with catheter drainage (all indications listed in Figure 1). The indications for relaparotomy were assessed by 3 authors (F.J.S., H.C.v.S., and I.Q.M.) independently, and discrepancies were resolved in consensus.

Patients were identified using existing prospective databases from the individual hospitals and by systematic screening of patient files. This study was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines[24] and approved by the Medical Ethics Review Committee of the University Medical Center Utrecht, the Netherlands, with waiver of informed patient consent.

Data Collection and Outcomes

Using a predefined, standardized case-record form, we collected data on multiple patient factors, including age, sex, coexisting conditions, body mass index, weight loss, and preoperative cholestasis, as well as details on endoscopic retrograde cholangiopancreatography and pancreatoduodenectomy. In addition, data were obtained on American Society of Anesthesiologists (ASA) class (I, healthy status; II, mild systemic disease; and III, severe systemic disease) and the severity of illness 24 hours before the first intervention for pancreatic fistula as measured by the Acute Physiology and Chronic Health Evaluation II (APACHE II) scale (score ranges from 0 to 71, with higher scores indicating more severe disease); systemic inflammatory response syndrome, as defined by the American College of Chest Physicians and the Society of Critical Care Medicine[25]; and the presence of single- or multiple-organ failure.

The primary outcome was in-hospital mortality. Secondary end points were major complications (ie, new-onset single- or multiple-organ failure or other complications requiring intervention), endocrine and exocrine pancreatic insufficiency, number and type of invasive interventions, length of hospital stay, need for admission to the intensive care unit (ICU), length of ICU stay, and duration of pancreatic fistula (ie, time to removal of last abdominal drain or completion pancreatectomy). Definitions are given in Table 1. Readmission within 10 days after discharge was considered to be the index admission, and follow-up was 90 days after discharge.

Table 1: Definitions of outcomes*

Outcome	Definition
New-onset	Not present any time in 24h before first intervention
Major complications	Single- or multiple-organ failure (e.g. failure of at least two organ systems), bile leakage or gastroenterostomy leakage, or post pancreatectomy hemorrhage requiring intervention
Organ failure	
Pulmonary	PaO2 <60mmHg, despite FiO2 of 0.3, or need for mechanical ventilation
Circulatory	Systolic blood pressure <90mmHg, despite adequate fluid resuscitation, or need for inotropic support
Renal	Creatinine level >177μmol/liter after rehydration or need for hemofiltration or hemodialysis
Postoperative pancreatic fistula	Amylase in drain fluid on or after postoperative day three of at least three times the upper level of normal serum amylase[4]
Grade A	Requiring no change in postoperative management, hospital stay not prolonged
Grade B	Requiring change in postoperative management (i.e. catheter drainage, discharge with intraoperatively placed drains in situ, no relaparotomy), length of hospital stay might be prolonged
Grade C	Requiring relaparotomy and/or admission to ICU and/or pancreatic fistula leading to death, length of hospital stay prolonged
Severe pancreatic fistula	Requiring additional drainage or were discharged with intraoperatively placed drain in place; Requiring relaparotomy (i.e. with surgical drainage or additional pancreatic resection)
Post-Operative Bile Leakage	Bilirubin in drain fluid on or after postoperative day three of at least three times the upper level of normal serum bilirubin (Adapted from Koch[42])
Delayed gastric emptying	Adapted from Wente[43]
Grade A	Nasogastric tube postoperative day 4 to 7 or need for replacement of tube after postoperative day 3; oral intake between day 7 and 14
Grade B	Nasogastric tube postoperative day 8 to 14 or need for replacement of tube after postoperative day 7; oral intake between day 14 and 21
Grade C	Nasogastric tube after postoperative day 14 or need for replacement of tube after postoperative day 14; oral intake after day 14
Gastroenteral leakage	As seen on abdominal imaging or during relaparotomy or secretion of faecal material from percutaneous drain or through surgical wound
Acute pancreatitis	Combination of abdominal pain, three-fold increased amylase and lipase levels or as seen on radiologic imaging
New-onset diabetes	Need for insulin or oral diabetic drugs within three months after discharge, not present before pancreatoduodenectomy
Exocrine pancreatic insufficiency	Need for oral pancreatic-enzyme supplementation within three months after discharge, not present before pancreatoduodenectomy

*FiO2 denotes fraction of inspired oxygen, PaO2 partial pressure of arterial oxygen

Statistical Analysis

Patients were divided into 2 groups based on the first intervention for pancreatic fistula: catheter drainage or relaparotomy. These treatment groups were compared for baseline characteristics and outcomes. The Kolmogorov-Smirnov test was used to assess whether continuous data were normally distributed ($P < .05$). Normally distributed continuous data are presented as mean (SD), and skewed distributions are given as median (interquartile range [IQR]). Dichotomous data were compared using a χ^2 test or Fisher

exact test as appropriate. Continuous data were compared using the Mann-Whitney test. Length of ICU stay and hospital stay, as well as the duration of pancreatic fistula, were calculated in the survivors.

Propensity score matching was used to minimize the impact of selection bias.[28,29] Predicted probabilities (ie, the propensity score) for relaparotomy as the first intervention were estimated for each patient using a logistic regression model. Patients undergoing primary relaparotomy were matched to patients undergoing primary catheter drainage with a similar score. All baseline variables possibly influencing the decision on primary treatment or mortality (based on literature and expert opinion) were included in the first model. The efficiency of this model was tested by evaluating the balance in baseline distribution.[29] The optimal model (ie, smallest differences in baseline distribution) was achieved by including sex, age, ASA class, APACHE II score, organ failure 24 hours before the first intervention, and whether a patient underwent another intervention before the first intervention for pancreatic fistula. For practical reasons, patients were excluded if any of these data were missing. We used a 1:1 ratio in nearest-neighbor matching in a random order without replacement and with a caliper fixed to 0.2. Equal distribution of baseline characteristics was tested using standardized differences, defined as the mean difference between the groups divided by the SD of the treatment group. We aimed to reach the smallest standardized mean differences as possible for baseline characteristics, but always less than 0.25, to achieve the best balance.[30] Matched dichotomous outcomes were compared using the McNemar test. Risk ratios (RRs) with 95% CIs were calculated by the method reported by Bonett and Price.[31] Matched continuous outcomes were analyzed using the paired-samples, 2-tailed t test for normally distributed data or Wilcoxon signed rank test for skewed data. Median differences with 95% CIs were calculated using the method reported by Bonett and Price.[32]

A predefined subgroup analysis for disease severity was performed within the entire cohort of patients. We divided patients undergoing primary relaparotomy into 3 subgroups based on the highest APACHE II score within 24 hours before the first intervention. Cutoff points (ie, <9, 9-12, and >12) were chosen so that the number of patients undergoing primary relaparotomy was equally distributed.

Data analysis was conducted from January to July 2016. Analyses were performed using SPSS, version 20.0 (SPSS Inc) and R, version 2.12.33 For the propensity score matching, the plugin designed by Thoemmes was used.[34] A 2-sided P value <.05 was considered statistically significant.

Results

Study Population

From January 1, 2005, to September 30, 2013, a total of 2196 consecutive pancreatoduodenectomies were performed in the participating hospitals for patients with a presumed malignant or (pre-)malignancy neoplasm. Of these, 328 patients (14.9%) developed severe pancreatic fistula. Nineteen (5.8%) of these patients were excluded: 1 patient with pancreatic fistula who died before undergoing an intervention and 18 patients undergoing primary relaparotomy indicated for a complication that could not have been managed through catheter drainage. Details on patient inclusion are provided in Figure 1.

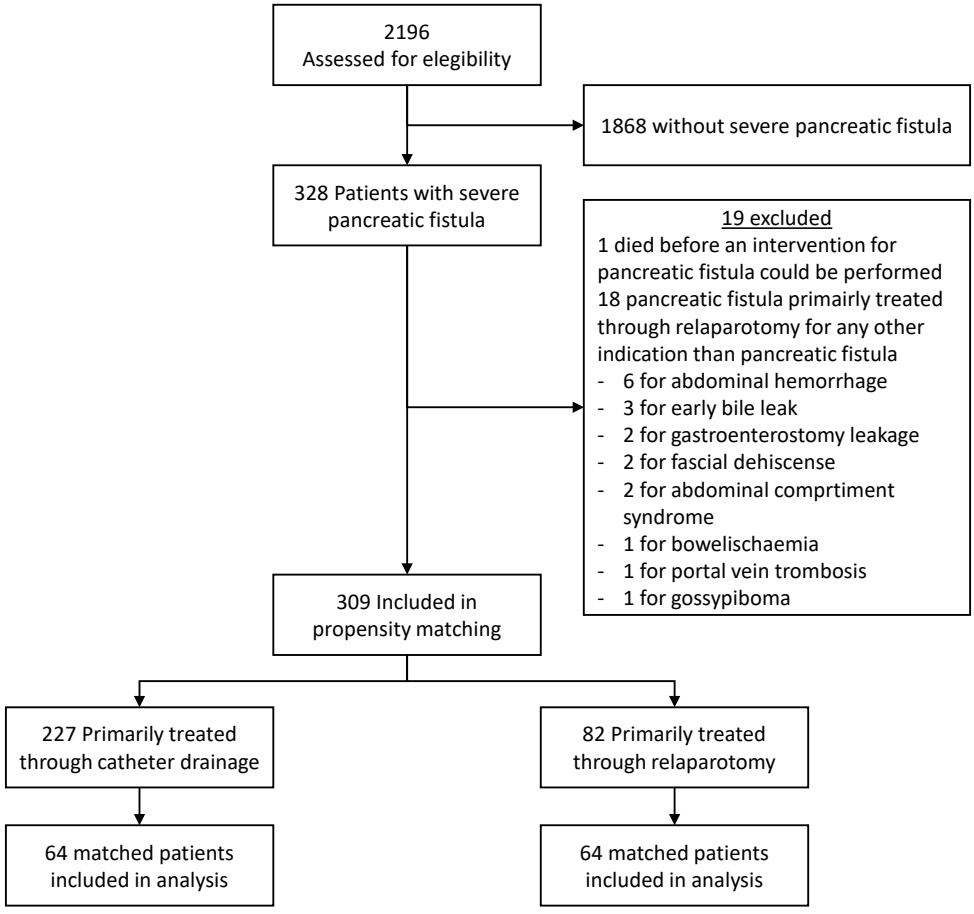

Figure 1. Inclusion of study patients

The final study cohort comprised 309 patients with severe pancreatic fistula after pancreatoduodenectomy; 209 patients (67.6%) were men, and mean (SD) age was 64.6 (10.1) years. In 10 patients, a pancreatogastrostomy was performed; all of the remaining patients underwent a pancreatojejunostomy. Overall in-hospital mortality was 17.8% (55 patients).

Of all 309 patients, 227 (73.5%) underwent catheter drainage and 82 patients (26.5%) underwent relaparotomy as the first intervention for pancreatic fistula. There was no tendency observed toward catheter drainage as the first intervention for severe pancreatic fistula over the years of inclusion (Figure 2). Primary catheter drainage was successful (ie, discharge without the need for relaparotomy) in 175 patients (77.1%).

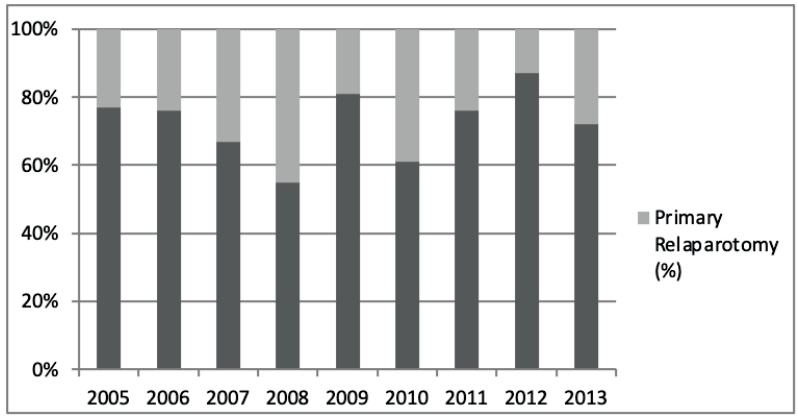

Figure 2. First intervention for postoperative pancreatic fistula over the years (%)

There were important baseline differences observed between the 2 treatment groups in the full cohort of patients, including significantly more men undergoing primary relaparotomy, a higher incidence of cardiovascular disease, a higher ASA class, and more patients who were severely ill 24 hours before the first intervention (eTable 1 in the Supplement). With propensity score matching, 64 of 82 patients (78.0%) undergoing primary relaparotomy were successfully matched to 64 patients undergoing primary catheter drainage. In this matched cohort, there were no significant differences in baseline characteristics (Table 2).

Table 2: Baseline characteristics*

Characteristics	Catheter Drainage (n=64)	Relaparotomy (n=64)	Standardized mean difference (%)	
			Before matching	After matching
Age – yr (median (IQR))	68 (57-73)	66 (57-71)	2.9	1.3
Male sex – no. (%)	50 (78)	50 (78)	25.1	0.0
Coexisting condition – no. (%)				
Cardiovascular disease	20 (31)	21 (33)	25.7	3.3
Pulmonary disease	6 (9)	8 (13)	15.3	9.4
Chronic renal insufficiency	2 (3)	1 (2)	4.4	12.5
History of upper abdominal surgery	13 (20)	17 (27)	1.7	14.0
ASA class on admission – no. (%)			30.2	4.6
I: healthy status	8 (13)	13 (20)		
II: mild systemic disease	43 (67)	25 (55)		
III: severe systemic disease	13 (20)	16 (25)		
Body-mass index (mean ±SD) †	26±3.2	26±3.7	8.1	3.1
Weight loss	30/61 (49)	30/60 (50)	7.3	1.6
Quantity – kg (median (IQR)) ‡	2 (0-7)	1 (0-8)	14.5	6.8
Preoperative ERCP – no. (%)			9.7	0.3
Without intervention	14/63 (22)	6 (9)		
With stenting/papillotomy	30/63 (47)	35 (55)		
Preoperative cholestasis – no. (%)‖	47 (73)	43 (67)	9.4	13.2
Details on pancreatoduodenectomy – no. (%)				
Pylorus preserving pancreatoduodenectomy	49 (77)	49 (77)	6.2	0.0
Reconstruction portal vein	1/63 (47)	4/63 (5)	2.7	14.8
Additional organ resection	3/63 (5)	8/63 (13)	23.6	23.6
Abdominal drain	63 (98)	62 (97)	14.7	8.9
Pathology (pre-)malignant – no. (%)	55 (86)	56 (88)	17.3	4.7
Disease severity 24h before first intervention				
APACHE II (median (IQR)) ¶	8 (6-11)	9 (6-13)	53.1	3.9
SIRS – no. (%) #	32 (50)	35 (55)	29.0	9.3
Organ failure – no. (%)	22 (34)	33 (34)	71.0	0.0
Single-organ failure – no. (%)	13 (20)	15 (23)	50.8	7.3
Multiple-organ failure – no. (%)	9 (14)	7 (11)	32.3	9.9
Previous re-intervention – no. (%)**	5 (8)	7 (10)	24.3	9.9

* Normal distributed values are presented as mean±SD, ASA denotes American Society of Anesthesiologists; Propensity Score Matching based on sex, age, ASA class on admission, APACHE II, SIRS, Organ Failure, and previous re-intervention

† Body-mass index, weight in kilograms divided by the square of the height in meters; mean±SD over 60 patients in drainage group and 62 patients in relaparotomy group

‡ Median (IQR) over 60 patients in drainage group and 58 patients in relaparotomy group

‖ Defined as jaundice, elevated bilirubin and/or need for preoperative biliary drainage

¶ Acute Physiology and Chronic Health Evaluation (APACHE II) scale from 0-71, higher scores indicating more severe disease

Systemic inflammatory response syndrome as defined by the American College of Chest Physicians and the Society of Critical Care Medicine

** Represents number of patients who have undergone an intervention after pancreatoduodenectomy before first intervention for pancreatic fistula for any other indication than pancreatic fistula

Primary Relaparotomy

The 64 matched patients underwent the following procedures during primary relaparotomy: 32 patients (50.0%) underwent extended lavage and drainage of the abdominal cavity, 17 patients (26.6%) received a direct completion pancreatectomy, the pancreatic anastomosis was revised in 12 patients (18.8%), and the pancreatic anastomosis was dismantled while pancreatic juice efflux was secured through a drain in the pancreatic duct in 3 patients (4.7%). Primary relaparotomy was performed a median of 8 (IQR, 5-11) days after pancreatoduodenectomy.

Primary Catheter Drainage

Of 64 matched patients undergoing primary catheter drainage, catheter drainage was performed percutaneously via interventional radiology in 60 patients (93.8%), endoscopic (transgastric) drainage was performed in 1 patient (1.6%), and 3 patients (4.7%) were discharged with an intraoperatively placed drain in place. Primary catheter drainage was performed a median of 9 (IQR, 7-11) days after pancreatoduodenectomy.

Primary and Secondary Outcomes

Clinical outcomes are given in Table 3. After primary relaparotomy, 23 of 64 patients (35.9%) died compared with 9 of 64 patients (14.1%) after primary catheter drainage (P = .007; RR, 0.39; 95% CI, 0.20-0.75).

New-onset organ failure occurred more often in the 64 patients undergoing primary relaparotomy vs 64 undergoing primary catheter drainage: single-organ failure in 13 (20.3%) vs 3 (4.7%) patients (P = .007; RR, 0.15; 95% CI, 0.03-0.60) and multiple-organ failure in 25 (39.1%) vs 10 (15.6%) patients (P = .008; RR, 0.40 (95% CI, 0.20-0.77). At 3 months' follow-up in 50 patients, new-onset diabetes was observed in 22 (44.0%) patients after relaparotomy vs 6 (12.0%) patients after primary catheter drainage (P < .001; RR, 0.27; 95% CI, 0.12-0.57). There were no significant differences in other clinically relevant outcomes occurring after the first intervention for pancreatic fistula (ie, postpancreatectomy hemorrhage, gastroenterostomy leakage, bile leakage, delayed gastric emptying, acute pancreatitis, and new-onset exocrine pancreatic insufficiency) (Table 3).

During the index admission in the matched cohort of 128 patients, completion pancreatectomy was more frequently performed in patients undergoing primary relaparotomy (18 [28.1%]) compared with primary catheter drainage (2 [3.1%]) (P < .001; RR, 0.11; 95% CI, 0.03 to 0.43). After primary relaparotomy, more additional relaparotomies were performed: a total of 54 in 29 patients following primary relaparotomy vs a total of 19 in 14 patients following primary catheter drainage (median difference, 0; 95% CI, −0.46 to 0.46; P = .006). The number of additional catheter drainages was similar in both groups: 57 in 38 patients after relaparotomy vs 90 in 36 patients after catheter drainage (median difference, 1; 95% CI, 0.35 to 1.65; P = .12). The total number of interventions during admission was 213 after relaparotomy vs 195

after catheter drainage (median difference, 1; 95% CI, −2.03 to 0.03; P = .35); of these interventions, 127 vs 150 were indicated owing to pancreatic fistula (median difference, 0; 95% CI, −1.03 to 1.03; P = .17).

More patients were admitted to the ICU after relaparotomy than after primary catheter drainage: 56 (87.5%) vs 24 (37.5%) patients (P < .001; RR, 0.43; 95% CI, 0.31 to 0.59). Length of ICU stay was longer after relaparotomy (median [IQR], 6 [1-13] vs 0 [0-3] days; median difference, 6 days; 95% CI, 3.31 to 8.69; P = .01), as was length of hospital stay (median [IQR], 55 [41-71] vs 29 [19-45] days; median difference, 26 days; 95% CI, 17.44 to 34.56; P = .001). All patients were discharged to their home in good clinical condition. The duration of the pancreatic fistula (ie, time to removal of the last abdominal drain or completion pancreatectomy) was similar in both groups (median [IQR], 37 [14-62] days after relaparotomy vs 29 [17-62] days after primary catheter drainage; median difference, 8 days; 95% CI, −26.73 to 10.7 = 3; P = .71).

Subgroup Analysis Based on APACHE II Score

In each of the 3 subgroups based on APACHE II score (ie, <9, 9-12, and >12), mortality was higher in patients undergoing primary relaparotomy (8 [24.2% vs 14 [10.3%], P = .04; 6 [31.6%] vs 7 [9.5%], P = .02; and 16 [57.1%] vs 4 [23.5%], P = .04, respectively). There was also a significantly higher incidence of new-onset single- and multiple-organ failure in patients after relaparotomy (full details in eTable 2 in the Supplement).

Table 3: Matched clinical endpoints*

Outcome	Catheter Drainage (n=64)	Relaparotomy (n=64)	Risk Ratio (95%CI)	P Value
Death – no. (%)	9 (14)	23 (36)	0.39 (0.20-0.76)	0.007
Secondary endpoints				
Major complications after first intervention POPF – no. (%)				
New-onset single-organ failure	3 (3)	13 (20)	0.15 (0.04-0.61)	0.007
New-onset multiple-organ failure	10 (16)	25 (39)	0.40 (0.21-0.77)	0.008
Post pancreatectomy hemorrhage †	14 (22)	14 (22)	1.00 (0.55-1.81)	>0.99
Gastroenterostomy leakage †	4 (6)	2 (3)	2.00 (0.43-9.33)	0.69
Bile leakage †	5 (8)	8 (13)	0.63 (0.22-1.82)	0.58
Other complications after first intervention POPF – no. (%)				
Delayed gastric emptying ‡				0.36
Grade B	3 (6)	4 (8)		
Grade C	4 (8)	9 (18)		
Acute pancreatitis §	2 (3)	3 (5)	0.66 (0.13-3.33)	>0.99
Long term complications – no. (%)				
New-onset diabetes ‖	6/50 (12)	22/50 (44)	0.27 (0.13-0.58)	<0.001
New-onset exocrine pancreatic insufficiency ‖	16/41 (39)	22/41 (53)	0.72 (0.46-1.16)	0.26

Outcome	Catheter Drainage (n=64)	Relaparotomy (n=64)	Risk Ratio (95%CI)	P Value
Interventions				
Completion pancreatectomy – no. (%)	2 (3)	18 (28)	0.11 (0.03-0.43)	<0.001
No. of additional relaparotomies				0.006
Median (range) per patient	0 (0-5)	0 (0-8)		
Total per study group	19	54		
No. of patients (%)	14 (22)	29 (45)	0.48 (0.27-0.85)	0.01
No. of additional catheter drainages				0.12
Median (range) per patient	1 (0-9)	0 (0-6)		
Total per study group	90	57		
No. of patients (%)	36 (56)	28 (43)	1.29 (0.91-1.82)	0.22
No. of interventions for pancreatic fistula				0.18
Total no. per study group	150	127		
Median (range) per patient	2 (0-9)	2 (1-7)		
No. of interventions during admission				0.35
Total no. per study group	195	213		
Median (range) per patient	2 (0-13)	3 (1-13)		
Hospitalization course				
New ICU admission after first intervention POPF – no. (%)	24 (37)	56 (87)	0.43 (0.31-0.59)	<0.001
Length of ICU stay (median (IQR)) #, ¶	0 (0-3)	6 (1-13)		0.01
Length of hospital stay (median (IQR)) #	29 (19-45)	55 (41-71)		0.001
Duration of pancreatic fistula (median (IQR)) #, **	29 (17-62)	37 (14-62)		0.71

* POPF denotes Postoperative Pancreatic Fistula; ICU denotes Intensive Care Unit, length of ICU stay, hospital stay, and duration of pancreatic fistula was calculated over survivors
† Occurrence any time during admission after first intervention for pancreatic fistula, requiring intervention
‡ Calculated over 50 pairs of patients
§ Defined as elevated serum amylase and lipase in combination with abdominal pain or as seen on CT-scan or during relaparotomy
|| Occurrence within 90 days after date of admission
¶ After first intervention for pancreatic fistula
# Calculated over 36 pairs of survivors
** Time between pancreatoduodenectomy and removal of last abdominal drain or completion pancreatectomy

Discussion

This multicenter matched cohort study showed that primary catheter drainage as the first intervention for severe pancreatic fistula after pancreatoduodenectomy is associated with a better clinical outcome, including lower mortality, less organ failure, fewer additional relaparotomies, and less new-onset diabetes compared with direct relaparotomy. From 2005 to 2013, one-fourth of the patients with severe pancreatic fistula were still treated with primary relaparotomy without a tendency toward a more conservative approach. Primary catheter drainage was successful (ie, survival without the need for relaparotomy) in 77.1% of the patients with severe pancreatic fistula.

To our knowledge, there have been no other studies comparing the first step in the treatment of severe pancreatic fistula. Several small, retrospective studies describe the general treatment of pancreatic fistula.[6,16-21,35] Most of these studies indicate that minimally invasive catheter drainage should be the treatment of choice in these patients. However, the studies also report a relaparotomy rate varying from 15% to 50%, suggesting at least some hesitation to treat pancreatic fistula in a minimally invasive approach. On the contrary, relaparotomy can be performed with good outcomes and might prevent the need for additional interventions during admission.[12,13] Previous studies contain a considerable selection bias that was not adjusted for in statistical analysis. To our knowledge, the present study is the largest data set of patients with severe pancreatic fistula that compares 2 management strategies in a matched cohort.

The success of catheter drainage can be explained by adhering to 2 main surgical principles: adequate source control and no further harm. Pancreatic fistula after pancreatoduodenectomy cause an intra-abdominal fluid collection filled with activated pancreatic juices. If drained adequately, even severe pancreatic fistula could resolve, as shown in 77.1% of the patients in the present study who were successfully treated with primary catheter drainage alone. In addition, catheter drainage is a minimally invasive procedure, which will provoke less surgical trauma (ie, tissue injury and systemic inflammatory response) compared with relaparotomy. Even a moderately small surgical trauma that induces a proinflammatory cytokine response can lead to organ failure in severely ill patients. In our unmatched cohort (eTable 1 in the Supplement), more severely ill patients underwent primary relaparotomy more frequently. These patients were more prone to developing organ failure due to the aforementioned cytokine response. However, even in the matched cohort, 39.1% of the patients developed new-onset multiple-organ failure after relaparotomy compared with just 15.6% of the patients after primary catheter drainage.

The obvious benefit of catheter drainage as the first intervention for severe pancreatic fistula is reduced mortality and prevention of major complications, such as new-onset organ failure. However, there are also other potential benefits from this treatment strategy. Patients in the present study who were treated primarily through relaparotomy more frequently underwent completion pancreatectomy. Consequently, new-onset diabetes was observed more often in patients undergoing primary relaparotomy. This type of diabetes tends to be difficult to control, leaving patients with a considerably elevated risk for severe hypoglycemia.[7,8,16] The main implication of these findings is that, when possible, catheter drainage should be the primary step in management of severe pancreatic fistula. Relaparotomy should be reserved for patients who are not candidates for a minimally invasive intervention or whose condition is progressively worsening with catheter drainage.

One limitation of this study is its retrospective design, causing an inevitable risk of selection bias and confounding. Propensity score matching was used to correct for

this form of bias. This is the best statistical method to mimic a randomized design. However, the success of this matching method is limited by the presence of unknown confounders. We collected extensive data on baseline characteristics to determine the most accurate model for matching. The best matching was achieved by implementing patient characteristics combined with the severity of disease at the time of the first intervention. The matching was successful (ie, resulted in a well-balanced baseline) as presented in Table 2, most importantly with regard to disease severity 24 hours before the first intervention. However, the outcomes of this study should be interpreted with care, for there was no assessment of effect modification or interaction between the covariates included in the matching procedure, and no correction for multiple testing was performed. To ensure the success of matching, it was not possible to include all patients undergoing primary relaparotomy. We were able to match 64 of 82 patients: 2 were excluded because of missing essential data for matching and 16 could not be matched to an equivalent cohort undergoing primary catheter drainage. There is a chance that these excluded patients have a biologically different type of fistula that could not have been managed successfully through catheter drainage. To minimize the risk of missing a certain subgroup of patients with matching, we performed a predefined subgroup analysis of all 309 patients with severe pancreatic fistula based on their APACHE II score 24 hours before the first intervention. Mortality was significantly higher in all subgroups in patients undergoing primary relaparotomy (eTable 2 in the Supplement).

Our results should ideally be confirmed by a large, randomized clinical trial. However, we question whether there is justification for such a trial since minimally invasive treatments are gaining popularity and seem to have few downsides. Because patients seem to benefit from early catheter drainage and, therefore, from early standardized detection of pancreatic fistula, we believe that future studies should focus on a sufficiently aggressive diagnosis and minimally invasive treatment of pancreatic fistula.

In this multicenter study on a matched cohort of patients, catheter drainage was superior to relaparotomy as the primary intervention for pancreatic fistula after pancreatoduodenectomy because primary catheter drainage was associated with lower mortality. Therefore, when minimally invasive drainage is feasible, primary catheter drainage should be the first step in treatment of severe pancreatic fistula.

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Responses to

Management of Severe Pancreatic Fistula after Pancreatoduodenectomy

"Step-Up Approach" for the Treatment of Postoperative Severe Pancreatic Fistula. Is It Really Possible and Useful?

E Rangelova, R Valente, M Del Chiaro

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Postoperative pancreatic fistula (POPF) remains the Achilles heel after pancreaticoduodenectomy and primary cause of operation-related death. At this time, there are no surgical techniques or specific medical treatments that can overcome the problem of POPF. Therefore, the correct approach to treatment of severe POPF is crucial to reduce the mortality and morbidity after pancreatic surgery. Smits and coauthors[1] suggest that percutaneous catheter drainage as the first interventional procedure for "relevant" POPF could improve clinical outcomes, compared with the use of relaparotomy. Even though this therapeutic approach to severe POPF is interesting, the data presented by the authors should be critically analyzed. The definition of "severe" POPF comprises what ISGPF[2] regards as types B and C fistulae. These categories include the wide range of patients in whom the fistula would resolve by leaving the operative drains in place longer, without further intervention, in patients with systemic inflammatory response syndrome, sepsis, and organ failure in whom completion pancreatectomy could be the only chance for rescue. In the Smits et al[1] study, the group that underwent relaparotomy seems to have a higher comorbidity burden, higher American Society of Anesthesiologists class, more severe systemic inflammatory response syndrome, and a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score before intervention compared with the primary catheter drainage group. Moreover, the use of the APACHE II score as a means for stratification of the patients in the matching subgroups is debatable. Although a relevant prognostic score for the severity of acute pancreatitis, the APACHE II scale has not been proven to accurately correlate with POPF-related morbidity after pancreatic surgery, as do most of the other widely used physiologic prognostic scores (eg, POSSUM, Apgar).[3,4] In addition, Gueroult et al[5] note that severely ill patients with postoperative peritonitis due to POPF who would require relaparotomy would generally have a mean APACHE II score of 18.6, which is significantly higher than the less than 9 and greater than 12 cutoff levels used in the Smits et al study. Finally, relaparotomy as the first intervention included solely open drainage in just half of the patients. The reason why open surgery was primarily needed, such as inability to access a peripancreatic collection by interventional radiology, personal preference of the surgeon, or patients'

deterioration, was not clarified. Clearly, the first 2 options should not be an indication for relaparotomy for most patients; instead, relaparotomy should probably be reserved for patients with severe POPF requiring completion pancreatectomy.

The study of Smits and colleagues[1] sends an important message: percutaneous drainage for POPF is an effective therapeutic method. The "step-up approach" in the management of this complication is probably preferable to direct surgery in patients without severe general sequelae from POPF. In our opinion, relaparotomy and completion pancreatectomy is a valuable, and sometimes necessary, tool for the treatment of severe POPF. The best timing and type of surgery for POPF remain issues that should be investigated in large prospective studies.

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Nonoperative Management of Pancreatic Fistula. Why Not an Endoscopic Approach?

TH Baron, RA Kozarek

JAMA Surg. 2018;153(1):94

To the Editor We read with interest the article in JAMA Surgery by Smits et al[1] and accompanying Editorial by Rangelova et al[2] on management of severe pancreatic fistula following pancreaticoduodenectomy. Although it is appreciated that percutaneous drainage is widely available as a nonoperative management strategy, we were quite surprised by the near complete omission of endoscopic therapy as a management strategy.

Endoscopic therapy for such leaks is performed routinely in tertiary care centers, and it can obviate surgery as well as avoid external drains and the formation of external fistula. Pancreatic fistula that develop into pancreatic fluid collections are often amenable to transmural drainage (transgastric or transjejunal), with or without endoscopic ultrasound guidance. Endoscopic therapy can also be used as an adjuvant to percutaneous drains for free fluid leaks, as the drain tract can be punctured transmurally using endoscopic ultrasound guidance and internalized. Additionally, endoscopic ultrasound–guided transgastric puncture of the pancreatic duct is also feasible to create a pancreaticogastrostomy to internalize pancreatic duct drainage.[3] Finally, balloon enteroscopes allow retrograde access to the surgical pancreaticojejunal anastomosis for pancreatic ductal therapy and internal stent placement.[4,5] Only 1 patient in the study by Smits et al[1] mentions a transgastric drainage. It would be interesting to know how many patients in their series would have been amenable to 1 or more of the endoscopic approaches mentioned in this letter.

The 2 articles in JAMA Surgery[1,2] illustrate the void in knowledge of new technology and procedures among surgical, radiologic, and endoscopic disciplines. Further refinements in endoscopic procedures are likely. Ultimately, more widespread availability of complex endoscopic procedures and the knowledge of their existence will allow dissemination of these approaches into the management of complex postpancreatic surgical complications.

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Nonoperative Management of Pancreatic Fistula—Reply

FJ Smits, HC van Santvoort, IQ Molenaar

JAMA Surg. 2018;153(1):94-95

In Reply We appreciate the comments by Baron and Kozarek and this opportunity to discuss the issues raised. The authors, both with a vast experience in endoscopy, make a plea for the use of an endoscopic approach for minimally invasive drainage in patients with postoperative pancreatic fistula. Endoscopic drainage for the management of symptomatic walled-off necrosis in patients with acute pancreatitis has gained popularity over the past years.[1,2] We fully agree that endoscopic drainage can also be valuable in the management of symptomatic postoperative pancreatic fistula. However, collections in necrotizing pancreatitis may differ from collections in patients with postoperative pancreatic fistula. The latter frequently occur within the first week after surgery and are often not well encapsulated at the time of clinical indication for drainage, which may require advanced technical endoscopic expertise. To our knowledge, there are currently no studies comparing outcomes of endoscopic drainage with percutaneous catheter drainage in the management of postoperative pancreatic fistula. This might be an explanation for the limited use of endoscopic drainage in our practice in the Netherlands.

In the current study,[3] we compared minimally invasive drainage with relaparotomy as first intervention for postoperative pancreatic fistula. In this cohort, a total 4 of 309 patients (1.3%) underwent endoscopic drainage at some time during admission to manage pancreatic fistula. Unfortunately, because this is a retrospective study, we do not have data on the number of patients who were amendable for endoscopic drainage. However, the evaluation of different approaches for minimally invasive drainage (ie, endoscopic vs percutaneous) has gained our interest. The Dutch Pancreatic Cancer Group is currently designing a stepped-wedge cluster randomized trial (ie, the PORSCH trial) to evaluate the implementation of a best practice algorithm for management of postoperative pancreatic fistula. This nationwide study will also evaluate minimally invasive drainage through endoscopic techniques.

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Chapter 7

Predicting Successful Catheter Drainage in Patients With Pancreatic Fistula After Pancreatoduodenectomy

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ABSTRACT

Objective
To identify predictors for successful minimally invasive catheter drainage (i.e. survival without relaparotomy) for pancreatic fistula after pancreatoduodenectomy.

Methods
Included were consecutive patients undergoing catheter drainage as first intervention for pancreatic fistula after pancreatoduodenectomy (2005-2013) in 9 Dutch centers. Possible prognostic factors for successful catheter drainage (i.e. survival without relaparotomy) were selected using Akaike Information Criterion.

Results
Included were 227 patients after 2196 pancreatoduodenectomies. Primary catheter drainage was successful in 175/227 patients (77%). Multivariable logistic regression revealed the following negative prognostic factors for success: male sex (odds ratio [OR] 0.46, 95% confidence interval [CI], 0.21-1.00, P = 0.049), higher age (for every 5 years over 50; OR, 0.69; 95% CI, 0.57-0.84; P < 0.001) and respiratory failure at time of catheter drainage (OR, 0.10; 95% CI, 0.03-0.33, P < 0.001). A prognostic model incorporating these factors yielded an area under the curve of 0.76 and demonstrated a success range of 98-14%.

Conclusions
Male sex, higher age and respiratory failure are associated with a low success rate of catheter drainage in patients with pancreatic fistula after pancreatoduodenectomy. These patients might benefit form an intensified postoperative monitoring for early detection and management of pancreatic fistula to prevent respiratory failure.

INTRODUCTION

In patients with pancreatic malignancy, resection followed by adjuvant chemotherapy provides the best chance of long term survival.[1–3] Pancreatic surgery, however, is complex and associated with a high risk of postoperative complications.[4–6] One of the most severe complications is postoperative pancreatic fistula, in which there is leakage of enzyme rich pancreatic juice into the abdomen.[7–9] A large meta-analyses demonstrated an incidence of clinically relevant pancreatic fistula of 12% after pancreatoduodenectomy.[10]

Leakage of enzyme rich fluid might cause bleeding through vessel erosion and a systemic inflammatory response, potentially leading to organ failure and death.[7,8,11] To prevent these severe complications, clinically relevant pancreatic fistula should be identified at an early stage and treatment should be prompt. Invasive management of clinically relevant pancreatic fistula is either through relaparotomy or minimally invasive catheter drainage. A minimally invasive management strategy, with percutaneous catheter drainage as the first step, appears to be the best approach. Percutaneous catheter drainage is associated with a better clinical outcome, including lower mortality, as compared to primary relaparotomy.[12–14] However, despite efforts to optimize the management of pancreatic fistula, clinically relevant postoperative pancreatic fistula is still associated with a mortality of 18 to 39%.[6,8,13,15]

One of the difficulties in the management of pancreatic fistula is the early distinction of a biochemical leak, a clinically relevant but mild leak and the life threatening subtype of pancreatic fistula.[7,8,11] According to the International Study Group on Pancreatic Surgery definition, all types include efflux of amylase rich fluid through an abdominal drain. However, only patients with a clinically relevant leak require a change in postoperative management.[9] Inadequate management of pancreatic fistula increases the risk of progression to the life threatening subtype, with a high risk of bleeding, organ failure and death. In this subgroup, patients clinically deteriorate under initial treatment (i.e. minimally invasive catheter drainage) and often require a relaparotomy.[16,9] Early identification of this subgroup of patients can be useful in patient counselling and communication with clinicians and to determine the postoperative management strategy for pancreatic fistula in an individual patient.

Therefore, the aim of this study is to identify predictors for successful minimally invasive catheter drainage (i.e. survival without relaparotomy) as first invasive intervention in the treatment of postoperative pancreatic fistula after pancreatoduodenectomy.

METHODS

Design and Study Population

For this retrospective observational study, a cohort of 328 consecutive patients with severe pancreatic fistula after pancreatoduodenectomy (January 2005 to September 2013) in 9 centers of the Dutch Pancreatic Cancer Group (DPCG) were evaluated for eligibility. Clinical outcomes of this cohort were previously described.13 This study was reviewed by the medical ethical committee and the need for informed consent was waived.

This study was conducted in accordance to the TRIPOD statement.[17] Included in the current analysis were all patients undergoing prolonged (i.e. discharge with preoperatively placed drain in place) or additional minimally invasive catheter drainage as primary intervention for pancreatic fistula after pancreatoduodenectomy. Excluded were patients undergoing relaparotomy as primary intervention for pancreatic fistula (see inclusion flow chart figure 1). Success of catheter drainage was defined as in-hospital survival without the need for relaparotomy. Pancreatic fistula was defined in accordance to the International Study Group on Pancreatic Fistula.[18] All relevant definitions were provided in table 1.

Data Collection

All data were retrospectively collected for the initial analysis using a predefined, standardized case record form through systematic patient file search or from existing prospective databases. The following baseline characteristics were evaluated: patient demographics (i.e. sex, age, American Society of Anesthesiologists [ASA] classification on admission, Body Mass Index [BMI], preoperative weight loss, preoperative cholestasis (i.e. jaundice, increased bilirubin level and the need for preoperative biliary drainage)), pancreatoduodenectomy details (i.e. procedure, operative time, placement of surgical abdominal drain), first postoperative serum amylase level, postoperative pathology diagnosis (i.e. pancreatic adenocarcinoma or pancreatitis vs. other diagnoses), disease severity at 24 hours or less before primary minimally invasive catheter drainage for pancreatic fistula (i.e. Acute Physiology and Chronic Health Evaluation II [APACHE II] score[19], systemic inflammatory response syndrome [SIRS], white blood cell count and organ failure [i.e. pulmonary, renal or circulatory failure]). Additionally, number of invasive interventions before first intervention for pancreatic fistula and timing of first catheter drainage for pancreatic fistula (i.e. days after index pancreatic resection), in-hospital mortality and the need for relaparotomy after primary catheter drainage were collected. Length of follow-up was equal to length of index admission, in which readmission within 10 days after discharge was considered to be part of the index admission.All definitions are provided in table 1.

Table 1: Definitions

Outcome	Definition
Success of catheter drainage	Discharge alive without need for relaparotomy
Postoperative pancreatic fistula	Amylase in drain fluid on or after postoperative day three of at least three times the upper level of normal serum amylase[4]
Clinically relevant pancreatic fistula	Requiring prolonged (i.e. discharge with preoperatively placed drain in place) or additional minimally invasive catheter drainage or relaparotomy (with e.g. surgical drainage or completion pancreatectomy)
Preoperative cholestasis	Need for preoperative biliary drainage; jaundice at physical examination or elevation of last preoperative bilirubin over upper limit of normal serum value.
Organ failure	Adapted from Bardley[13]
Pulmonary	PaO2 <60 mmHg, despite FiO2 of 0.3, or need for mechanical ventilation
Circulatory	Systolic blood pressure <90 mmHg, despite adequate fluid resuscitation, or need for inotropic support
Renal	Creatinine level >177 μmol/liter after rehydration or need for hemofiltration or hemodialysis

FiO2 denotes fraction of inspired oxygen, PaO2 partial pressure of arterial oxygen

Statistical Analysis

Patients were divided into two groups based on the success of catheter drainage. The relation between possible predictors and success of catheter drainage was evaluated using univariable logistic regression analysis. All predictors possibly associated with the success of catheter drainage in univariable analysis ($P < 0.1$) were included in multivariable logistic regression analysis. The Akaike Information Criterion (AIC), combining the number of variables in the model and the likelihood function, was used to determine the best performing model. The lower the AIC, the better the model fit for the prognostic model.[20] The discriminatory ability of the model was expressed in the area under the curve (AUC) in the receiver operating characteristics curve (ROC). The model was internally validated using 500 bootstrap resamples. Regression coefficients obtained for the multivariable logistic regression analysis were visualized in a nomogram. This nomogram provides prognostic information on the predicted success of catheter drainage for each patient.

To utilize a complete dataset for logistic regression, we used multiple imputation for missing data in baseline characteristics. Initial analysis showed missing data in BMI (7%), weight loss (4%), length of surgery (3%), first postoperative serum amylase (18%) and white blood cell count (2%). The imputation model was created using all baseline characteristics as predictors. Pooled data from the imputed dataset with five dummy cases for each patient were used for the construction of a prediction model. After checking assumptions in the possible predictors, age was transformed into steps for every 5 years and was truncated. The cut points (i.e. <50 years and >80 years, respectively) were based on clinical relevance and chosen so every group contained at least 10 patients.

Normally distributed continuous data were presented as mean with standard deviation (±SD), data with skewed distribution as median with interquartile range (IQR). Outcomes of regression analysis are presented as odds ratio (OR) with a 95% confidence interval (CI).

A 2-tailed P < 0.05 was considered statistically significant. All analyses were performed in SPSS version 21.0 (Chicago, IL).

RESULTS

Patients

In the entire cohort of 2196 consecutive patients undergoing pancreatoduodenectomy, 328 patients (15%) developed clinically relevant pancreatic fistula (Grade B/C). Clinical outcomes of this cohort were described previously.[13] Included in this analysis were all 227 consecutive patients undergoing catheter drainage as first intervention for pancreatic fistula. Catheter drainage was successful (i.e. survival without the need for relaparotomy) in 175 patients (77%). Forty patients (18%) underwent one or more relaparotomies after primary catheter drainage. Completion pancreatectomy was performed in 7 patients (3%). Mortality during admission in patients undergoing primary catheter drainage for pancreatic fistula was 11% (25 patients), 12 of these patients died without undergoing a relaparotomy (see figure 1).

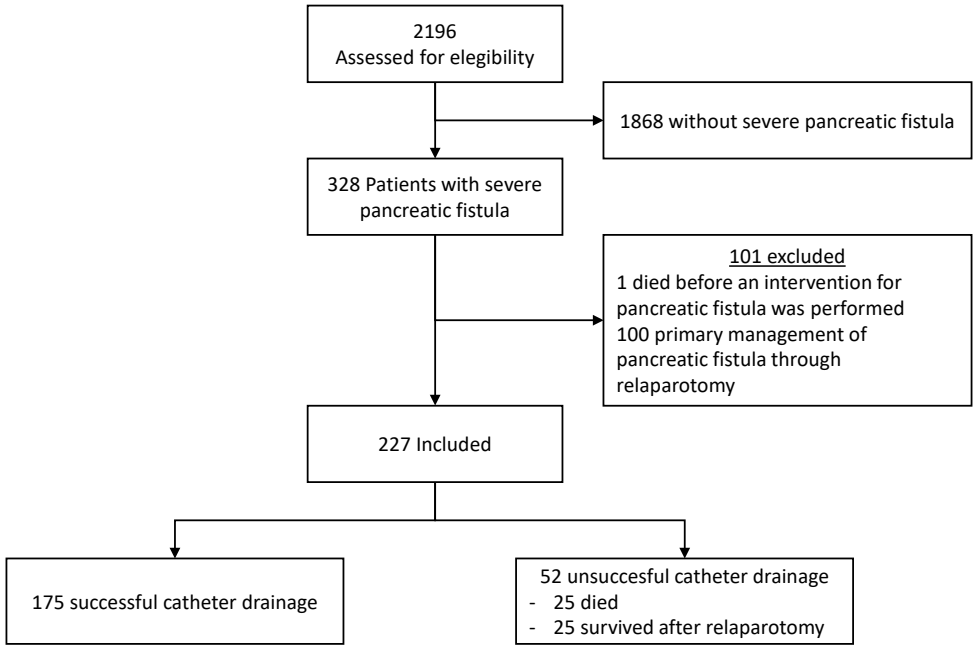

Figure 1. Flow chart of patient inclusion

Baseline characteristics are shown in table 2. The first catheter drainage was performed at a median of 9 days after pancreatoduodenectomy (IQR, 6-13). Catheter drainage was performed percutaneous in 196 patients (86%) and transgastric in 2 patients (1%). A total of 29 patients (13%) were discharged with the peroperatively placed drain in place without undergoing additional catheter drainage. In 121 patients (53%) one drainage procedure was performed, 47 patients (21%) underwent 2 drainages, 22 patients (10%) underwent 3 drainages and 37 patients (16%) underwent 4 or more drainage procedures. A median of 1 invasive intervention was performed to resolve pancreatic fistula (IQR, 1-3). Clinical outcomes are presented in Table 3.

Table 2: Baseline Characteristics*

Characteristics	Primary catheter drainage (n=227)
Male sex – no. (%)	147 (65)
Age – yr (median (IQR))	65 (59-72)
ASA classification on admission – no. (%)	
I: healthy status	50 (22)
II: mild systemic disease	150 (66)
III: severe systemic disease	27 (12)
Body-mass index (mean ±SD) †	26.4 ±3.6
Preoperative weight loss – kg. (median (IQR)) ‡	2 (0-6)
Preoperative cholestasis – no. (%) ‖	165 (73)
Jaundice – no. (%)	137 (60)
Serum bilirubin – µmol/L (median (IQR)) §	15.5 (8.0-56.8)
Biliary drainage – no. (%)	122/226 (54)
Pancreatoduodenectomy details	
Pylorus preserving pancreatoduodenectomy – no. (%)	183 (81)
Operative time – minutes (median (IQR)) #	294 (241-373)
Placement surgical abdominal drain – no. (%)	225 (99)
First postoperative serum amylase – U/L (median (IQR)) **	295 (58-657)
Low risk pathologic disease (i.e. pancreatic adenocarcinoma or pancreatitis) – no. (%)	62 (27)
Disease severity 24h before first intervention	
APACHE II score (median (IQR)) ††	8 (6-10)
SIRS – no. (%) ‡‡	99 (44)
White blood cell count (x10^9/L) – median (IQR) §§	15 (12-21)
Organ failure – no. (%)	27 (12)
Respiratory failure – no. (%)	17/226 (8)
Renal failure – no. (%)	11 (5)
Circulatory failure – no. (%)	9 (4)
Previous invasive interventions – no. (%)	10 (4)
Timing first catheter drainage after resection (days; median (IQR))	9 (6-13)

* Normal distributed values are presented as mean ±SD, ASA denotes American Society of Anesthesiologists
† Body-mass index, weight in kilograms divided by the square of the height in meters; calculated in 212 patients
‡ Calculated in 220 patients
‖ Defined as jaundice, elevated bilirubin and/or need for preoperative biliary drainage
§ Last peroperative value; calculated in 172 patients
# Calculated in 220 patients
** Measured within the first 3 days after resection, calculated in 187 patients
†† Acute Physiology and Chronic Health Evaluation (APACHE II) scale from 0-71, higher scores for more severe disease
‡‡ Systemic inflammatory response syndrome as defined by the American College of Chest Physicians and the Society of Critical Care Medicine
§§ Calculated in 222 patients

Table 3: Clinical outcomes*

Outcome	Primary catheter drainage (n=227)
Death – no. (%)	25 (11)
Major complications after first intervention POPF – no. (%)	58 (26)
New-onset single-organ failure – no. (%)	46 (20)
New-onset multiple-organ failure – no. (%)	25 (11)
Post pancreatectomy hemorrhage – no. (%) †	40 (18)
Gastroenterostomy leakage – no. (%) †	5 (2)
Bile leakage – no. (%) †	17 (8)
Other complications after first intervention POPF – no. (%)	
Delayed gastric emptying – no. (%) ‡	
Grade B	0 (0)
Grade C	23 (11)
Acute pancreatitis – no. (%) §	11 (5)
Long term complications – no. (%)	
New-onset diabetes – no. (%) ‖	28 (14)
New-onset exocrine pancreatic insufficiency – no. (%) ‖	85 (43)
Hospitalization course	
New ICU admission after first intervention POPF – no. (%)	67 (30)
Length of ICU stay (median (IQR)) ¶, #	0 (0-2)
Length of hospital stay (median (IQR)) #	29 (21-48)
Duration of pancreatic fistula (median (IQR)) #, **	28 (17-51)

* POPF denotes Postoperative Pancreatic Fistula; ICU denotes Intensive Care Unit, length of ICU stay, hospital stay, and duration of pancreatic fistula was calculated over survivors

† Occurrence any time during admission after first intervention for pancreatic fistula, requiring intervention

‡ Calculated over 186 patients

§ Defined as elevated serum amylase and serum lipase in combination with abdominal pain or as seen on CT-scan or during relaparotomy

‖ Occurrence within 90 days after date of admission¶ After first intervention for pancreatic fistula

Calculated over survivors

** Time between pancreatoduodenectomy and removal of last abdominal drain or completion pancreatectomy

Prediction of successful catheter drainage

Outcomes of univariable logistic regression are shown in Supplementary Table 1, http://links.lww.com/MPA/A726. Potential negative predictors for successful catheter drainage ($P < 0.1$ in univariable logistic regression) were: male sex, higher age, preoperative cholestasis, APACHE II score, the presence of any form of organ failure and the presence of respiratory failure at time of first intervention. In multivariable analysis, the best performing model (i.e. with the lowest AIC) included the following negative predictors: male sex (OR, 0.46; 95% CI, 0.21-1.00; $P = 0.049$); higher age (i.e. for every additional 5 years over 50, truncated at 80; OR, 0.70; 95% CI, 0.57-0.84; $P < 0.001$); and the presence of respiratory failure in 24 hours before first catheter drainage (OR, 0.10; 95% CI, 0.03-0.33; $P < 0.001$). This model was internally validated using 500 bootstrap resamples, showing no major indication for bias. Therefore, all variables were included in the final model (table 4). This model yielded an AUC of 0.76 (95% CI, 0.68-0.83; see Supplementary Fig. 1, http://links.lww.com/MPA/A726).

Table 4: Risk Prediction Model for Success of Catheter Drainage *

Characteristics	Odds ratio (95% confidence interval)	Regression coefficient	P	Points
Sex (male vs. female)	0.46 (0.21-1.00)	-0.78	0.049	2
Age (continuous; per 5 years; from 50 up to 80 years)	0.69 (0.57-0.84)	-0.37	<0.001	0 to 7
Respiratory failure at time of intervention (yes vs. no)	0.10 (0.03-0.33)	-2.26	<0.001	6
Intercept: 3.78				

The prognostic value of each of these variables is visualized in a nomogram in figure 2. This nomogram was designed using intercept and regression coefficients of the independent predictors in the final model. Each patient is awarded a number of points based on their characteristics at time of intervention (e.g. 0 points for reference values; 2 points for male sex, 0 to 7 points for every 5 years over 50 years of age and 6 points for the presence of respiratory failure at time of first intervention). The sum of these points correlates to a predicted percentage for the success of catheter drainage: for example, a female patient of 49 years without respiratory failure has a success chance of 98% (0 points); a male patient of 85 years with respiratory failure has a success chance of only 14% (15 points).

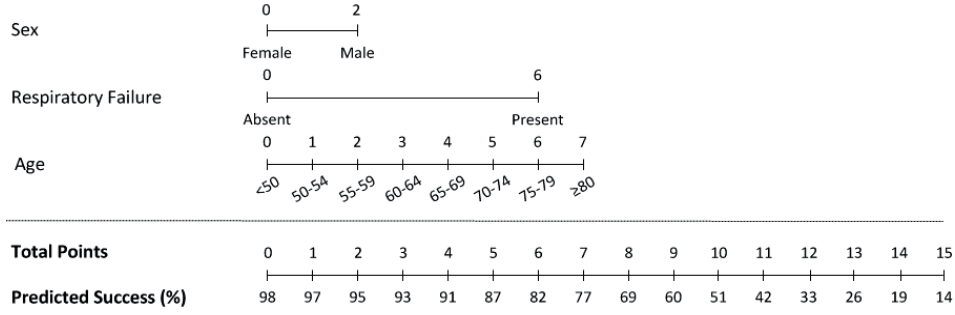

Figure 2. Nomogram for successful catheter drainage as first step in management of grade B/C pancreatic fistula after pancreatoduodenectomy. The presence or absence of each predictor is awarded points. The sum of these points (0 to 15 points) represents a success percentage of catheter drainage (98% to 14% respectively). The probability of success of catheter drainage can be read from the bottom ruler shown in this figure.

DISCUSSION

In this multicenter cohort of patients undergoing minimally invasive drainage for pancreatic fistula after pancreatoduodenectomy, male sex, higher age and the presence of respiratory failure were negatively associated with the success of catheter drainage (i.e. survival without the need for relaparotomy). For respiratory failure is the only independent predictor that can be influenced, we believe clinical outcomes could be

improved through implementation of an intensified postoperative monitor strategy focused on early detection and early catheter drainage for pancreatic fistula before the phase of respiratory failure. In addition, the proposed nomogram can be used to provide information on individual patient prognosis in patient counselling and communication with clinicians.

Even though the relation of these predictors with relaparotomy is not clear in patients undergoing pancreatic resection, all have been associated with the worst outcome in previous studies in other diseases. Male patients appear to be at greater risk of developing sepsis and are treated more aggressively, tend to undergo more invasive interventions and are more frequently admitted to the ICU.[21–23] The sex difference in outcome might be explained by the combination of chronic disease burden, social and environmental factors and genetic predisposition causing differences in the host immune response.[24] Higher age has been associated with more severe sepsis and increased mortality in critically ill patients, possibly partly due to comorbidity.[19,21,25] Organ failure can be considered a sign of more advanced stage of systemic inflammation, which could in itself be associated with a worse clinical outcome.[19,21] We only found a negative association between respiratory failure and successful drainage. This might be explained by the fact that renal and circulatory failure occurred less often (see table 2). These data suggest that early signs of sepsis, especially in elderly men, should promote a more aggressive search for and treatment of clinically relevant pancreatic fistula, for pre-emptive minimally invasive catheter drainage may prevent organ failure and subsequent mortality.

This study has several limitations. Because this was a retrospective study, there is an inevitable risk of confounding by indication. To limit the effect of bias, we have analyzed only objective, predefined predictors for success of catheter drainage (table 1). Multiple imputation was used to deal with missing data and therefore we were able to include 226 complete cases in the logistic regression model. All patients were selected from 9 out of the 18 hospitals performing pancreatic surgery in the Netherlands. Even though we believe the sample is representative for the other 9 hospitals, this could limit the external validity of this study. Finally, although we performed an internal bootstrap validation of our results, ideally this model should be validated in an external cohort.

This study demonstrates the importance of good clinical decision-making, for respiratory failure is the only negative predictor for successful drainage that can be influenced. Future studies should focus on early adequate management of postoperative pancreatic fistula to prevent respiratory failure. Strict protocols to perform diagnostic imaging based on biochemical and clinical inflammatory parameters in the early postoperative phase after pancreatoduodenectomy should be evaluated to determine whether early management of pancreatic fistula can prevent organ failure and ultimately improves clinical outcome in these patients. The nationwide PORSCH trial aims to determine if an intensified, standardized 'best practice' algorithm for early detection and minimally

invasive management of pancreatic fistula leads to less major complications and mortality after pancreatic resection (NCT03400280).

Furthermore, this prediction model can be used to provide information on the prognosis of the individual patient. This information can help the clinician in communication with patients and their family and with fellow clinicians. It should be stressed that the proposed nomogram is not supposed to discourage a minimally invasive approach in patients with a low predicted success chance (i.e. elderly men with respiratory failure), for even those patients could benefit from a minimally invasive approach over relaparotomy.[13]

This study shows that the success of catheter drainage in patients with clinically relevant pancreatic fistula after pancreatoduodenectomy can accurately be predicted by using sex, age and respiratory failure. Emphasis of future studies should be on the impact of intensive monitoring of patients to utilize early adequate management of pancreatic fistula before the phase of respiratory failure.

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Chapter 8

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[1]. 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[2]. 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[3].

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[4]. Completion pancreatectomy is the most aggressive strategy which aims to remove completely the focus 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[5,6]. Few studies have been performed on the clinical outcomes of different surgical strategies in patients with pancreatic fistula after pancreatoduodenectomy[4].

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[7] 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[8].

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[9]. In addition, an existing database[2] 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[10]. 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[11,12]. SIRS was considered in cases of two or more positive criteria[12]. 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[13–15]. 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[16]. 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[17]. 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 (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).

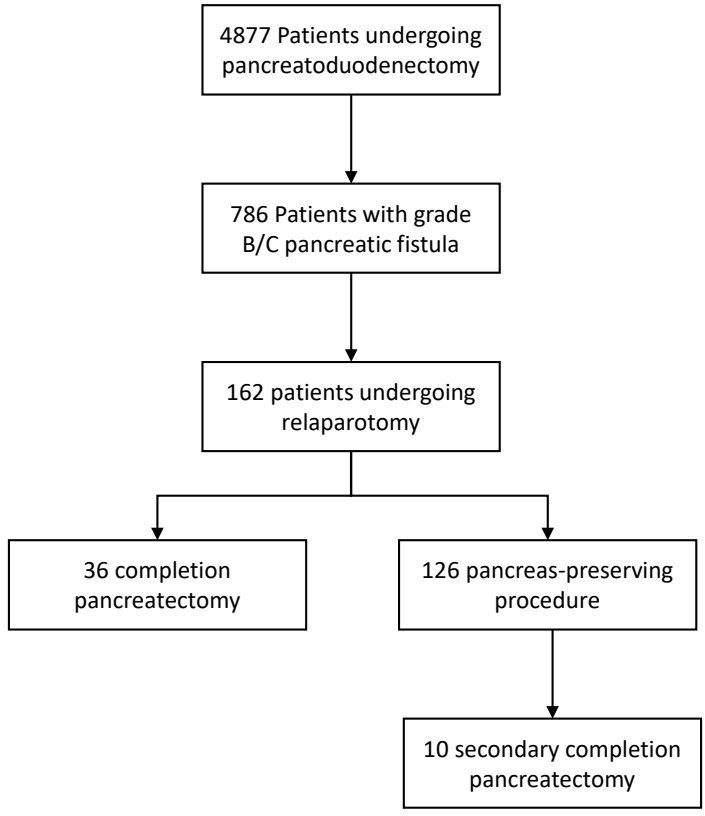

Figure 1 Flow chart of patient selection

Table 1. Baseline characteristics by surgical strategy for pancreatic fistula

	Completion pancreatectomy		Pancreas- preserving		
	N	**%**	**N**	**%**	**P-value**
Total	**36**	**22.2**	**126**	**77.8**	**-**
Sex – female	8	22.2	36	28.6	0.45
Age – median (IQR)	70 (66 - 73)		64 (58 - 71)		0.025
BMI – medina (IQR) *	26.8 (24.2 - 28.9)		26.1 (23.4 - 28.7)		0.45
ASA III or IV	13	36.1	26	20.6	0.06
Type of resection					
Whipple	11	30.6	28	22.2	0.30
PPPD	25	66.4	96	77.8	
Vascular resection	4	11.1	7	5.6	0.24
Additional organ resection	4	11.1	16	12.7	0.80
Pancreatic anastomosis	28	77.8	113	89.7	0.11
Duct-to-mucosa PJ					
Duct-to-mucosa PG	0		1	0.8	
Dunking PJ	8	22.2	12	9.5	
Pathology	12	33.3	39	31.0	0.79
Pancreatic cancer/pancreatitis					
Other	24	66.7	87	69.0	
Previous reintervention	17	47.2	57	45.2	0.83
Radiological intervention	15	41.7	52	41.3	0.97
Relaparotomy	5	13.9	7	5.6	0.09
Previous reintervention for PPH	6	16.7	12	9.5	0.23
Radiological intervention for PPH	5	13.9	10	12.6	0.28
Relaparotomy for PPH	1	2.8	2	1.6	0.64
Organ failure 24h before*					0.035
Single	6	16.7	39	31.5	
Multiple	11	30.6	17	13.7	
APACHE II score 24h before – median (IQR)*	14 (10 - 18)		12 (8 - 15)		0.06
Postoperative day of initial relaparotomy for POPF – median (IQR)	10 (4 - 14)		9 (6 - 14)		0.50

Abbreviations: POPF: postoperative pancreatic fistula; BMI: Body Mass Index; IQR: interquartile range; ASA: American Society of Anesthesiologists; PPPD: pylorus-preserving pancreatoduodenectomy ; PJ: pancreatojejunostomy; PG: pancreatogastrostomy; PPH: postpancreatectomy haemorrhage; APACHE: Acute Physiology And Chronic Health Evaluation; IQR: interquartile range; ICU: Intensive Care Unit

*Missing data: BMI (N=6), organ failure 24h before (N=2), highest APACHE II score 24h before (N=14),

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).

Table 2. Main outcomes by surgical strategy for pancreatic fistula

	Completion pancreatectomy		Pancreas-preserving		
	N	**%**	**N**	**%**	**P-value**
Total	**36**	**22.2**	**126**	**77.8**	
Mortality	19	52.8	38	30.2	0.012
Organ failure 24h after*					0.17
Single	5	13.9	26	21.0	
Multiple	25	69.4	64	51.6	
Highest APACHE II score 24h after – median (IQR)*	18 (15 - 23)		15 (11 - 18)		<0.001
ICU admission	35	97.2	107	84.9	0.048
Duration ICU admission – median (IQR)	13 (3 - 32)		7 (2 - 17)		0.09
Additional reintervention	23	63.9	84	66.7	0.76
Radiological intervention	16	44.4	71	56.3	0.21
Relaparotomy	14	38.9	40	31.7	0.42
Secondary completion pancreatectomy	-	-	10	7.9	
Additional reintervention for PPH	6	16.7	21	16.7	>0.99
Radiological intervention for PPH	2	5.6	12	9.5	0.46
Relaparotomy for PPH	4	11.1	10	7.9	0.55
Duration of hospital stay – median (IQR)	38 (24 - 61)		53 (31 - 66)		0.07
Duration of hospital stay in survivors – median (IQR)	55 (31 - 70)		56 (40 - 71)		0.59
New onset pancreatic exocrine insufficiency in survivors*	-	-	32	43.2	-
New onset postoperative diabetes mellitus in survivors*	-	-	19	25.7	-

Abbreviations: POPF: postoperative pancreatic fistula; APACHE: Acute Physiology And Chronic Health Evaluation; IQR: interquartile range; ICU: Intensive Care Unit; PPH: postpancreatectomy haemorrhage

*Missing data: organ failure 24h after (N=2), highest APACHE II score 24h after (N=28), new onset postoperative pancreatic exocrine insufficiency (N=14), new onset postoperative diabetes mellitus (N=14)

Table 3. Multivariable analysis for mortality

	Odds ratio	95% CI	P-value
Completion pancreatectomy during initial relaparotomy	2.44	1.02 - 5.85	0.045
Sex - female	1.61	0.71 - 3.68	0.26
Age	1.08	1.03 - 1.14	0.001
BMI*	1.01	0.92 - 1.11	0.88
ASA score III or IV	0.83	0.36 - 1.96	0.68
Previous reintervention	1.04	0.50 - 2.18	0.92
Organ failure 24h before*			
Single organ	1.32	0.58 - 3.14	0.53
Multiple organ	2.35	0.87 - 6.36	0.09

Abbreviations: CI: confidence interval; BMI: Body Mass Index; ASA: American Society of Anesthesiologists
*Missing data: BMI or organ failure 24h before (N=7)

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.

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).

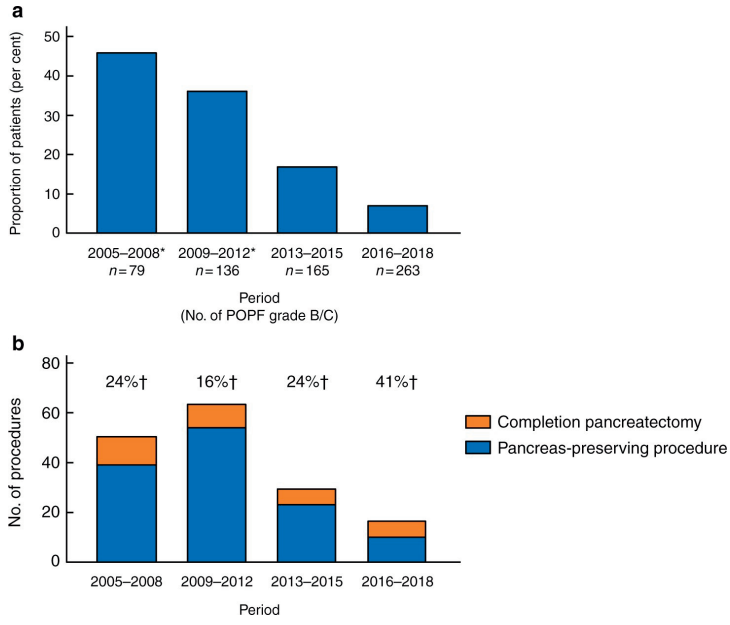

Figure 2. a Proportion of patients undergoing relaparotomy for postoperative pancreatic fistula (POPF). $P < 0.001$ for χ^2 for linear trend. b Proportion of patients undergoing completion pancreatectomy or a pancreas-preserving procedure during relaparotomy for pancreatic fistula. $P = 0.228$ for χ^2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

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).

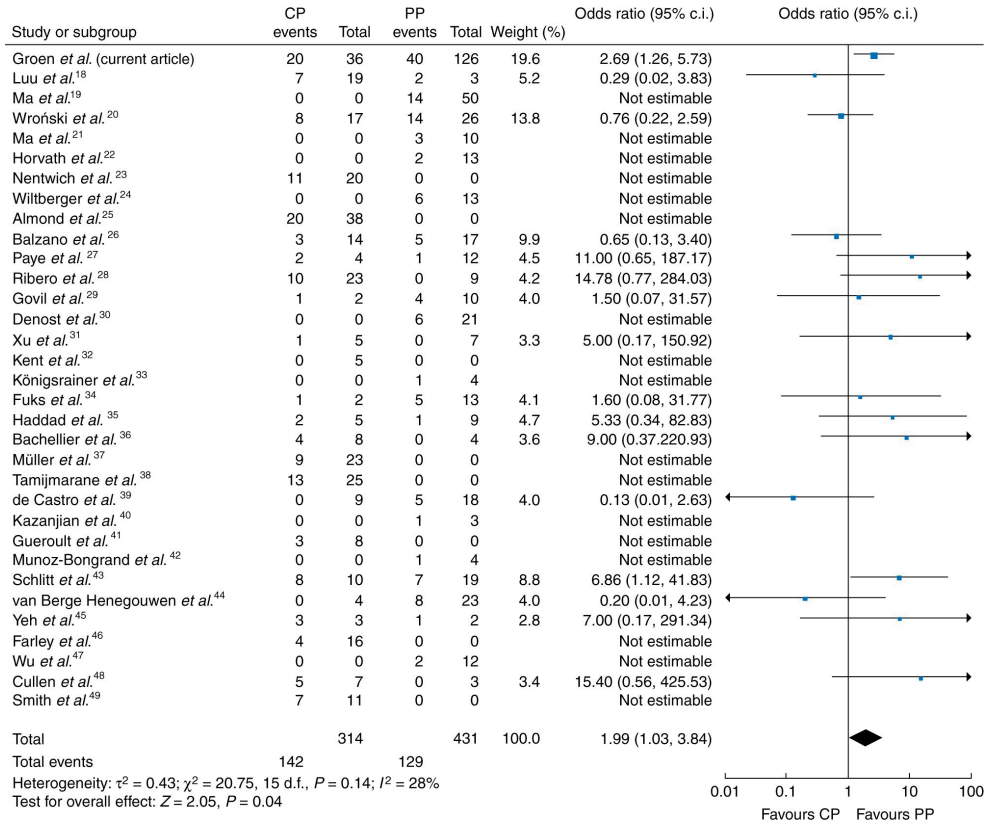

Figure 3. Forest plot of death after initial relaparotomy by surgical strategy for pancreatic fistula: completion pancreatectomy (CP) versus pancreas-preserving (PP) procedure (random-effects model)[18–49]

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 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), as was the rate of relaparotomy for pancreatic fistula (21 versus 17–37 per cent)[1,50]. A recent study showed large variation in overall reoperation rate (6–17 per cent) between several pancreatic surgery registries in the USA and Europe[51]. 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[5,52], 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[53].

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[54] and in a matched cohort study in patients with pancreatic fistula in which relaparotomy was compared with catheter drainage as primary treatment[2]. 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[55]. 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[5,52]. The present and previous studies[2,54] 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[56]. A recent study showed that pancreatic fistula and postpancreatectomy haemorrhage can develop independently and have a major impact on organ failure and mortality[57]. The Dutch Pancreatic Cancer Group is currently analysing the data of the nationwide PORSCH 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[58]. 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)59. More studies reported on new-onset diabetes mellitus, ranging 26–50 per cent (26 per cent in the present study)[52,59–62]. A recent meta-analysis showed an acceptable rate of diabetes-related morbidity and levels of HbA1c 1 year after elective or emergency total pancreatectomy[63]. 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[63]. In the Netherlands, initiatives like the PACAP-1 trial are aimed at improving pancreatic enzyme replacement therapy in patients with pancreatic cancer[64].

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[9]. 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[1], 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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Chapter 9

Diagnosis and management of postpancreatectomy hemorrhage: a systematic review and meta-analysis

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Abstract

Background
Postpancreatectomy hemorrhage is a potentially lethal complication after pancreatic resection. The objective of this systematic review is to provide insight in the current status of incidence, detection, management and clinical outcomes of late postpancreatectomy hemorrhage.

Methods
A systematic search was conducted on the literature from February 2007 to July 2018 in PubMed, Embase and the Cochrane library. Included were clinical studies with clinical outcomes on late postpancreatectomy hemorrhage defined according to the International Study Group of Pancreatic Surgery definition (i.e. occurring >24 h after pancreatic resection).

Results
A total of 14 studies on 467 patients with late postpancreatectomy hemorrhage were included. The incidence of late postpancreatectomy hemorrhage ranged from 3% to 16% (weighted mean: 5%). Seventy-four patients received conservative treatment; 252 patients underwent primary endovascular intervention; 82 patients underwent primary relaparotomy; 56 patients underwent primary endoscopic intervention; and three patients died before any intervention could be performed. CT-scan and diagnostic angiography were able to identify the source of hemorrhage in 67% (66/98) and 69% (114/166) of patients, respectively. The most frequent origin of the hemorrhage was the gastroduodenal artery stump (79/275; 29%), followed by the common hepatic artery (51/275; 19%) and splenic artery (32/275; 12%). Overall mortality was 21% (98/464 patients; range 0%–38%). Mortality was lower after primary interventional angiography as compared to primary relaparotomy (16% vs 37% respectively).

Conclusions
This systematic review provides a comprehensive overview of the current literature for severe late postpancreatectomy hemorrhages. CT-scan and diagnostic angiography are equally sensitive in detecting the bleeding source. Interventional angiography appears to be associated to lower mortality as compared to relaparotomy and endoscopy as first intervention for postpancreatectomy hemorrhage.

Introduction

Pancreatic surgery is complex and remains, despite a drastic decline in mortality rates to under 3% in high volume centers, associated with an undesirably high postoperative morbidity (20–60%).[1-5] Postpancreatectomy hemorrhage is one of the most feared complications after pancreatectomy, for it is associated with a high mortality. In accordance to the International Study Group on Pancreatic Surgery (ISGPS) definition, postpancreatectomy hemorrhage is graded based on onset, location and severity. Where early postpancreatectomy hemorrhage (i.e. occurring <24 h after index pancreatic resection) is often due to inadequate hemostasis or an underlying coagulopathy, late postpancreatectomy hemorrhage is often the result of a multifactorial pathophysiological mechanism, including an association with other pancreatectomy specific complications, such as postoperative pancreatic fistula. Leakage of activated amylase rich fluid in the close approximation of peripancreatic vessels may lead to erosion of the vessels and hemorrhages.[6]

Severe postpancreatectomy hemorrhage requires a fast and effective management. The management of early postpancreatectomy hemorrhage is mostly through relaparotomy, whereas the management of late postpancreatectomy hemorrhage is more complex.[7,8] The general assumption is that a minimally invasive endovascular approach currently offers the best treatment available through embolization or covered stenting.[9-13] However, the incidence of postpancreatectomy hemorrhage is low and literature on postpancreatectomy hemorrhage mostly consists of retrospective cohorts and small case series. Therefore, a complete overview of the literature might provide more insight in the best treatment strategy of this potentially lethal complication.

The objective of this systematic review is to provide an overview of the incidence, detection, management and clinical outcomes of treatment strategies for late postpancreatectomy hemorrhage.

Methods

Literature search strategy

This study was performed in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[14] A systematic literature search was conducted from February 2007 to July 2018. The search was restricted to the publication date of the consensus definition of postpancreatectomy hemorrhage established by the ISGPS in February 2007.[6] The search was applied to the following electronic databases: Pubmed/MEDLINE, Embase and Cochrane Library using the subsequent terms, including their synonyms, abbreviations and related spellings: 'pancreatic surgery', 'pancreatic resection', 'pancreatoduodenectomy', 'postpancreatectomy hemorrhage', 'relaparotomy', 'angiography', 'endovascular', 'stent', 'coiling', and 'endoscopy'. Title

and abstract of all studies identified were screened for the eligibility criteria. Possible, eligible studies were screened full text by two authors (AFvO and FJS) before inclusion in this analysis. Additional studies were identified by scanning reference lists of primary studies.

Eligibility criteria

Included were studies evaluating clinical outcomes of late postpancreatectomy hemorrhage requiring (minimally) invasive interventions, as well as conservative treatment. Excluded were studies not reporting mortality or number of re-interventions after initial intervention for postpancreatectomy hemorrhage, studies not using the ISGPS definition on postpancreatectomy hemorrhage, studies reporting solely on pancreatic transplantation or post-trauma pancreatectomy, non-English studies, reports on less than five patients and studies not reporting separate outcomes for early and late postpancreatectomy hemorrhage. Late postpancreatectomy hemorrhage was defined according to the ISGPS definition as a postoperative hemorrhage occurring at least 24 h after pancreatic resection.[6]

Assessment of risk of bias

The Newcastle–Ottawa Scale (NOS) for nonrandomized studies was used to assess methodological quality of included studies.[15]

Data extraction

A data extraction sheet was developed and pilot-tested on five included studies and then refined accordingly. The following data were extracted from included studies: (i) study characteristics (i.e., publication year, study period, country of origin, study design, number of included patients, incidence of postpancreatectomy hemorrhage, length of follow-up), (ii) patient characteristics (i.e., age, gender, underlying pathology, details on index pancreatectomy, and incidence of postoperative pancreatic fistula), (iii) details on (minimally) invasive interventions for late postpancreatectomy hemorrhage, and (iv) outcome measures (including mortality, rebleeding and re-intervention rates). If available, data on diagnostic accuracy of abdominal imaging, including data on source of hemorrhage and incidence of other (invasive intervention) related complications were extracted. Authors were contacted if any of these data were not presented in the paper.

Statistical analysis

Mean [standard deviation (SD)] or median (range) values for al continuous outcomes were extracted or obtained from authors if not available in the publications. Using the mean (SD) values, the weighted mean (SD) values were calculated, or calculated from median (range) values, using the method reported by Hozo et al.[16] Weighted incidences were calculated for dichotomous outcomes. For statistical analysis, patients were divided into groups based upon the initial invasive intervention for postpancreatectomy hemorrhage (i.e. endovascular interventions, endoscopy, and relaparotomy). Primary outcome measure was 30-day mortality after first (minimally) invasive intervention.

Secondary outcome measures included success rate of first invasive intervention, defined as discharge alive without need for additional invasive intervention. Abstentions of angiographic interventions due to an inability to find the source of the hemorrhage, were regarded as diagnostic failure instead of interventional failure, in which case the subsequent intervention was considered to be the initial intervention.

Results

The search identified 2.077 unique studies for title and abstract screening. Forty-two studies were eligible for full-text reviewing, after which a total of 14 studies were included (see Fig. 1 for a summary of the selection process). The characteristics of the studies are shown in Table 1. Seven studies described outcomes after endovascular interventions, relaparatomy and endoscopic interventions,[7,9,10,17-20] three studies described outcomes after endovascular interventions and relaparotomy,[11,21,22] and four studies only described outcomes after endovascular interventions.[12,13,20,23]

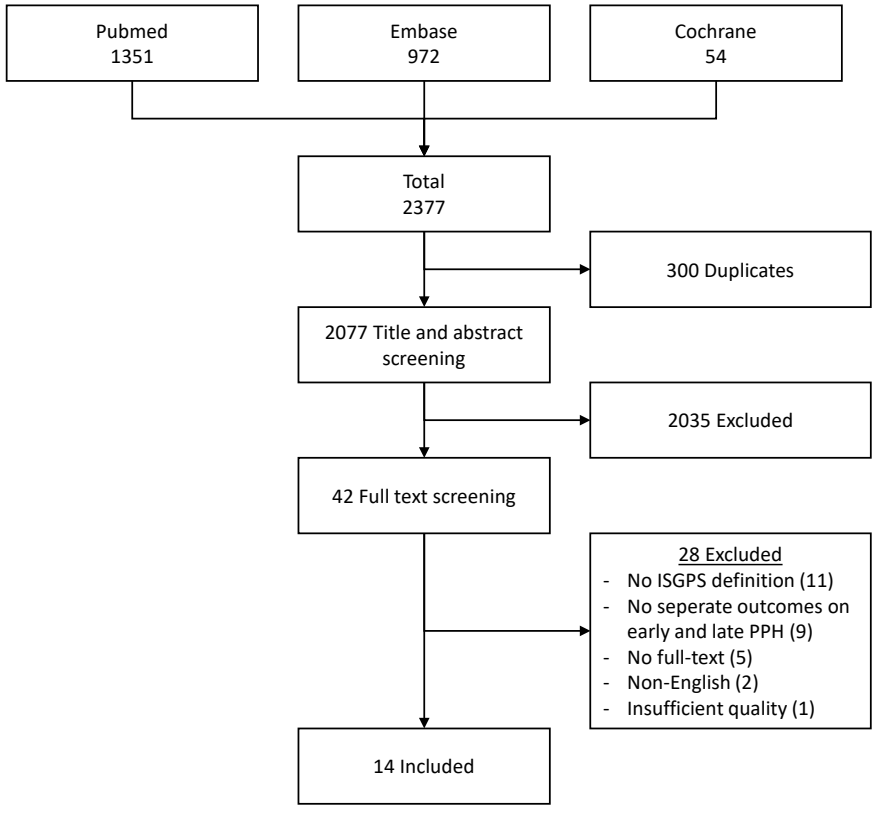

Figure 1. Flow-chart depicting selection process of studies for review

Table 1: Study Characteristics.

Study	Study Period	Country	Study Design	Pancrea-tectomies (n)	Incidence PPH (%)	Patients Included (n)	Therapy (n)				
							Cons.	Endo.	Endovascular		Relap.
									CSP	Embo.	
Asari	2003-2013	Japan	RR	553	35 (6%)	29	5 (17%)	3 (10%)	-	17 (59%)	3 (10%)
Beyer	2005-2008	France	RR	87	9 (10%)	9	-	-	1 (11%)	7 (78%)	1 (11%)
Ching	2007-2014	USA	RR	NR	NR	28	-	-	18 (67%)	9 (33%)	-
Correa-Gallego	2006-2011	USA	RR	1.122	33 (3%)	26	11 (42%)	3 (11%)	-	8 (31%)	3 (11%)
Darnis	2005-2010	Germany	RR	285	46 (16%)	46	15 (33%)	3 (7%)	-	14 (30%)	14 (30%)
Feng	2000-2010	China	RR	840	73 (9%)	54	18 (33%)	12 (22%)	1 (2%)	11 (21%)	11 (21%)
Hassold	2008-2015	Germany	RR	366	NR	27	-	-	16 (59%)	11 (41%)	-
Huo	2008-2013	China	RR	357	29 (8%)	21	-	-	8 (38%)	10 (48%)	3 (14%)
Jilesen	1992-2012	NL	RR	1.035	NR	47	19 (40%)	-	14 (30%)		13 (28%)
Khalsa	2003-2013	USA	RR	337	10 (3%)	10	1 (10%)	3 (30%)	5 (50%)		4 (40%)
Pottier	2005-2013	France	RR	NR	NR	69	-	-	6 (10%)	52 (90%)	-
Sanjay	2002-2011	UK	RR	120	9 (8%)	9	1 (11%)	-	3 (33%)	5 (56%)	-
Wang	2009-2014	China	RR	1.056	78 (7%)	58	-	24 (41%)	27 (47%)		10 (17%)
Wei	1980-2007	Taiwan	RR	628	58 (9%)	31	2 (7%)	-	9 (29%)		20 (65%)
Total							72 (16%)	56 (12%)	252 (54%)		82 (18%)

RR, retrospective review; NR, not reported; Cons., conservative; Endo., endoscopy; CSP, covered stent placement; Embo., embolization; Relap., relaparotomy; -, not performed; POPF, postoperative pancreatic fistula.

A total of 464 patients with late postpancreatectomy hemorrhage were included in this study (range 9–69 patients per study). Seventy-five percent of patients was male, mean age was 63 years (range 32–85 years). Eleven studies reported both the total number of pancreatectomies and the incidence of late postpancreatectomy hemorrhage. The incidence of late postpancreatectomy hemorrhage ranged from 3% to 16% (weighted mean: 5%). Pancreatic fistula rate was reported in 9 studies. In 161/284 (57%) patients with late hemorrhage suffered from clinically relevant pancreatic fistula. Patient characteristics are described in Table 2.

Methodological assessment

The results of the methodological quality assessment are presented in Table 3. All studies were retrospective cohort studies, seven of these studies extracted data from a prospectively maintained database.[7,12,13,17,19,22] Ten studies failed to report the source of their data, which may have led to inclusion bias. In 11 studies, the late postpancreatectomy hemorrhage patients were selected in a consecutive matter within a fixed inclusion period. Three studies only included late postpancreatectomy hemorrhage patients who received angiographic interventions, resulting in an intermediate risk of selection bias.[12,13,23] One study included all patients with postpancreatectomy hemorrhage. The researchers were, however, only able to trace back the time of onset of 55% of the postpancreatectomy hemorrhage patients.[24] Seven studies used multivariable regression analysis to correct for confounders in the comparison of different interventions. Ideally, all studies would have reported on predefined criteria for late postpancreatectomy hemorrhage intervention, as well as re-interventions. However, the report rates were low, and if they were reported the criteria varied substantially per study. The follow-up time was reported in 9 studies with a median duration of 90 days (range 30 days to 21.6 months). In general, the methodological quality was assessed to be low to moderate, resulting in an uncertain risk of bias.

Diagnostic measures

Nine studies described the accuracy of diagnostic tests to identify the source of late postpancreatectomy hemorrhage. Accuracy of abdominal computed tomography with angiography (CTA) was described in two studies evaluating 55 patients with (suspected) postpancreatectomy hemorrhage and was able to identify the source of the hemorrhage in 31 patients (mean sensitivity 56%). Conventional computed tomography (CT) was used in 5 studies evaluating 126 patients with postpancreatectomy hemorrhage and was able to identify the source of the hemorrhage in 66 patients (mean sensitivity 67%). Diagnostic angiography without prior CT was described in 5 studies and diagnostic angiography with prior CT was reported in 1 study evaluating in total 166 patients and was able to identify the source of the hemorrhage in 114 patients (mean sensitivity 69%). In addition, one study correlated the initially identified vessels on CT-scan with secondary diagnostic angiography in 69 patients.[12] In 48 patients (70%), the identified vessel matched between the CT-scan and diagnostic angiography.

Table 2: Patient Characteristics*

Reported in (n)	**10 studies, 299 patients**
Male	223
Female	76
Age (median (IQR))	63 (32-85)
Underlying Pathology	
Reported in (n)	**14 studies, 465 patients**
PDAC	102 (22%)
Ampullary carcinoma	38 (8%)
Cholangiocarcinoma	34 (7%)
NET	25 (5%)
IPMN	24 (5%)
Papillary Carcinoma	11 (2%)
Pancreatitis (chronic or acute)	11 (2%)
Benign lesions	20 (4%)
Other	80 (17%)
Not reported	120 (26%)
Index pancreatectomy	
Reported in (n)	**12 studies, 465 patients**
Pancreaticoduodenectomy	262 (57%)
PPPD	94 (20%)
Distal Pancreatectomy	23 (5%)
Central Pancreatectomy	11 (2%)
Total Pancreatectomy	9 (2%)
Enucleation	8 (2%)
Other	14 (3%)
Not Reported	44 (10%)
Location of the bleed	
Reported in (n)	**8 studies, 236 patients**
Intraluminal	95 (40%)
Extraluminal	128 (54%)
Both	4 (2%)
Other	2 (1%)
Unknown	7 (3%)
Origins of the Bleeding	
Reported in (n)	**11 studies; 300 patients**
Gastroduodenal Artery Stump (GDA)	79 (26%)
Common Hepatic Artery (CHA)	51 (17%)
Splenic Artery (SA)	32 (11%)
Superior Mesenteric Artery (SMA)	21 (7%)
Proper Hepatic Artery (PHA)	20 (7%)
Other	64 (21%)
Unknown	33 (11%)
Postoperative Pancreatic Fistula	
Reported in (n)	**9 studies; 284 patients**
Co-occurrence with PPH	161 (57%)

* Values reported as sum (percentage) or as median (range).

Study	Oxford Level of Evidence	Study Design	Representative of exposed cohort	Outcome of Interest	Comparability	Outcome Assessment	Follow-up Duration	Follow-up Complete
Asari *et al.*(10)	2b	RR	●	●	○	●	●	○
Beyer *et al.*(11)	2b	RR	●	●	○	●	○	○
Ching *et al.*(20)	2b	RR	◌	●	●	●	●	○
Correa-Gallego *et al* (7)	2b	RR	●	●	●	●	●	○
Darnis *et al.* (19)	2b	RR	●	●	○	●	○	●
Feng *et al.* (18)	2b	RR	●	●	●	●	○	○
Hassold *et al.* (23)	2b	RR	◌	●	○	●	●	○
Huo *et al* (21)	2b	RR	●	●	○	●	●	○
Jillesen *et al* (22)	2b	RR	●	●	●	●	○	○
Khalsa *et al.* (9)	2b	RR	●	●	○	●	●	○
Pottier *et al.* (12)	2b	RR	◌	●	●	●	●	○
Sanjay *et al.* (13)	2b	RR	◌	●	○	●	●	○
Wang *et al.* (17)	2b	RR	●	●	●	●	●	○
Wei *et al.* (24)	2b	RR	○	●	●	●	○	○

Table 3. Methodological Quality Assessment. RR, retrospective review; , Has met the criteria: low risk of bias; , has partly met the criteria, moderate risk of bias; failed to meet criteria, high risk of bias; NA, not applicable.

The source of the hemorrhage was reported in 11 studies and identified in 275/335 patients. The hemorrhage source was not found in 11 patients in the endoscopy group (31%), 26 patients in the endovascular radiology (13%) group and 2 patients in the relaparotomy group (3%). Most hemorrhages originated from the gastroduodenal artery stump (79/275; 29%), followed by the common hepatic artery (51/275; 19%) and the splenic artery (32/275; 12%; Table 2).

Clinical outcomes

Clinical outcomes are presented in Table 4. Overall mortality, reported in all 14 studies, was 98 patients out of 464 patients with postpancreatectomy hemorrhage (weighted mean: 21%; range 0%–38%). Nine studies specified the mortality rate per primary interventional group. Endovascular interventions, relaparotomy, endoscopic interventions, resulted in 31/202 (15%), 14/38 (37%) and 5/21 (24%) reported deaths, respectively. Mortality was lower in the interventional angiography group as compared to the relaparotomy group (16% vs 37% respectively). The number needed to treat through angiography in order to prevent one death is 5 patients.

Table 4: Mortality*

Study	Total patients	Overall Mortality		Initial Treatment						
				Before Interv.	Cons	Endosc	Endovascular			Relap
							CS	Embo.	NOS	
Asari	23	6	(21%)	1/29	1/5	0/3		3/17		1/3
Beyer	9	0	(0%)				0/1	0/7		0/1
Ching	27	2	(7%)				NR	NR	2/28	
Correa-Gallego	25	1	(4%)	1/26	0/11	0/3		0/8		0/3
Darnis	46	10	(22%)		0/15	NR		NR		NR
Feng	54	16	(30%)		0/18	4/12	0/1	6/11		6/11
Hassold	27	9	(34%)				3/16	3/11		
Huo	21	5	(24%)				0/8	3/10		2/3
Jilesen	38	6	(13%)	1/47					1/14	4/13
Khalsa	13	2	(20%)			1/3			0/5	1/4
Pottier	58	6	(9%)				NR	NR	6/57	
Sanjay	9	3	(33%)		0/1		3/3	0/5		
Wang	61	22	(38%)			NR			NR	NR
Wei	31	10	(32%)				NR	NR		NR
Total	464	98	(21%)		1/50 (2%)	5/21 (24%)	7/29 (24%)	15/69 (22%)	9/104 (9%)	14/38 (37%)

*interv, intervention; cons, convervative; endosc, endoscopic; CS, covered stent; embo, embolization; NOS, not otherwise specified; relap, relaparotomy; NR, not reported. Values presented as whole and as percentage per total interventions performed.

Sixty-five patients underwent primary endoscopic intervention, 82 patients underwent primary relaparotomy and 252 patients underwent primary endovascular intervention. Success rates, defined as percentage of late postpancreatectomy hemorrhage patients discharged alive without need for re-intervention, were described in 14 studies and did not differ between the endoscopic group, with 23 out of 48 patients, and interventional angiography groups, with 47 out of 84 patients (48% vs 56% respectively). The comparison of interventional angiography and relaparotomy was also similar. Interventional angiography was successful in 81 out of 133 patients and relaparotomy in 46 out of 82 patients (61% vs 56% respectively) (see Table 5).

Covered stent versus embolization

In the studies that evaluated specific subgroups of endovascular treatment, 52 patients received a covered stent and 133 patients underwent embolization. Covered stent placements were successful in 36/52 patients (69%). A re-bleed occurred in 10 unsuccessful stent placements, of which 7 occurred at a new site, 1 at the old site and 2 were not reported. Six patients died due to multi-organ failure (n = 3), renal failure (n = 2) and acute myocardial infarction (n = 1). Embolization was successful in 62/94 patients (68%), and success rate was unreported in 39 patients. A re-bleed occurred in 27 patients and 4 patients died to multi-organ failure (n = 3) and hepatic failure (n = 1).

The mortality after covered stent placement and embolization was at 21% (6/29) and 22% (15/69) respectively.

Table 5: Success Rate Primary Intervention*

Study	Total patients	Success Rate Initial Treatment					
				Angiography			Relaparotomy
		Conservative	Endoscopy	Covered Stent	Embolization	NOS	
Asari	23		3/3 (100%)		13/17 (77%)		2/3 (67%)
Beyer	9			1/1 (100%)	4/7 (57%)		0/1 (0%)
Ching	27			12/18 (67%)	8/9 (89%)		
Correa-Gallego	25	11/11 (100%)	3/3 (100%)		8/8 (100%)		3/3 (100%)
Darnis	46	15/15 (100%)	2/3 (67%)		7/14 (50%)		8/14 (57%)
Feng	54	18/18 (100%)	4/12 (33%)			3/13 (23%)	5/11 (46%)
Hassold	27			11/16 (69%)	8/11 (73%)		
Huo	21			8/8 (100%)	5/10 (50%)		1/3 (33%)
Jilesen	38	19/19 (100%)				9/14 (64%)	9/13 (69%)
Khalsa	13	1/1 (100%)	0/3 (0%)			4/5 (80%)	1/4 (25%)
Pottier	58			4/6 (67%)	34/52 (65%)		
Sanjay	9	1/1 (100%)		0/3 (0%)	4/5 (80%)		
Wang	61		11/24 (46%)			12/27 (44%)	1/10 (10%)
Wei	31					7/11 (64%)	16/20 (80%)
Total		65/65 (100%)	23/48 (48%)	36/52 (69%)	91/133 (68%)	35/70 (50%)	46/82(56%)

*NOS, not otherwise specified; Values represented as a whole and as percentage of total treatment group.

Discussion

This systematic review provides a comprehensive overview of the current literature on severe hemorrhage after pancreatectomy. According to the current literature, late postpancreatectomy hemorrhage remains a relatively uncommon complication with a mean incidence of 5%. However, overall mortality continues to be high at 21%. This review showed that sensitivity of angiography (69%) to identify the source of the hemorrhage was comparable to the CT-scan (67%). Endoscopy failed to identify the location of bleeding in 31% of patients with an overt luminal bleeding. The mortality rate was lower after a primary endovascular approach as compared to primary relaparotomy and primary endoscopy (i.e. 15%, 37%, 24%, respectively). Endovascular approach was the primary treatment for most late postpancreatectomy hemorrhage cases. However, 17% of patients is still primarily treated through relaparotomy. However, these results should be interpreted with care, for included studies were subjective to considerable confounding by indication.

Late postpancreatectomy hemorrhage is the result of a multifactorial pathogenesis in which postoperative pancreatic fistula play an important role. Intraoperatively, the peripancreatic vessels are often manipulated and injured due to lymphadenectomy and the ligation of the arteries.[25] This can lead to the corrosion of the vessel wall and subsequent vascular lesions, rendering the peripancreatic vessels vulnerable to further damage. Postoperative pancreatic fistula is associated with late postpancreatectomy hemorrhage for leakage of enzyme rich fluid into the abdomen might cause vessel erosion, which can result in the formation of a pseudoaneurysm. Pseudoaneurysms are known to rupture and as a consequence can cause late hemorrhage.[26]

A possible explanation for the difference in mortality rates between the interventional strategies, might lay in their respective indications. In most cases, relaparotomy is used as a last resort for hemodynamic instable patients.[7,10,17,19] Major surgical trauma can lead to a lethal systemic inflammatory response, especially considering that these patients are often severely ill and potentially affected by postoperative pancreatic fistula.[6,8,27] Moreover, identification of the source of the hemorrhage during relaparotomy can be challenging, especially in a patient with severe postoperative pancreatic fistula. In this systematic review, especially the studies that focussed solely on an endovascular approach for late postpancreatectomy hemorrhage, started implementing embolization and covered stenting in hemodynamic instable cases.[7,23] As for endovascular treatment the indications for different techniques (with respect to the origin of the hemorrhage and preference of interventional radiologist) often go unreported in most studies.[11,22,23] Interventional endoscopy, on the other hand, prevails as the first-line intervention for intraluminal hemorrhage. Even in intraluminal hemorrhage, endoscopy fails to adequately identify the source of the hemorrhage and therefore almost always results in a delay of the adequate treatment, resulting in possible fatal outcomes.

This systematic review has attempted to elucidate the best diagnostic measure for late postpancreatectomy hemorrhage. Controversy remains between the use of a CT-scan and the use of diagnostic angiography. Angiography appears to be the most specific and sensitive diagnostic measure to detect late postpancreatectomy hemorrhage.[27] On the other hand, the CT-scan is an effective, less invasive alternative to detect late postpancreatectomy hemorrhage, as well as related pancreatectomy specific complications.[8] However, the advantage of the use of diagnostic angiography is that it can immediately resolve a postpancreatectomy hemorrhage once it is detected. Nevertheless, one study reports that diagnostic angiography fails to identify the hemorrhage in 25% of the cases.[12] This is likely due to the intermittent nature of postpancreatectomy hemorrhage. In these instances, a CT scan can provide extra information such as location of hematoma and a (partially) thrombosed false aneurysm. Future prospective trials should evaluate the true sensitivity and specificity of CT-scans and diagnostic angiography for late postpancreatectomy hemorrhage. Endoscopy fails to identify the hemorrhage source in a substantial number of patients and may therefore be of limited use as a first line

diagnostic measure for overt luminal bleeding. Diagnostic angiography or CT-scan have a higher sensitivity and are more informative for physicians.

This systematic review has several limitations. First, few studies directly compare the clinical outcomes of different interventions and usually have relatively small sample sizes. As the decision on what invasive intervention should be performed is most likely dictated by the clinical presentation of postpancreatectomy hemorrhage: i.e. confounding by indication. Especially, since only a few studies report the indications of the intervention, limiting our abilities to correct for this form of bias. Second, all studies are designed as a retrospective review and this introduces several forms of bias. However, it should be noted that due to the lack of RCTs it remains difficult to properly compare the invasive interventions and draw strong conclusions from the results.

The current literature shows postpancreatectomy hemorrhage is relatively rare, with an incidence of 5%, yet associated with a mortality of 21%, making it the most lethal pancreatectomy specific complication. Diagnostic accuracy of CT and angiography are similar, both show a sensitivity of almost 70%. Hemorrhage occurs in about 30% of patients from the gastroduodenal stump. Endovascular approach appears to be superior to relaparotomy and endoscopy as primary treatment for late postpancreatectomy hemorrhage, for this is associated with a lower mortality.

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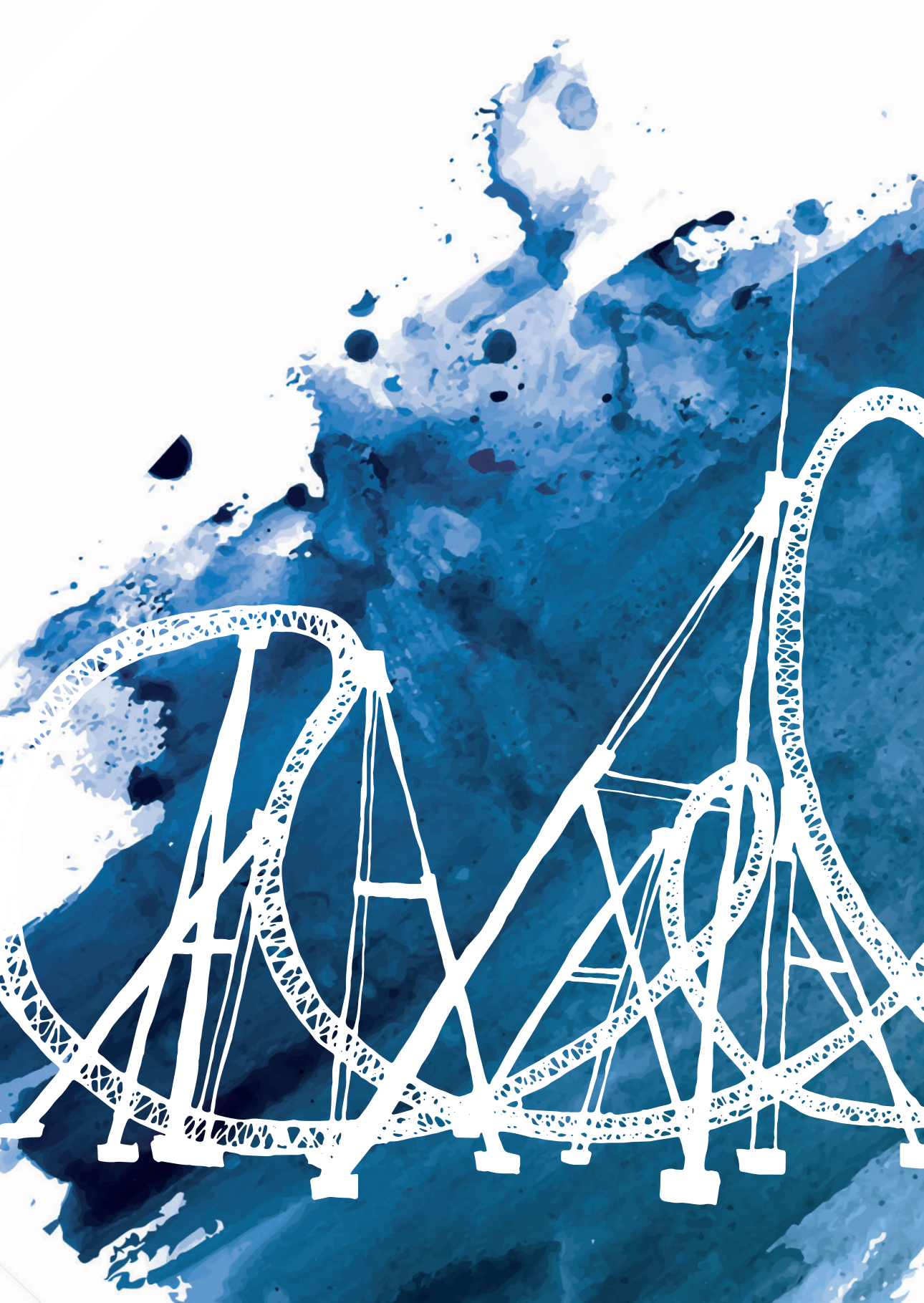

PART IV

Implementing Best Practice in Pancreatic Surgery

Chapter 10

Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in the Netherlands: an open-label, nationwide, stepped-wedge cluster-randomised trial

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Abstract

Background
Early recognition and management of postoperative complications, before they become clinically relevant, may improve outcomes of surgical patients, especially in high-risk procedures such as pancreatic resection.

Methods
We conducted a nationwide stepped-wedge cluster randomised trial. All patients undergoing pancreatic resection over a 22-month period in The Netherlands were included. In this trial design, all 17 centres were randomised for time to crossover from usual care (control group) to treatment according to a multimodal, multidisciplinary algorithm for early recognition and minimally invasive management of postoperative complications (intervention group). A smartphone application was designed incorporating the algorithm, which included daily evaluation of clinical and biochemical markers. It determined when to perform abdominal computed tomography, radiologic drainage, start antibiotic treatment and remove abdominal drains. Outcomes of the control group were compared to those of the intervention group. The primary outcome was assessed by a blinded adjudication committee and was a composite of bleeding requiring invasive intervention, organ failure, and 90-day mortality. Analyses were by intention to treat. This trial was registered in the Netherlands Trial Register, number NL6671.

Results
1748 patients were included. The primary outcome occurred in 73 of 863 patients (8·5%) in the intervention group and in 124 of 885 patients (14·0%) in the control group (adjusted odds ratio [RR] 0·48, 95% confidence interval [CI] 0·38-0·61, P<0·0001). There was a decrease in bleeding requiring intervention (47 patients [5·4%] vs 51 patients [5·8%]; adjusted RR 0·65, 95% CI 0·42-0·99, P=0.046), organ failure (39 patients [4·5%] vs 92 patients [10·3%]; adjusted RR 0·35, 95%CI 0·20-0·60, P=0·00013) and a lower 90-day mortality (23 patients [2·7%] vs 44 patients [5·0%]; adjusted RR 0·42, 95%CI 0·19-0·92, P=0·029) in patients treated according to the algorithm.

Conclusion
The algorithm for early recognition and minimally invasive management of complications after pancreatic resection considerably improved clinical outcomes compared to usual care. This included an approximate 50% reduction of nationwide mortality.

Introduction

Postoperative complications occur in more than 20% of patients after major surgery and are the greatest contributors to health care utilization and costs.[1,2] Despite continuous improvements in a wide variety of care processes over the last decades, postoperative complications are not always preventable.[2] It has therefore been suggested that focus for improving outcomes further should include timely recognition and management of complications, once they have occurred.[2-4] Recognizing early signs of complications before they lead to clinical deterioration is, however, challenging. Noticing subtle changes in vital signs, biochemical markers, and radiologic features requires training and experience of the multidisciplinary medical team.[5] Improving the 'failure to rescue' rate (ie, mortality in patients with major complications) has emerged as a main target for quality improvement by the international surgical community.[2-4] There is clear need for studies to develop effective interventions that can be broadly implemented to improve failure to rescue rates worldwide.[2-4]

Pancreatic resection is an example of a complex operation with a high risk of postoperative complications (30 to 73%).[6,7] The most common is pancreatic fistula, resulting in intra-abdominal leak of amylase-rich fluid.[8] This may lead to life-threatening consequences such as sepsis, bleeding, and multiple organ failure.[8,9] Mortality in patients with clinically relevant pancreatic fistula is 12 to 18%.[9-11] Outcomes following pancreatic resection have improved with centralization in high-volume centres, due to a focus on technical aspects of the surgery, process measures, and institutional factors.[6,12] Nevertheless, even in high-volume centres, complications after pancreatic resection remain a serious problem.[6,10,11] Moreover, most patients worldwide undergo surgery in low-volume or mid-volume centres.[13-15] Nationwide 90-day mortality rates range from 7 to 12%.[15-17] Improving failure to rescue has therefore also been prioritized in pancreatic surgery.[18,19]

We designed a multimodal algorithm for early recognition and minimally invasive management of postoperative complications in patients undergoing pancreatic resection for all indications. We hypothesised that implementation of this multimodal algorithm would result in better clinical outcomes than usual care.

Methods

Study design and participants

The Care After Pancreatic Resection According to an Algorithm for Early Detection and Minimally Invasive Management of Pancreatic fistula versus Current Practice (PORSCH) trial is a nationwide stepped-wedge cluster randomised controlled trial. The study protocol has been published previously.[20] Pancreatic surgery is centralized in The Netherlands in centres performing at least 20 pancreatoduodenectomies annually. All 17 centres performing pancreatic surgery, including all eight university hospitals, participated. All patients undergoing pancreatic resection for all indications were included. There were no exclusion criteria for centres or patients (ie, nationwide complete enumeration).

The institutional review boards of all centres approved the study and waived the need for individual patient informed consent. Local principal investigators provided informed consent for trial participation on behalf of their institution (ie, gate keeper informed consent, see appendix).[21] Protocol adherence was monitored continuously by study coordinators who were not involved in clinical care, through an online platform. This platform was also the basis of a smartphone application facilitating the use of the algorithm (see appendix). Adverse events potentially related to the study intervention were discussed at periodic study meetings that were open for all clinicians from centres that had crossed over to the intervention. The study was performed in accordance with the declaration of Helsinki and Dutch law. We adhered to the CONSORT (Consolidated Standards of Reporting Trials) guidelines for stepped-wedge cluster randomised trials.[22] The corresponding author has full access to all data, and vouches for the completeness and accuracy of the data and analyses.

Randomisation and masking

As per the stepped-wedge cluster randomised trial design, all centres (clusters) delivered usual care at the start of the study (control group) and crossed over to care according to the algorithm (intervention group) in a randomly assigned order. At the end of the trial all centres have crossed over to the intervention group. Randomisation was performed by an independent statistician using a computer-generated scheme. Stratification was used to ensure low/medium-volume centres vs. high-volume centres (ie, >45 pancreatic resections annually) alternated in randomisation order. Randomisation order was concealed, except for the local principal investigator who was informed at the start of the trial on the time of crossover for that centre.

Procedures

The process of designing the algorithm included a comprehensive systematic literature review, an inventory of guidelines on postoperative care, several retrospective studies, and consensus meetings.[20, 23] To limit the risk of contamination of usual care, only one pancreatic surgeon from each centre was involved in the design. The final evidence-

based algorithm was reviewed by an advisory committee of three international experts from high-volume pancreatic centres. More details are provided in the appendix and the study protocol.[20]

Evaluation through the algorithm was carried out for each patient, daily, from postoperative day 3 to 14. An overview of the algorithm is shown in figure 1. The first part of the algorithm focuses on early recognition of complications through standardized evaluation of vital signs, abdominal drain output, and serum inflammatory markers (ie, white blood cell count and C-reactive protein). If predefined cut off values were exceeded, abdominal computed tomography (CT) scan was indicated. Evaluation of CT scans was standardized, focusing on radiologic signs of postoperative pancreatic fistula and other postoperative complications. The complete list of criteria for assessment of CT scans is shown in the appendix. In the case of inadequately drained intra-abdominal fluid potentially related to a postoperative complication, radiologic drainage was recommended. Treatment with intravenous antibiotics was indicated in all patients with pancreatic fistula or a systemic inflammatory response syndrome. The last level of the algorithm focused on removal of abdominal drains, to ensure removal at the earliest possibility. The algorithm also included daily assessment by the treating pancreatic surgeon, who was responsible for the final clinical decisions (appendix). An intraoperative drain was placed in all patients. Other details on surgical technique were left to the discretion of local surgeons.

After entering all data in the smartphone application, the algorithm produced an advice on indication for CT scan, radiologic drainage, antibiotic treatment, and removal of drains. An impression of the smartphone application is supplied the appendix. A version of the application that is modified for daily clinical use is available through the appendix.

At crossover, clinicians were educated on the algorithm during a 4-week wash-in period. Education consisted of on-site presentations for all surgeons and residents, nursing staff, diagnostic and interventional radiologists, and intensive care staff. A nationwide online expert panel of pancreatic surgeons and interventional radiologists was available.

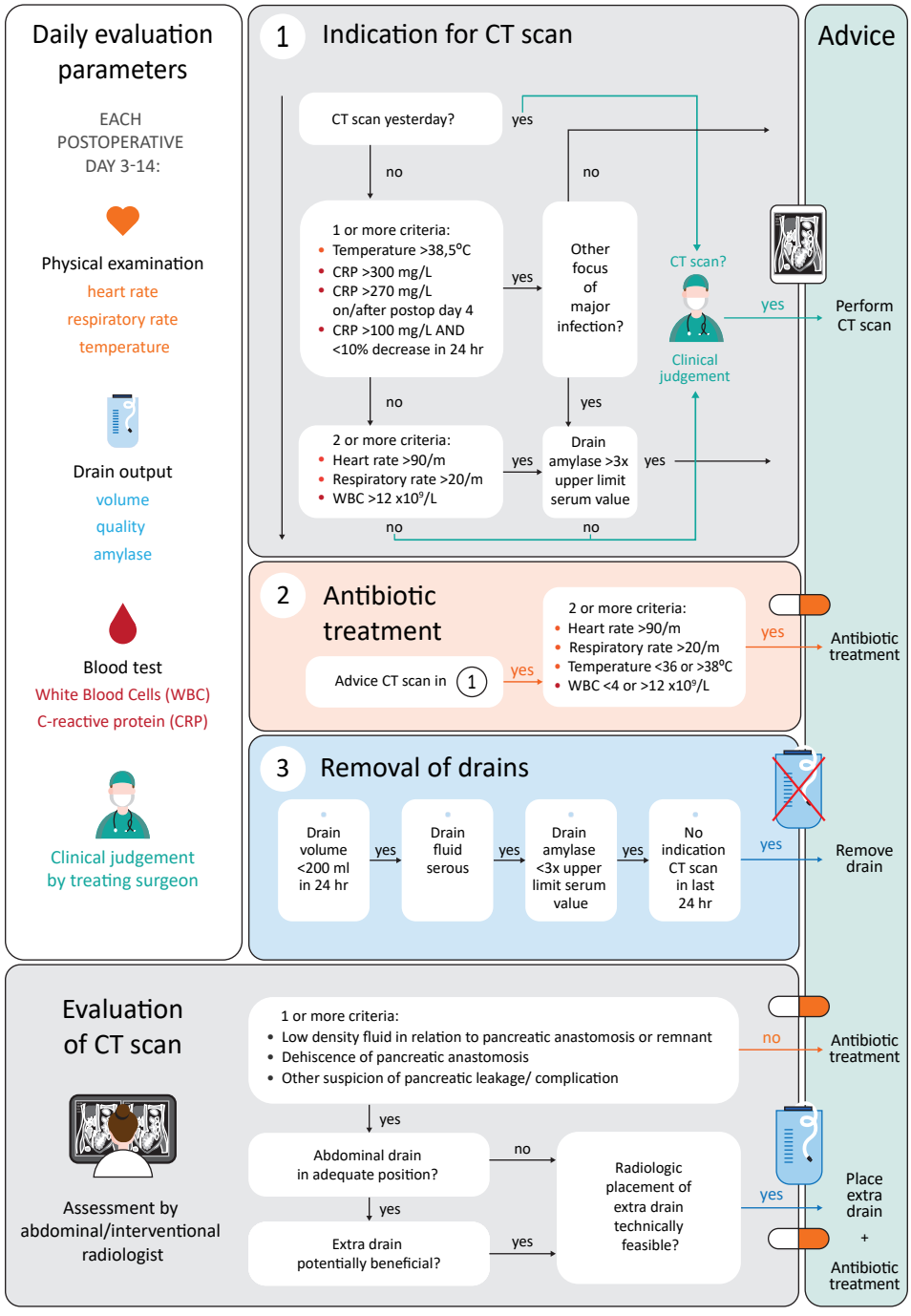

Figure 1. Overview of the multimodal, multidisciplinary algorithm for early recognition and management of complications after pancreatic resection

Outcomes

The primary outcome was a composite of the most severe postoperative complications: bleeding requiring invasive intervention, new-onset organ failure, or death during admission or 90 days after resection. The outcome was met if any of the three occurred. The individual components of the primary outcome were analysed as secondary outcomes. Predefined secondary outcomes also included postoperative pancreatic fistula, postoperative bile leak, gastroenterostomy leak, chyle leak, delayed gastric emptying, number and timing of CT scans, antibiotic treatment, radiologic drainage, and reoperations, ICU admission, length of ICU stay, length of hospital stay, readmission rate and number of patients receiving adjuvant chemotherapy and costs. A complete list of all secondary outcomes and definitions is included in the appendix. Outcomes were assessed up to 90 days after index pancreatic resection or (if patients were still admitted after 90 days) until discharge. No patients were lost to follow-up.

Data were collected using a web-based predefined case record form. In addition, baseline data were extracted from the mandatory prospective Dutch Pancreatic Cancer Audit.[24] All data were checked for accuracy and completeness with source data by researchers not involved in clinical care. Before statistical analysis, all potential primary outcomes were individually assessed by members of a blinded adjudication committee consisting of pancreatic surgeons and interventional radiologists. Disagreements were resolved during a plenary consensus meeting with blinding still in effect.

Statistical analysis

The sample size calculation was performed for the subgroup of patients undergoing pancreatoduodenectomy to ensure adequate power for this population. We assumed an expected relative reduction of 50% in the incidence of the primary outcome after pancreatoduodenectomy coming from 13·8%, a two-sided alpha of 0·05, a power of 0·80, an intra-cluster correlation of 0·009 and a cluster autocorrelation of 1.[9,20,22,24] This resulted in a required sample size of 1186 pancreatoduodenectomies in 17 centres. The planned study duration was therefore 22 months. The total sample size was expected to be 25% higher because all types of pancreatic resections were included. A planned interim analysis was performed at 11 months to allow for extension of the study duration in case enrolment was less than 47·5% of the planned sample size.

Analyses were performed according to the intention-to-treat principle, comparing patients assigned to usual care with patients assigned to algorithm centred care. Date of pancreatic resection determined what study group patients were in (ie, before or after planned date of cross-over). As predefined, patients undergoing pancreatic resection during the wash-in period were excluded from analyses. Missing baseline data were imputed using multiple imputation. The study protocol defined mixed-effects logistic regression analyses of the binary outcomes with odds ratio's as index of effect size. However, because risk ratios are preferred in terms of interpretation, collapsibility, and less susceptibility to sparse-data bias, for the final analyses we used mixed-effects

Poisson regression with cluster robust standard errors to estimate the presented risk ratios (RR) with 95% confidence interval (CI). Time-to-event analyses were performed using shared frailty Cox proportional hazards model (ie, from date index pancreatic resection to 90 days postoperatively). Count data were analysed using a (zero-inflated) negative binomial model. All analyses were adjusted for study design (ie, hospital as random effect, normalized calendar time as fixed effect, and the volume strata as fixed effect) and baseline variables (all fixed effect) associated with the primary outcome (ie, male sex, increasing age, American Society of Anaesthesiologists (ASA) classification >2, pancreatoduodenectomy vs other types of pancreatic resection) or postoperative pancreatic fistula (ie, soft pancreatic texture, small-diameter pancreatic duct, increasing blood loss during pancreatic resection and underlying disease that is not pancreatitis or pancreatic adenocarcinoma). Normalization of calendar time was achieved by subtraction of the numerical representation of calendar date from the group mean, divided by the standard deviation. Presented are total in hospital costs (ie, hospital and intensive care unit admission, laboratory tests, diagnostic imaging, endoscopy, radiologic interventions, and surgical procedures). Outpatient hospital costs and other health care costs were not included. Mean costs are presented with two-sided bias-corrected and accelerated 95% confidence intervals derived by bootstrapping with 5000 samples. A two-sided P value <0·05 indicates statistical significance. For statistical analysis we used R studio version 1.3.959. This trial was registered in the Netherlands Trial Register, number NL6671. For details on the statistical analysis, including several exploratory analyses, see the appendix.

Role of the funding source

Funding was provided by the Dutch Cancer Society (UU2017-8272) and the UMC Utrecht (Alexandre Suerman stipend). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

All 17 centres performing pancreatic surgery in The Netherlands were randomised. One centre stopped performing pancreatic surgery before crossover to the intervention. From Jan 8, 2018 to Nov 9, 2019, a total of 1805 patients underwent pancreatic resection in the Netherlands and all patients were eligible and included in this study: 885 patients received usual care (control group), 57 patients underwent resection during the wash-in phase and 863 patients received algorithm centred care (intervention group, figure 2 and appendix). Baseline characteristics are provided in table 1.

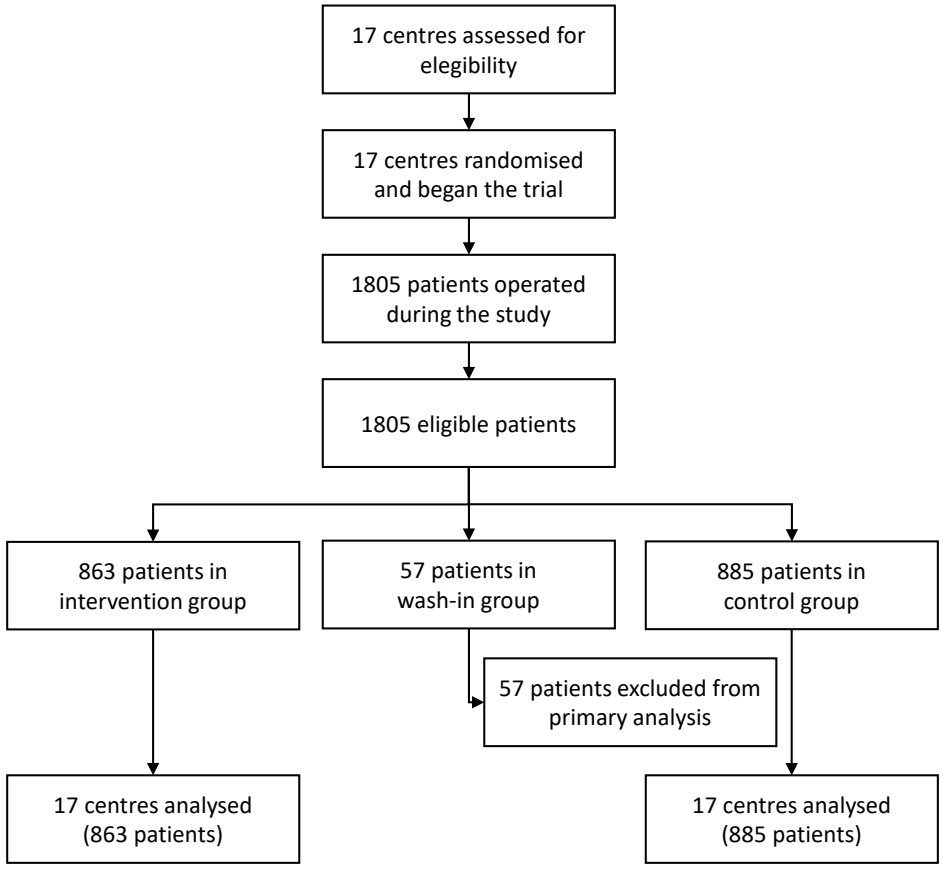

Figure 2. Trial profile

The algorithm in the smartphone application completed 9308 times. On 7631 of 8137 (94%) included patient days (post-operative day 3 to 14), the algorithm data were entered into the smartphone application. A CT scan was performed in 814 of 1086 times (75%) it was recommended. The recommendation to administer antibiotics was followed 253 of 360 times (70%). The recommendation on drain removal was followed in 4802 of 5807 given advices (83%). A total of two complications potentially related to minimally invasive drainage were reported (one perforation of the stomach and one bowel perforation; 0·2% of all drainage procedures).

Table 1: Baseline characteristics*

Characteristic	Intervention (n=863)	Control (n=885)
Sex - female	427 (49·5)	444 (50·2)
Age (years)	65·7 ± 11·6	65·0 ± 11·7
ASA score		
I	68 (7·9)	74 (8·3)
II	501 (58·1)	575 (65·0)
III	287 (33·3)	230 (26·0)
IV	7 (0·8)	6 (0·7)
Neoadjuvant treatment	90 (10·4)	81 (9·2)
Type of pancreatic resection		
Pancreatoduodenectomy	643 (74·5)	671 (75·8)
Distal pancreatectomy	188 (21·8)	187 (21·1)
Other	32 (3·7)	27 (3·1)
Laparoscopic or robotic-assisted resection	230 (26·7)	254 (28·7)
Hard pancreatic texture †	239 (32·7)	284 (35·1)
Diameter pancreatic duct (mm) ‡	4 (2-5)	3 (2-5)
Perioperative blood loss (ml) §	450 (200-900)	400 (200-850)
Underlying disease		
Pancreatic ductal adenocarcinoma	319 (37·0)	330 (37·3)
Ampullary carcinoma	83 (9·6)	100 (11·3)
Cholangiocarcinoma	98 (11·4)	78 (8·8)
IPMN	72 (8·3)	84 (9·5)
Pancreatic neuroendocrine tumour	75 (8·7)	69 (7·8)
Chronic pancreatitis	37 (4·3)	45 (5·1)
Other	179 (20·7)	179 (20·2)

* Data are n (%), mean (SD), or median (IQR) unless otherwise stated. Percentages may not sum to 100 because of rounding. ASA denotes American Society of Anaesthesiologists, and IPMN intraductal papillary mucinous neoplasm.

The primary outcome occurred in 73 of 863 patients (8·5%) in the intervention group and in 124 of 885 patients (14·0%) in the control group (adjusted RR 0·48, 95% CI 0·38-0·61, P<0·0001) (table 2). Bleeding requiring intervention occurred in 5·4% (47 patients) in the intervention group vs. 5·8% (51 patients) in the control group (adjusted RR 0·65, 95% CI 0·42-0·99, P=0·046) New-onset organ failure, including failure of all individual organ systems, occurred less often in the intervention group compared to the control group (39 patients [4·5%] *vs* 92 patients [10·4%], adjusted RR 0·35, 95% CI 0·20-0·60, P=0·00013). 90-day mortality was lower in the intervention group than in the control group (23 patients [2·7%] *vs* 44 patients [5·0%], adjusted RR 0·42, 95% CI 0·19-0·92, P=0·029).

Table 2: Primary outcome*

Outcome	Intervention (n=863)	Control (n=885)	Adjusted RR (95%CI)	P Value
Primary composite outcome: major complications or death	73 (8·5)	124 (14·0)	0·48 (0·38-0·61)	<0·0001
Bleeding requiring intervention	47 (5·4)	51 (5·8)	0·65 (0·42-0·99)	0·046
New-onset organ failure	39 (4·5)	92 (10·4)	0·35 (0·20-0·60)	0·00013
Circulatory failure	28 (3·2)	70 (7·9)	0·32 (0·23-0·46)	<0·0001
Respiratory failure	22 (2·5)	55 (6·2)	0·35 (0·24-0·50)	<0·0001
Renal failure	12 (1·4)	29 (3·3)	0·37 (0·16-0·85)	0·019
Death	23 (2·7)	44 (5·0)	0·42 (0·19-0·92)	0·029

* Data are n (%). Mixed model Poisson regression analyses adjusted with random intercept at hospital level, calendar time, pancreatic texture, diameter pancreatic duct, blood loss pancreatic resection, underlying disease, sex, age (years), American Society of Anaesthesiologists (ASA) class, type of pancreatic resection and hospital volume.

Results of other clinical events and health care utilization are presented in table 3. It appeared that CT scan, antibiotic treatment and radiologic drainage were performed both more often and earlier in patients in the intervention group compared to patients in the control group. Patients in the intervention group less often underwent reoperation and less often were admitted to the intensive care unit than patients in the control group (table 3). Mean total costs per patient were €23,202 (95% CI €22,024 to €24,498) in the intervention group and €23,450 (95% CI €22,100 to €24,450) in the control group (mean difference €248, 95% CI -€1,395 to €1,890, see appendix). Results of other secondary outcomes are provided in the appendix.

Results were consistent across all predefined exploratory analyses (appendix). In the subgroup of patients undergoing pancreatoduodenectomy, the primary outcome occurred in 56 of 643 patients (8·7%) in the intervention group and in 105 of 671 patients (15·6%) in the control group (adjusted RR 0·46, 95% CI 0·34-0·61). In this subgroup, 90-day mortality was 2·6% in the intervention group (17 of 643 patients) and 5·2% in the control group (35 of 671 patients, adjusted RR 0·40, 95% CI 0·18-0·85).

The reduction of the primary outcome in the intervention group compared to the control group, occurred in both the subgroup of patients operated in low/medium-volume centres (ie, performing 20-45 pancreatic resections annually) (25 of 291 patients [8·6%] *vs* 42 of 294 patients [14·3%], adjusted RR 0·49, 95% CI 0·25-0·68) and the subgroup of patients operated in high-volume centres (48 of 572 patients [8·4%] *vs* 82 of 591 patients [13·9%], adjusted RR 0·46, 95% CI 0·32-0·66 The intervention also reduced 90-day mortality in both low/medium volume centres (8 of 291 patients [2.7%] *vs* 20 of 294 patients [6·8%], adjusted RR 0·35, 95% CI 0·11-1·16) and high-volume centres (15 of 572 patients [2·6%] *vs* 24 of 591 patients [4·1%], adjusted RR 0·48, 95% CI 0·18-1·32).

Table 3: Key secondary outcomes*

Outcome	Intervention (n=863)	Control (n=885)	Adjusted RR (95% CI) †	P value
Clinical events ‡				
Postoperative pancreatic fistula	239 (27·7)	187 (21·1)	1·23 (0·97-1·56)	0·084
Postoperative bile leak §	66 (10·2)	57 (8·5)	0·90 (0·60-1·33)	0·59
Gastroenterostomy leak §	8 (1·2)	11 (1·6)	0·88 (0·30-2·62)	0·82
Chyle leak	61 (7·1)	69 (7·8)	0·95 (0·59-1·54)	0·84
Delayed gastric emptying	134 (15·5)	144 (16·3)	1·17 (0·76-1·80)	0·48
Health Care Resource Utilization				
Abdominal CT scans				
Patients undergoing CT scan	562 (65·1)	473 (53·4)	1·18 (1·01-1·36)	0·031
CT scans per patient ‖	1 (0-2)	1 (0-2)	1·23 (1·00-1·53)	0·049
Total CT scans per study group	1533	1189		
First CT scan (postoperative day) ¶	5 (4-9)	7 (5-13)	1·53 (1·23-1·91)	0·00012
Antibiotics				
Patients receiving antibiotics	395 (45·8)	335 (37·9)	1·19 (0·97-1·48)	0·10
Duration of antibiotics treatment (days) ‖	2 (0-8)	0 (0-7)	1·02 (0·71-1·46)	0·91
Start antibiotics (postoperative day) ¶	7 (4-11)	8 (5-15)	1·29 (1·00-1·66)	0·046
Radiologic drainage				
Patients undergoing radiologic drainage	253 (29·3)	207 (23·4)	1·21 (0·93-1·57)	0·16
Radiologic drainage procedures per patient ‖	0 (0-1)	0 (0-0)	1·05 (0·73-1·52)	0·77
Total radiologic drainage procedures per study group	505	474		
First drainage (postoperative day) ¶	8 (5-11)	9 (7-13)	1·32 (0·95-1·84)	0·099
Reoperation				
Patients undergoing reoperation	42 (4·9)	70 (7·9)	0·63 (0·43-0·92)	0·017
Reoperations per patient ‖	0 (0-0)	0 (0-0)	0·55 (0·31-0·99)	0·045
Total reoperations per study group	50	86		
Removal surgical drain (postoperative day) ¶	5 (3-9)	5 (4-8)	1·03 (0·86-1·24)	0·09
ICU admission **	57 (6·6)	80 (9·0)	0·57 (0·43-0·76)	0·0001
Length of ICU stay (days) ††	4 (3-9)	4 (2-8)	1·19 (0·74-1·93)	0·47
Length of hospital stay (days) ¶	11 (8-18)	10 (7-15)	0·95 (0·81-1·11)	0·52
Readmission to hospital	168 (19·5)	188 (21·2)	1·04 (0·84-1·29)	0·70
Adjuvant chemotherapy ‡‡	172 (53·9)	185 (56·1)	1·02 (0·87-1·22)	0·74

* Data are n (%), mean (SD), or median (IQR) unless otherwise stated. CT denotes Computed Tomography, and ICU intensive care unit. All analyses are adjusted for calendar time, pancreatic texture, diameter pancreatic duct, blood loss pancreatic resection, underlying disease, sex, age (years), American Society of Anaesthesiologists (ASA) class, type of pancreatic resection and hospital volume.

† Mixed model Poisson regression analyses adjusted with random intercept at hospital level.

‡ Only grade B/C complications according to the International Study Group on Pancreatic Surgery are included in analyses.

§ Calculated in a subset of patients undergoing pancreatoduodenectomy (643 intervention patients vs. 671 control patients).

‖ Presented is the adjusted rate ratio from a negative binominal regression model (no offset term) adjusted with random intercept at hospital level.

¶ Presented is the hazard ratio from a Cox proportional hazard ratio, in which hazard ratios over 1 indicate a shorter time to event in the intervention group.

** Calculated in a subset of patients admitted to the ICU after postoperative day 3 (ie, new-onset ICU admission).

†† Presented is the conditional rate ratio from a zero inflated negative binominal regression model; zero inflated inverted OR 0·52 (95% CI 0·31-0·87).

‡‡ Calculated in a subset of patients with pancreatic adenocarcinoma who survived the index admission (330 control patients vs. 319 intervention patients).

Discussion

This randomised trial demonstrated that the use of a novel algorithm for early recognition and management of postoperative complications in patients undergoing pancreatic resection greatly improved clinical outcomes. This included an approximate 50% reduction of mortality nationwide. Our findings support a strategy in which all patients undergo a structured daily evaluation to identify and treat complications before they become clinically relevant. The smartphone application that was designed for bedside use of the algorithm can be used for this purpose.

Pancreatic resection is a widely performed operation, mostly for patients with malignant disease. These patients usually have a survival of only a few years.[25] Pancreatic resection is also performed for chronic pancreatitis and prophylactically in young patients with asymptomatic pancreatic cysts.[7,26] In all patients, the impact of severe complications is crucial in the shared decision-making process on performing major abdominal surgery.

The 90-day mortality in our study before introduction of the intervention was 5%. This is higher than the mortality of below 2% that has been reported by international expert centres.[6] This might be explained by the fact that we studied 90-day mortality, whereas other studies often report 30-day mortality.[6] It has been shown that, in patients with pancreatic resection, 90-day mortality is generally twice as high as 30-day mortality.[16] A recent systematic review of 44 studies on the effect of centralization in pancreatic surgery demonstrated a 90-day mortality of 9 to 16% in low-volume centres and 0 to 5% in high-volume centres.[12] Moreover, we studied mortality on a nationwide level, which reflects outcomes not only from selected expert centres. Nationwide 90-day mortality in the Europe and the United States ranges from 7 to 12%.[15-17] We therefore believe the reduction of nationwide 90-day mortality from 5 to 2.7% in our study is clinically relevant.

The rationale for the multimodal, multidisciplinary algorithm is based on two concepts. The first concept is timely identification of complications before they become clinically relevant. Complications of abdominal operations can lead to sudden clinical deterioration with a cascade of sepsis, multiple organ failure, and death.[27] There often exists a short time window in which early signs of these complications may be visible on CT scan, before they have clinical consequences. For this reason, the algorithm recommends abdominal CT scan once a certain threshold of subtle changes in vital signs and serum inflammatory markers is reached, even in patients with no clinical suspicion of complications. Use of the algorithm resulted in an increase in number of CT scans performed in the intervention group. Patients in the intervention group also underwent their first CT scan two days earlier than patients in the control group. These findings support the efficacy of the algorithm with regard to timely identification of complications.

The second concept for the algorithm is timely treatment of complications using a minimally invasive approach, as opposed to reoperation. Patients in the intervention group underwent treatment with antibiotics and radiologic drainage more often, and earlier, than patients in the control group. Fewer patients in the intervention group underwent reoperation. It is known that general anaesthesia required for surgery and the pro-inflammatory 'second hit' of the surgical trauma may worsen the physiological downward spiral of organ failure in critically ill patients.[28,29] Radiologic drainage has long been recognized in the treatment of complications after elective pancreatic surgery, but few studies have been performed on this topic.[30] One recent observational study suggested that radiologic drainage decreases complications and death compared to primary reoperation for pancreatic fistula.[9] Our study provides further evidence for this concept.

Although the individual changes in clinical management induced by the algorithm may not appear large, the combined effect of changes led to a clinically relevant reduction of the primary outcome. We did not investigate the beneficial effect of each individual component of the algorithm, including general awareness for the patient's wellbeing because of the daily clinical assessment by a pancreatic surgeon. This could be focus for future research, potentially leading to a leaner algorithm. It has been suggested that the use of modern technology, like artificial intelligence, might facilitate the decision to operate, identification and mitigation of modifiable risk factors and decisions regarding postoperative management. These modalities are gaining popularity in many fields of medicine, but have only been sparsely studied in surgery.[31]

The main strength of our study is its generalizability to everyday surgical practice. The nationwide effect of the intervention was similar in subgroups of low/mid-volume centres and high-volume centres in the Netherlands. This supports the notion that, even in centres with substantial experience in pancreatic surgery, outcomes of patients may be improved further using a standardized and more intensive approach for early recognition and management of complications. The parameters for the algorithm include vital signs and serum inflammatory markers that are already widely used in daily practice. CT scan and radiologic drainage are also commonly available techniques. This implies that implementation of the algorithm is feasible also in most countries, regardless of potential differences in the healthcare system of the Netherlands. It does, however, require the commitment of the involved clinicians and the hospital capacity to perform diagnostic and interventional radiologic procedures in around two-third of postoperative patients. There were no apparent downsides from the use of the algorithm. Total costs were not increased. The algorithm is safe, low cost, and easy to use, which was also underlined by the completion of the algorithm using the smartphone application tool. Nevertheless, it was observed that, in some centres, it was challenging to persistently adhere to the recommendations given by the algorithm. Compliance by the treating pancreatic surgeons was 70-83%. This can be considered a limitation of our study. The effect of the algorithm may have been even greater if adherence would have

been higher. The observed level of adherence, however, can still be considered quite high, taking into account that it is counterintuitive for clinicians to perform diagnostics or and inventions in patients who do not show any clinical signs of a postoperative complication. Although it did not reach statistical significance, there appeared to be an increase in the incidence of pancreatic fistula in the intervention group. This was expected because radiologic drainage and antibiotic treatment was recommended in the algorithm at a low threshold, which is classified as grade B postoperative pancreatic fistula according to international definitions.[8] It has been recognized, however, that adequately drained grade B pancreatic fistula are of limited clinical significance.[9,11] This is supported by our finding of the substantial reduction in the primary endpoint of major complications and death in the intervention group. There appears to be a specific 'number needed to treat' for abdominal CT, antibiotics and radiologic drainage in patients who are not clinically ill, to prevent one potentially fatal event as a result of a pancreatic fistula, thereby reducing the failure to rescue rate. In addition, data might be subjective to sparse data bias.

Failure to rescue has become an internationally endorsed, publicly reported quality measure for all types of surgery with potentially life-threatening complications.[2-5] Early recognition and management of postoperative complications have been proposed as the main focus to decrease mortality in elective surgical patients.[2-5] In our study, the first randomised clinical trial on this topic, failure to rescue has been decreased from 15.1% (44 of 290 patients with major complications) to 7.6% (23 of 301 patients with major complications, appendix). We are not aware of other algorithms that have been studied to improve early detection and timely management of postoperative complications. We only included patients undergoing pancreatic resection. One may therefore question the generalizability to other patient populations. In the future, the algorithm may, however, be modified to study it's use in other diseases or surgical procedures with a high risk of postoperative complications (eg, major liver resection, colorectal, gastric and oesophageal surgery).

In conclusion, our trial showed that early recognition and minimally invasive management of complications after pancreatic resection reduces the composite outcome of bleeding requiring invasive intervention, organ failure, and death compared to usual care.

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Supplementary appendix to

Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in the Netherlands: an open-label, nationwide, steppedwedge cluster-randomised trial

SUPPLEMENTARY METHODS

Study oversight

This trial was designed and conducted in accordance to the requirements of the Helsinki Declaration and Good Clinical Practice. Central ethical approval was confirmed from the Medical Ethical Committees United (MEC-U), reference number W17.057. The local medical ethical and local scientific committees of the participating centres approved this study and waived the need for informed consent. Patients were informed on the routine data collection to evaluate the quality of care according to local procedures. It was not thought to be possible to obtain individual patient informed consent for several reasons. The intervention proposed in this trial comprised of education of local clinicians on this best practice algorithm and, therefore, the aim all patients treated in centres that have crossed-over to algorithm centred care would be exposed to the intervention. Asking for informed consent would introduce bias, for this would only be asked from patients in the intervention group. Selective non-use of the algorithm in patients who would not provide informed consent was not thought to be feasible, because the algorithm induced a general change in practice on the level of the hospital and contamination would occur. Selective use of the algorithm was also expected to hamper successful broad implementation among the all involved clinicians from different departments of the hospital. Finally, an important condition for waiver of individual informed consent was that patients did not suffer from additional risk or burden from the study intervention. Therefore, before start of inclusion, consensus was reached among surgeons from every centre of the Dutch Pancreatic Cancer Group and from the leading surgeons from three renowned international centres that the algorithm represents the best quality of care. All elements included in the algorithm were already used in daily practice before start of the study, no new interventions were introduced. The principal investigator of every participating centre signed a declaration of intent for participation before the start of this study (ie, gate keeper informed consent)[1]. During the study, potential adverse events were monitored continuously. These events were discussed during regular meetings that were open for all clinicians from centres that had crossed-over to algorithm centred care. Discussed were a total of 2 complications potentially related to minimally invasive drainage (0·2% of all drainage procedures; one perforation of the stomach and one bowel perforation).

Design of the study intervention

The study intervention was the multimodal, multidisciplinary algorithm for early recognition and minimally invasive management of complications after pancreatic resection. The design of the algorithm was based on: 1) an evaluation of current practice through retrospective cohort studies[2,3]; 2) an inventory of guidelines on postoperative care[1]; 3) a systematic review of the literature[4]; 4) consensus meetings with the steering committee; 5) validation in a retrospective patient cohort; 6) a national consensus meeting with one pancreatic surgeon from every centre; and 7) evaluation by an international advisory committee. Details have been previously published.[1]

1. Evaluation of current practice
   Current practice at the time of designing the study in the Netherlands was evaluated by two previously published nationwide observational cohort studies:

   - *Failure to rescue in the Netherlands*
     1300 consecutive patients undergoing pancreatic resection who were included in the nationwide mandatory Dutch Pancreatic Cancer Audit in 2014 and 2015 were retrospectively analysed for failure to rescue (ie, mortality in a patient with major complications).[2] The 18 hospitals were divided into quartiles based on in-hospital death. In the first hospital quartile (327 patients in 4 hospitals), death was 0·9%, and in the fourth quartile (310 patients in 5 hospitals), death was 8·1%. Patients in hospitals with a high death rate had a slightly increased major complication rate (ie, Clavien-Dindo grade III and higher) (40% increase), but a much higher failure to rescue rate (560% increase), as compared with hospitals with low mortality. These findings supported the concept that complication management should be the focus to improve outcomes after pancreatic resection.

   - *Management of postoperative pancreatic fistula in the Netherlands*
     A retrospective, propensity-score matched cohort study was performed in 9 centres of the Dutch Pancreatic Cancer Group to investigate the superiority of radiologic drainage over primary relaparotomy for postoperative pancreatic fistula.[3]

   A total of 309 out of 2196 patients undergoing pancreatoduodenectomy had severe postoperative pancreatic fistula and were included. Overall, 227 patients (73%) underwent primary radiologic drainage and 82 patients (27%) underwent primary relaparotomy. Radiologic drainage was successful (ie, survival without relaparotomy) in 77% of patients. Using propensity-score matching, 64 patients undergoing primary relaparotomy were matched to 64 patients undergoing primary catheter drainage. Death was lower after catheter drainage (14% vs. 36%; P=0·007). New-onset single-organ failure (3% vs. 20%; P=0·007) and new-onset multiple-organ failure (16% vs. 39%; P=0.008) were also lower after radiologic drainage. Comparison of management strategies between the participating centres showed a range of 12% to 67% of patients undergoing relaparotomy as primary intervention for pancreatic fistula.

   These findings demonstrated that primary reoperation after pancreatic resection was performed often and was associated with poorer outcomes than a minimally invasive approach using radiologic drainage.

2. Guideline inventory
   A systematic inventory of guidelines on postoperative management of pancreatic resection in the Dutch hospitals was performed. Most centres used vital signs and inflammatory markers (ie, serum C-reactive protein and white blood cell count) only one centre used predefined cut-offs. An overview is available in the published study protocol.[1]

3. Systematic literature review
   A systematic review of published data was performed to investigate the diagnostic accuracy of different physical examination parameters, biochemical tests and diagnostic imaging modalities for pancreatic fistula after pancreatic resection. This systematic review has been published previously.[4]

4. Consensus meetings with the steering committee
   Results from step 1-3 were used to design version 1 of the algorithm. This was discussed during several consensus meetings with the members of the Steering Committee, which included a small group of pancreatic surgeons and radiologists from 3 centres of the Dutch Pancreatic Cancer Group.

5. Validation in a retrospective patient cohort
   The anticipated effect of the algorithm on the number and timing of abdominal CT scans performed in daily clinical practice was evaluated in a retrospective cohort of 174 patients undergoing pancreatic resection in 3 high-volume centres of the Dutch Pancreatic Cancer Group in 2016. To prevent contamination (ie, clinicians changing their practice after reviewing the algorithm), we did not perform a formal prospective pilot study.

   Data on patient characteristics, pancreatic resection, postoperative parameters (ie, body temperature, respiratory rate, heart rate, C-reactive protein, white blood cell count, and drain amylase) and details on hospitalization course were collected. In the 174 patients, the algorithm yielded an accuracy of 73%, a positive predictive value of 15%, and a negative predictive value of 96% for postoperative pancreatic fistula. A total 65 patients underwent an abdominal CT scan in real-life practice, whereas a total of 85 patients would have undergone a CT scan according to the algorithm. 22 out of 23 patients with severe pancreatic fistula (ie, requiring invasive intervention) would have received a CT scan according to the algorithm. The median timing of first CT scan was postoperative day 5 in real-life practice (interquartile range 3 to 7) and postoperative day 3 according to the algorithm (interquartile range 3 to 4). Initiating the algorithm on postoperative day 3 appeared to be sufficient because 20% of patients ultimately underwent radiologic drainage based on a CT scan performed on postoperative day 3. In summary, the algorithm appeared to lead to an increase of CTs, performed earlier in the postoperative course, and seemed to be effective in detecting patients who ultimately developed severe pancreatic fistula.

6. A national consensus meeting
   The version of the algorithm that was validated in the retrospective patient cohort was discussed at a meeting with pancreatic surgeons from each centre of the Dutch Pancreatic Cancer group. To prevent contamination in daily clinical practice, only one pancreatic surgeon from every centre was invited. All participants vowed confidentiality. Suggestions for improvement were made after which consensus was reached on both the algorithm and the general study design.

7. Evaluation by an international advisory committee
   Three pancreatic surgeons from high-volume pancreatic centres who are considered to be international experts agreed to serve in an international advisory committee. These experts reviewed the final version of algorithm and study design, which were also presented at Johns Hopkins medical centre. All comments received from the expert surgeons were processed in the final version of the algorithm and study protocol before start of the study.

Details of the study intervention

The algorithm is followed from postoperative day 3 to 14. Postoperative day 3 was chosen as the first day because pancreatic fistula only rarely occurs within the first 3 days and the inflammatory response induced by the index operation limits the accuracy of inflammatory markers for complications in the early postoperative phase.[5-7] In short, the algorithm provides a multilevel advice:

1. Indication for abdominal CT
   Based on information from vital signs, biochemical inflammatory markers, amylase in drain fluid, clinical assessment by the pancreatic surgeon and whether or not a CT has been performed in the past 24 hours, the algorithm provided an advice to perform abdominal CT. The inclusion of the individual parameters (ie, fever, serum C-reactive protein, white blood cell count, systemic inflammatory response syndrome [SIRS]), drain amylase) and their specific cut-offs were based on an extensive systematic literature search. Results are presented in the published systematic review.[4]

2. Evaluation of abdominal CT: additional radiological drainage and antibiotic treatment
   All CT scans were assessed by a dedicated abdominal radiologist in each centre according to a predefined list of criteria. The information was used to compete the algorithm with main focus on three aspects: suspicion of a pancreatic fistula (ie, low density fluid in relation to the pancreatic anastomosis or pancreatic remnant, dehiscence of the pancreatic anastomosis, or other signs of pancreatic leakage), other postoperative complications, position of current abdominal drain(s), whether additional drainage was deemed beneficial and whether this was technically feasible. If additional drainage was advised by the algorithm, it was recommended to place

a radiological drain with the tip at the presumed origin of fluid (eg, the pancreatic anastomosis). Based on information from vital signs and biochemical inflammatory markers, the algorithm generated an advice to start or continue intra-venous antibiotics in case of a systemic inflammatory response syndrome.

An online expert panel of pancreatic surgeons and interventional radiologists was available to aid in clinical decisions and to assess technical aspects of radiologic drainage. On request of a local clinician, the study coordinator would upload an anonymized video of the CT images and a standardized electronic form with clinical details through a secure and private messenger application to the expert panel. The individual members provided an advice on technical feasibility of radiologic drainage as soon as possible, always within 12 hours, which was forwarded to the local medical team.

3. Removal of abdominal drains
   As long as abdominal drains were situated, the algorithm provided an advice on whether or not to remove these drains. This was based on information regarding drain fluid appearance, drain output volume and drain amylase levels. The inclusion of these parameters and their specific cut-offs were based on an extensive systematic literature search. Results are presented in the published systematic review.[4] A separate advice was given for each drain in place. In general, the aim was to remove drains at the earliest possibility, since they may be a source of infection.

The algorithm was designed to aid the early recognition and minimally invasive management of postoperative pancreatic fistula. It was anticipated, however, that other complications such as hepatojejunostomy leakage would also be detected. Guidelines for management of hepatojejunostomy leakage and bleeding were also provided as part of the study intervention. Details are available in the published study protocol.[1]

The final decision on diagnostics and therapeutic intervention were always left to the discretion of the treating pancreatic surgeon.

Smartphone application

An application was designed to aid in the daily use of the algorithm. The application was made available for download to clinicians by the study coordinator once their centre had cross-over to algorithm centred care. A live on-site demonstration of this application was provided by the study coordinator for each centre. The application was published on both the apple store and google play store, in addition a web-based version was published. Each clinician involved (eg, local pancreatic surgeons, physician assistants, surgical residents) received a login and password for personal use of the application. Patients undergoing pancreatic resection were registered in the application for each centre, after removal of identifiable data. Only clinicians from that specific centre, who were part of the medical team for that patient, had access to the data.

On each postoperative day 3 to 14, clinical and biochemical data for each registered patient were entered in the application by the treating local clinician. Using the algorithm, an advice was generated by the application on initiating or continuing antibiotic treatment, performing an abdominal CT scan, and abdominal drain removal. If CT was performed, selected information from the standardized assessment of the CT scan was subsequently entered in the application. This information was used by the application to generate an advice on whether or not to perform radiological drainage procedure. Members of the local medical team could monitor patients through the history record in the application.

Figure 1 shows a pictorial of the smartphone application that was used during the trial. Data obtained using the application was used to generate a secure online dashboard for the study coordinator, who was not involved in clinical care. This dashboard was used to prospectively monitor study progress and protocol adherence (ie, completion of the algorithm for each patient on postoperative day 3 to 14 and the advice to perform abdominal CT). Continuous feedback on protocol adherence was given to local clinicians through daily reminders if the application was not jet filled out.

The application was designed solely to be used for study purposes. An international approved (ie, CE marking) version of the application, designed for using the algorithm in clinical care, without central data storage and monitoring functionalities, is currently being prepared. This application will become available, free of charge, after publication of the results of the PORSCH study through online app stores.

Figure 1. Pictorial of the smartphone application used during the trial to facilitate the use of the study intervention.

Outcomes

The primary outcome was a composite of:

- Bleeding requiring invasive intervention (ie, radiological, surgical or endoscopic)
- New-onset organ failure (ie, pulmonary, circulatory or renal)
- Death

Definitions are provided in Box S1. We chose a composite endpoint which includes the most severe clinical events that can occur in these patients. Bleeding was included in the endpoint because this can occur as a direct consequence of a pancreatic leakage (or other septic complications) that is not adequately treated. Organ failure can occur as a result of severe systemic inflammation because of pancreatic leakage. Both complications can lead to death. It was anticipated that there would not be enough statistical power to study mortality as individual primary endpoint and therefore a composite endpoint was chosen.

The primary aim of the trial was to study the effect of the study intervention (ie, the algorithm for early recognition and minimally invasive management of complications). It was reasoned those complications occurring during the index pancreatic resection or directly postoperative cannot be prevented by the algorithm, which by design is initiated on postoperative day 3. We designed the algorithm to start at postoperative day 3 because for several reasons. First, the aim was to improve outcome by early recognition and treatment of postoperative complications, before they become clinically manifest. These complications do not include complications that occur during the index operation/directly postoperatively (eg, an early bleeding due to technical error) because they become clinically apparent very fast. Instead, the algorithm was mainly focused pancreatic fistula and other septic complications, which take a few days after the operation to occur and to be visible on imaging. Secondly, even if they would occur early, diagnosis of these complications by CT is very difficult in the first few days after the operation. Morphologic/reactive changes due to the surgery make early CT scans difficult to interpret. A low threshold to perform CT on day 1-2- postoperatively would have led to serious interpretation issues. Thirdly, in the first 1-2 days postoperatively, vital signs and measurements of inflammatory parameters are often abnormal as a direct consequence of the index operation, and therefore not reliable for diagnosing complications. This would have led to many unnecessary CTs.

Care during the first 48 hours was standardized in all centres, and included admission to the ICU or post-operative-anaesthesia care unit (PACU) during the first night after surgery, with focus on respiratory and hemodynamic support and analgesics according to an enhanced recovery program. At least one postoperative intra-abdominal drain was left in place after pancreatic resection. Routine laboratory measurements were performed daily, including serum inflammatory parameters used in the algorithm at postoperative day 3.

Box 1: Definitions of the primary and secondary clinical outcomes

Outcome	Definition
Primary composite outcome	
Bleeding requiring invasive intervention	Bleeding requiring invasive intervention: angiography with coiling or stenting, or endoscopy with electrocoagulation or clipping, or reoperation.
New-onset organ failure	New onset (ie, not present any time in 24 hrs before study intervention, set at postoperative day 3 in both study groups) failure of one or more organ systems.
Circulatory failure	Systolic blood pressure <90mmHg, despite adequate fluid resuscitation, or need for inotropic support
Respiratory failure	PaO2 <60mmHg, despite FiO2 of 0·3, or need for mechanical ventilation
Renal failure	Creatinine level >177μmol/litre after rehydration or need for hemofiltration or haemodialysis
Death	Death occurring within 90 days after index pancreatic resection or, if index admission exceeds 90 days, during admission
Secondary clinical outcomes	
Postoperative pancreatic fistula	Amylase in drain fluid on or after postoperative day three of at least three times the upper level of normal serum amylase. Adapted from Bassi et al.[10]
Grade A / Biochemical leak	Requiring no change in postoperative management, hospital stay not prolonged
Grade B	Persistent drainage >3 weeks, change in postoperative management (ie, catheter drainage, or angiographic procedure for bleeding, no organ failure, no relaparotomy), all related to pancreatic fistula
Grade C	Grade B with reoperation, organ failure or death related to pancreatic fistula
Postoperative bile leakage	Bilirubin in drain fluid on or after postoperative day three of at least three times the upper level of normal serum bilirubin. Adapted from Koch et al.[12])
Delayed gastric emptying	Adapted from Wente et al[13]
Grade A	Nasogastric tube postoperative day 4 to 7 or need for replacement of tube after postoperative day 3; oral intake between day 7 and 14
Grade B	Nasogastric tube postoperative day 8 to 14 or need for replacement of tube after postoperative day 7; oral intake between day 14 and 21
Grade C	Nasogastric tube after postoperative day 14 or need for replacement of tube after postoperative day 14; oral intake after day 14
Gastroenterostomy leakage	As seen on abdominal imaging or during relaparotomy or secretion of faecal material from percutaneous drain or through surgical wound
New onset-acute pancreatitis	Combination of abdominal pain, three-fold increased amylase and lipase levels or as seen on radiologic imaging
Comprehensive complication index (CCI)	This summarizes all postoperative complications, other than pre-existed complications, in a score from 0 (no complications) to 100 (death). The CCI can be readily computed on the basis of tabulated complications according to the Clavien-Dindo classification (available at www.assessurgery.com).[14,15]

To avoid bias, outcomes in both study groups were assessed by the blinded adjudication committee during the same time period: from postoperative day 3 onward, up to 90 days after pancreatic resection, or if patients were still admitted to hospital at 90 days, during the entire hospital admission. Before any analyses were performed, however, the adjudication committee decided to also include any deaths that occurred before day 3 as component of the composite outcome, in both study groups, because it was felt that implementation of the algorithm may also have a general beneficial effect on patient population level and omitting the clinically most relevant outcome of death would potentially underestimate the effect of the intervention.

Statistical analysis

The required sample size was calculated using the formula for stepped wedge designs using an expected incidence of 13·8%, a relative reduction of 50%, a two-sided alpha of 0·05 and a power of 0·8032. The intra-cluster correlation (ICC) was estimated from the Dutch Pancreatic Cancer Audit at 0·009 (95% CI 0·006-0·049). Because cluster autocorrelation was defined by the division of the within-period and between-period ICC and these periods were exactly the same, the cluster autocorrelation was 1. This resulted in a sample size of 1186 pancreatoduodenectomies in 17 participating centres.

Missing values were evaluated across centres and procedures. Based on rationale, there was no pattern or explanation found for missing data. Therefore, we moved to multiple imputation. Included in the multiple imputation model were all baseline characteristics (ie, sex, age, body mass index, ECOG performance score, ca 19.9 values, preoperative biliary drainage, neoadjuvant therapy, American Society of Anaesthesiologists score, use of somatostatin analogues type of pancreatic resection, minimally invasive pancreatic resection, pancreatic texture, diameter pancreatic duct, perioperative blood loss, underlying disease, fistula risk score), study group, hospital, time and the primary endpoint. Multiple imputation was run with 10 iterations creating a total of 20 complete datasets. Non-normally distributed data were normalized before implementation, by the subtraction of the value from the group mean, divided by the standard deviation. All categorical variables were identified as such, with reference category as lowest value. Imputed values were visualized and as there were no clusters of imputed values, missing was considered to be random.

The study protocol predefined mixed-effects logistic regression analyses of the binary outcomes with odds ratio's as index of effect size. However, because risk ratios are preferred in terms of interpretation, collapsibility, and less susceptibility to sparse-data bias, for the final analyses we performed mixed-effects Poisson logistic regression analysis with robust standard errors to take clustering into account. The trial protocol stated that two separate analyses would be performed1. First, a crude analysis only adjusting for study design by including a random intercept and random slope at the level of the hospital. Second, an adjusted analysis including a random intercept and random slope and, in addition, calendar time and time since cross-over and several baseline variables. The baseline variables included known risk factors from the literature for pancreatic fistula (ie, soft pancreatic texture, small-diameter pancreatic duct, increasing blood loss during pancreatic resection and underlying disease that is not pancreatitis or pancreatic adenocarcinoma) and predictors for the primary outcome that we identified in a multivariable regression analysis of 1686 patients undergoing pancreatic resection included the Dutch Pancreatic Cancer Audit (ie, male gender, increasing age, American Society of Anaesthesiologists (ASA) classification > 2, pancreatoduodenectomy or other type of pancreatic resection).1,2 As predefined, relevant model assumptions were checked. Linearity for quantitative predictors was checked visually by plotting the predictor against the response residuals in the regression models. There were no signs of nonlinearity. For both the crude and

adjusted models, inclusion of a random slope resulted in an unstable model. Because there was no difference in the slopes between hospitals, we included a random intercept at the level of the hospital and fixed slope in the final model. Introduction of the variable time since crossover (0 for patients in the control group) in the adjusted model introduced statistical uncertainty. Further exploration of the role of this variable showed there was no significant association between this variable and the primary endpoint, inclusion of this variable did not change the point estimate of the primary outcome and resulted in a similar Akaike Information Criterion (AIC). We therefore excluded this variable to obtain a more parsimonious model. In addition, hospital volume was added to the variables corrected for in adjusted analysis, for this criterium was used for stratification in the randomisation process. Outcomes are presented as risk ratio's (RR) with 95% confidence interval (CI). The study protocol stated that both crude RR's and adjusted RR's would be reported. The adjusted RR's are considered primary analysis, as the cluster-randomized design harbours an inherent risk of confounding due to changes in patient population or management over time not related to the intervention. The crude RR's are reported in the supplementary appendix.

For analysis of length of hospital stay (ie, time to hospital discharge), a Cox proportional hazards models was used with a frailty for hospital, in which patients who died during index hospitalization were censored at time of death. A Cox model was also used for time to event analysis on start of antibiotics, first CT scan, first drainage and start of adjuvant chemotherapy. As predefined, relevant model assumptions, were checked. Linearity for quantitative predictors was checked visually by plotting the predictor against the martingale residuals in the cox model. There were no signs of nonlinearity. Outcomes are presented as crude and adjusted hazard ratios with 95% CI's, in which a higher hazard ratio indicating a shorter time to event.

For analysis of count data on length of ICU stay, days to resolution of postoperative pancreatic fistula, a zero inflated negative binominal regression model was used. Outcomes are presented as the adjusted conditional risk ratios with 95% CI's for the count and the adjusted inverted odds ratio's with 95% CI's for the zero inflated model component.

For analysis of the count data days on antibiotic treatment, number of CT scans, number of radiologic drainage procedures, number of reoperations, and CCI, a negative binominal regression model was used. Outcomes are presented as crude and adjusted rate ratio's with 95% CI's. P values are not corrected for multiple testing. For all analyses, a normal distribution of random effects was assumed.

Cost analysis

As a secondary outcome, total direct costs were calculated from a healthcare perspective. All medical costs up to 90 days after pancreatic resection, or if patients were still admitted to hospital at 90 days, during the entire hospital admission were assessed according to the Dutch guidelines for (pharmaco-)economic research.[8] Guideline unit costs were used for

hospital stay and ICU stay. Costs for antibiotics were derived from the Dutch pharmaceutical unit cost listings.[9] Weighted means for unit costs for laboratory measurements, radiological tests and procedures, endoscopic procedures and surgical procedures were calculated at one large non-academic teaching hospital and at one academic hospital in 2019. This included all personnel costs, costs of materials, costs of equipment, and overhead costs. Costs per patient were calculated by multiplying volumes of resource with unit costs. All costs in Euro's were set at the year 2019 price level using the price index rate of the Dutch health care sector. Mean hospital costs with 95% CI per treatment arm are presented. CI's were created using bias-corrected and accelerated (BCa) non-parametric bootstrapping, by drawing 5,000 samples with replacement of the same size as the original for each treatment group. An overview of total costs is provided in Table 1.

The original protocol described a formal cost-effectiveness analysis including quality of life, total direct and indirect costs and budget impact analysis. These analyses have not yet been performed and will be published separately.

Table 1: Total direct medical costs*

	Intervention (n=863)		**Control (n=885)**		**Difference †**
	Total costs	**Mean costs per patient**	**Total costs**	**Mean costs per patient**	**Mean costs per patient (95% CI)**
Pancreatic resection	7,043,229	8,161	7,257,174	8,200	39 (-89-167)
Admission					
General ward stay	6,922,800	8,022	6,886,212	7,781	-241 (-930-448)
Intensive Care Unit stay	4,825,142	5,591	5,033,808	5,688	97 (-1,095-1,288)
Laboratory tests	86,533	100	54,204	61	-39 (-45 - -33)
Antibiotics	30,887	36	29,109	33	-3 (-9-3)
Abdominal CT-scans	321,264	372	248,980	281	-91 (-134- -47)
Endoscopic interventions					
Diagnostic gastroscopy	263	0	2,367	3	2 (0-5)
Therapeutic gastroscopy for bleeding	3,307	4	2,362	3	-1 (-5-2)
Feeding tube placement	73,634	85	85,731	97	12 (-9-32)
Transluminal drainage	14,750	17	26,550	30	13 (-17-42)
Radiologic interventions					
Percutaneous catheter drainage	221,283	256	205,754	232	-24 (-78-30)
Percutaneous transhepatic biliary drainage	42,533	49	35,061	40	-10 (-34-5)
Angiographic procedures	83,954	97	66,831	76	-22 (-66-23)
Reoperation	317,486	368	562,739	636	268 (53-484)
Total direct medical costs	19,987,064	23,160	20,416,948	23,236	76 (-1,655 -1,807)
Mean direct medical costs per patient ‡	**23,202 (22,024-24,498)**		**23,450 (22,100-24,450)**		**248 (-1,395-1,890)**

* Amounts are in Euro's, for conversion to US dollars multiply by 1,20.

† This is the difference in costs between postoperative treatment according to usual care and postoperative treatment according to the algorithm.

‡ Mean and 95% confidence intervals were estimated using the percentile bootstrap method with 5000 replications.

SUPPLEMENTARY RESULTS

Details on protocol adherence

The smartphone application was completed 9308 times. In 94% of patients, the application was completed on each postoperative day 3-14.

The recommendation to perform a CT scan was followed in 75%. The recommendation to start (or continue) antibiotic treatment was followed in 70%. Reasons not to follow the advice were: not deemed 'necessary' by the treating surgeon based on clinical assessment of the patient (65%), because the patient had recently undergone an invasive intervention (15%) or due to logistic reasons (eg, due to pressure on radiologic department 19%). The rate of not followed recommendations was consistent over postoperative days. If all recommended CT scans were followed, this would not have resulted in a significant increase in costs, namely a mean of €23,219 per patient versus the actual costs of €23,160 per patient (Table 1).

The recommendation on abdominal drain removal was followed 83% of the time. Of recommendations that were not followed, 64% of drains were removed earlier and 36% of drains were left in longer than recommended by the study intervention. The checklist for radiology was filled out in 48% of CT scans.

Expert panel consultation

The expert panel was consulted 25 times. Reasons for consultation were related to diagnosis of postoperative pancreatic fistula (eg, is this CT scan suspected for pancreatic leakage, n=7) or related to management of complications (eg, can drainage can be optimized, what route should be used to approach this fluid collection, n=18).

Exploratory analyses

In tables 2 to 7 (starting next page) different subgroup- and sensitivity analyses are presented. All crude analyses were adjusted with random intercept for hospital and calendar time. In addition to these, adjusted analysis with adjustment for pancreatic texture, diameter pancreatic duct, blood loss pancreatic resection, underlying disease, sex, age, American Society of Anaesthesiologists (ASA) class, type of pancreatic resection and hospital volume.

Table 2: Primary and secondary outcomes: crude and adjusted analyses*

Outcome	Intervention (n=863)	Control (n=885)	Crude RR (95%CI) †	Adjusted RR (95%CI) †
Primary composite outcome: major complications or death	73 (8·5)	124 (14·0)	0·47 (0·39-0·56)	0·48 (0·38-0·61)
Bleeding requiring intervention	47 (5·4)	51 (5·8)	0·61 (0·41-0·91)	0·65 (0·42-0·99)
New-onset organ failure	39 (4·5)	92 (10·3)	0·32 (0·25-0·41)	0·35 (0·20-0·60)
Single-organ failure	21 (2·4)	44 (5·0)		
Multiple organ failure	18 (2·1)	48 (5·4)		
Circulatory failure	28 (3·2)	70 (7·9)	0·30 (0·19-0·44)	0·32 (0·23-0·46)
Respiratory failure	22 (2·5)	55 (6·2)	0·31 (0·22-0·46)	0·35 (0·24-0·50)
Renal failure	12 (1·4)	29 (3·3)	0·35 (0·17-0·74)	0·37 (0·16-0·85)
Death	23 (2·7)	44 (5·0)	0·42 (0·19-0·94)	0·42 (0·19-0·92)
Pancreatectomy specific complications ‡				
Postoperative pancreatic fistula	239 (27·7)	187 (21·1)	1·18 (0·93-1·50)	1·23 (0·97-1·56)
Days to resolution – median (IQR) §	36 (25-56)	42 (28-65)	0·92 (0·75-1·13)	0·88 (0·73-1·06)
Postpancreatectomy haemorrhage	66 (7·6)	76 (8·6)	0·72 (0·52-0·99)	0·74 (0·54-1·03)
Postoperative bile leakage ‖	66 (10·2)	57 (8·5)	0·80 (0·50-1·28)	0·90 (0·60-1·33)
Gastroenterostomy leakage ‖	8 (0·9)	12 (1·4)	0·87 (0·30-2·50)	0·88 (0·30-2·62)
Chyle leakage	61 (7·1)	69 (7·8)	0·92 (0·59-1·45)	0·95 (0·59-1·54)
Delayed gastric emptying	134 (16·5)	144 (16·9)	1·16 (0·75-1·78)	1·17 (0·76-1·80)
New-onset acute pancreatitis	3 (0·3)	9 (1)	0·23 (0·05-1·10)	0·22 (0·05-0·87)
CCI ¶	15 ± 24	17 ± 29	0·77 (0·72-0·81)	0·80 (0·76-0·84)
CCI excluding study interventions ¶	7 ± 20	11 ± 26	0·51 (0·45-0·56)	0·54 (0·48-0·60)
Major complications (ie, Clavien-Dindo[3] grade 3)	301 (34·9)	290 (32·7)	0·95 (0·80-1·12)	0·99 (0·83-1·19)
Failure to rescue (ie, mortality in patients with major complications)	23/301 (7·6)	44/290 (15·1)	0·44 (0·18-1·10)	0·45 (0·21-0·95)
Hospitalization course				
ICU admission **	57 (6·6)	80 (9·0)	0·54 (0·34-0·85)	0·57 (0·43-0·76)
Length of ICU stay (days, median (IQR)) ††	4 (3-9)	4 (2-8)	0·77 (0·41-1·45)	1·19 (0·74-1·93)
Length of hospital stay (days, median (IQR))‡‡	11 (8-18)	10 (7-15)	0·92 (0·83-1·01)	0·95 (0·81-1·11)
Readmission	168 (19·5)	188 (21·2)	1·05 (0·86-1·28)	1·04 (0·84-1·29)
Adjuvant chemotherapy §§	176 (58·4)	182 (60·5)	0·96 (0·81-1·16)	1·02 (0·87-1·22)
Adjuvant chemotherapy (time to start, days) ‖‖	56 (47-71)	56 (42-69)	0·93 (0·71-1·22)	1·00 (0·76-1·33)

* Plus–minus values are means ±SD. Data are n (%), mean (SD), or median (IQR) unless otherwise stated. Percentages may not sum to 100 because of rounding. CCI denotes comprehensive complication index. ICU denotes intensive care unit.

† Mixed model Poisson regression analyses.

‡ According to International Study Group definitions. Only grade B/C complications are included in analysis.

§ Presented is the conditional risk ratio from a zero inflated negative binominal regression model, a value <1 means lower time to resolution in the intervention group; zero inflated inverted adjusted odds ratio 1·72 (95% CI 1·33 to 2·21).

‖ Calculated over patients undergoing pancreatoduodenectomy (671 control patients vs. 643 intervention patients).

¶ Presented is the rate ratio from a negative binominal regression model.

** Calculated over subset of patients admitted to the ICU after postoperative day 3.

†† Calculated over subset of patients admitted to the ICU after postoperative day 3, presented is the conditional risk ratio from zero inflated binominal regression model; zero inflated inverted adjusted odds ratio 0·52 (95% confidence interval 0·31-0·87).

‡‡ Presented is the hazard ration from a cox proportional hazard analysis.

§§ Calculated over subset of PDAC patients surviving index admission (330 control patients vs. 319 intervention patients)

‖‖ Calculated over subset of PDAC patients surviving index admission (330 control patients vs. 319 intervention patients), presented is the hazard ration from a cox proportional hazard analysis

Table 3: Subgroup of patients undergoing pancreatoduodenectomy*

Outcome	Intervention (n=643)	Control (n=671)	Crude RR (95% CI) †	Adjusted RR (95% CI) †
Primary composite outcome: major complications or death	56 (8·7)	105 (15·6)	0·44 (0·35-0·56)	0·46 (0·34-0·61)
Bleeding requiring intervention	38 (5·9)	44 (6·6)	0·60 (0·39-0·95)	0·64 (0·39-1·05)
New-onset organ failure	33 (5·1)	79 (11·8)	0·33 (0·25-0·44)	0·35 (0·25-0·50)
Circulatory failure	24 (3·7)	60 (8·9)	0·29 (0·18-0·45)	0·33 (0·22-0·49)
Respiratory failure	22 (3·4)	48 (7·1)	0·44 (0·29-0·66)	0·46 (0·28-0·72)
Renal failure	10 (1·5)	26 (3·9)	0·34 (0·14-0·83)	0·36 (0·15-0·87)
Death	17 (2·6)	35 (5·2)	0·39 (0·20-0·74)	0·40 (0·18-0·85)
Clinical events ‡				
Postoperative pancreatic fistula	186 (29·0)	138 (20·6)	1·25 (0·94-1·66)	1·34 (0·98-1·83)
Postoperative bile leakage	66 (10·3)	57 (8·4)	0·80 (0·50-1·28)	0·90 (0·60-1·33)
Gastroenterostomy leakage	8 (1·2)	11 (1·6)	0·87 (0·30-2·51)	0·88 (0·30-2·59)
Chyle leakage	45 (7·0)	62 (9·2)	0·99 (0·60-1·64)	1·04 (0·56-1·93)
Delayed gastric emptying	126 (20·3)	138 (21·2)	1·11 (0·69-1·78)	1·12 (0·68-1·85)
Hospitalization course				
ICU admission §	48 (7·5)	67 (10·0)	0·55 (0·36-0·85)	0·60 (0·47-0·76)
Length of ICU stay (days, median (IQR)) ‖	5 (3-9)	4 (2-8)	0·65 (0·32-1·34)	1·34 (0·78-2·32)
Length of hospital stay (days, median (IQR)) ¶	13 (8-21)	12 (8-18)	1·06 (0·89-1·26)	0·99 (0·83-1·17)
Readmission	117 (18·5)	133 (20·6)	1·14 (0·79-1·64)	1·17 (0·85-1·63)
Adjuvant chemotherapy **	146 (57·0)	149 (55·6)	0·97 (0·81-1·16)	1·02 (0·78-1·21)
Adjuvant chemotherapy (time to start, days) **	57 (48-71)	56 (44-70)	1·09 (0·81-1·46)	1·10 (0·81-1·49)

* Plus–minus values are means ±SD. Data are n (%), mean (SD), or median (IQR) unless otherwise stated. Percentages may not sum to 100 because of rounding. ICU denotes intensive care unit.

† Mixed model Poisson regression analyses.

‡ Only grade B/C complications are included in analysis.

§ Calculated over subset of patients admitted to the ICU after postoperative day 3.

‖ Calculated over subset of patients admitted to the ICU after postoperative day 3, presented is the conditional risk ratio; zero inflated inverted adjusted odds ratio 0·95 (95% confidence interval 0·56-1·50).

¶ Calculated time to event analysis using cox proportional hazard model. Hazard ratio's over 1 indicate a shorter time to event in the intervention group.

** Calculated over PDAC patients surviving index admission (268 control patients vs. 256 intervention patients).

Table 4.a: Exploratory analysis with stratification on hospital volume (presented is the subgroup of patients in low/mid-volume centre (≤45 pancreatic resections annually))*

Outcome	Intervention (n=291)	Control (n=294)	Adjusted RR (95%CI) †
Primary composite outcome: major complications or death	25 (8·6)	42 (14·3)	0·49 (0·25-0·68)
Bleeding requiring intervention	14 (4·8)	14 (4·8)	0·65 (0·44-1·97)
New-onset organ failure	18 (6·2)	30 (10·2)	0·42 (0·26-0·71)
Death	8 (2·7)	20 (6·8)	0·35 (0·11-1·16)

*Cut-off is based on the median number of pancreatic resections performed annually according to the Dutch Pancreatic Cancer Audit years 2014-2015.
† Mixed model Poisson regression analyses.

Table 4.b: Exploratory analysis with stratification on hospital volume (presented is the subgroup of patients in high-volume centre (>45 pancreatic resections annually))*

Outcome	Intervention (n=572)	Control (n=591)	Adjusted RR (95% CI) †
Primary composite outcome: major complications or death	48 (8·4)	82 (13·9)	0·46 (0·32-0·66)
Bleeding requiring intervention	33 (5·8)	37 (6·2)	0·67 (0·34-1·32)
New-onset organ failure	21 (3·6)	62 (10·5)	0·27 (0·24-0·32)
Death	15 (2·6)	24 (4·1)	0·48 (0·18-1·32)

*Cut-off is based on the median number of pancreatic resections performed annually according to the Dutch Pancreatic Cancer Audit years 2014-2015.
† Mixed model Poisson regression analyses.

Table 5: Exploratory analysis including wash-in patients*

Outcome	Intervention (n=915)	Control (n=890)	Adjusted RR (95% CI) †
Primary composite outcome: major complications or death	79 (8·6)	124 (13·9)	0·51 (0·41-0·65)

* Date of pancreatic resection determines in which study phase a patient is in. All patients undergoing pancreatic resection after the first implementation presentation as given in a centre were included in the intervention group.
† Mixed model Poisson regression analyses.

Table 6: Exploratory analysis of primary outcome using generalized estimating equations*

Outcome	Intervention (n=863)	Control (n=885)	Crude RR (95%CI) †	Adjusted RR (95%CI) †
Primary composite end-point: major complications or death	73 (8·5)	124 (14·0)	0·47 (0·39-0·58)	0·49 (0·37-0·64)
Bleeding requiring intervention	47 (5·4)	51 (5·8)	0·60 (0·40-0·91)	0·66 (0·40-1·09)
New-onset organ failure	39 (4·5)	92 (10·3)	0·32 (0·25-0·42)	0·35 (0·27-0·46)
Single-organ failure	21 (2·4)	44 (5·0)		
Multiple organ failure	18 (2·1)	48 (5·4)		
Circulatory failure	28 (3·2)	70 (7·9)	0·31 (0·21-0·46)	0·29 (0·20-0·41)
Respiratory failure	22 (2·5)	55 (6·2)	0·32 (0·21-0·49)	0·35 (0·24-0·51)
Renal failure	12 (1·4)	29 (3·3)	0·34 (0·16-0·71)	0·35 (0·15-0·82)
Death	23 (2·7)	44 (5·0)	0·44 (0·20-0·98)	0·43 (0·20-0·94)

* Data are n (%), mean (SD), or median (IQR) unless otherwise stated. Percentages may not sum to 100 because of rounding.

† Presented are risk ratio's with 95% confidence interval from generalized estimating equations with clustering on facility and adjustment for calendar time, pancreatic texture, diameter pancreatic duct, blood loss pancreatic resection, underlying disease, gender, age and American Society of Anaesthesiologists (ASA) class and type pancreatic resection.

Table 7: Analysis using mixed effects logistic regression*

Outcome	Intervention (n=863)	Control (n=885)	Adjusted OR (95%CI)	P Value
Primary composite outcome: major complications or death	73 (8·5)	124 (14·0)	0·42 (0·27-0·66)	0·0001
Bleeding requiring intervention	47 (5·4)	51 (5·8)	0·64 (0·35-1·17)	0·13
New-onset organ failure	39 (4·5)	92 (10·4)	0·30 (0·18-0·50)	<0·0001
Circulatory failure	28 (3·2)	70 (7·9)	0·28 (0·16-0·51)	<0·0001
Respiratory failure	22 (2·5)	55 (6·2)	0·32 (0·17-0·62)	0·00067
Renal failure	12 (1·4)	29 (3·3)	0·36 (0·16-0·84)	0·016
Death	23 (2·7)	44 (5·0)	0·38 (0·18-0·82)	0·013

* Data are n (%). Mixed model logistic regression analyses adjusted with random intercept at hospital level, calendar time, pancreatic texture, diameter pancreatic duct, blood loss pancreatic resection, underlying disease, sex, age, American Society of Anaesthesiologists (ASA) class, type of pancreatic resection. Analysis as defined in study protocol.

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Chapter II

Verkrijgen van Lokale Goedkeuring voor een Niet WMO Plichtige Studie

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Medisch Contact 2019

Bureaucratie hindert veel onderzoek. Eindeloos veel papierwerk om een niet-WMO-plichtige studie op te zetten.

Voor onderzoek dat buiten de WMO valt, bijvoorbeeld cohortonderzoek of registratiestudies, ontbreekt regelgeving. Het gevolg is een wildgroei aan lokale afspraken, regels en voorwaarden. Dat is onwerkbaar.

De Wet medisch-wetenschappelijk onderzoek met mensen (WMO) beschrijft de regels voor het doen van kwalitatief goed wetenschappelijk onderzoek. Deze wet geldt echter alleen voor wetenschappelijk onderzoek waarbij personen aan handelingen worden onderworpen of hen gedragsregels worden opgelegd. Verreweg de meeste klinische studies voldoen niet aan dit criterium; dit zijn bijvoorbeeld prospectieve registratiestudies en retrospectieve cohortstudies. Voor de opzet, uitvoering en toetsing van dit soort studies ontbreekt regelgeving, en dat leidt ertoe dat elk ziekenhuis hiervoor z'n eigen procedures hanteert.

Om te laten zien waar dit in de praktijk toe leidt, hebben we een prospectieve evaluatie gedaan van het toetsingsproces van de PORSCH-trial. Dit is een multicenter 'stepped-wedge' cluster gerandomiseerde niet-WMO-plichtige studie die wordt uitgevoerd in acht academische en tien topklinische ziekenhuizen in Nederland.

Pancreaschirurgie is complex en geassocieerd met een 50-procent risico op complicaties. Eerder onderzoek laat zien dat het adequaat behandelen van deze complicaties essentieel is om de uitkomsten op landelijk niveau te verbeteren.

In de PORSCH-trial evalueren we de implementatie van een 'best practice'-vorm van zorg na pancreaschirurgie in alle achttien Nederlandse ziekenhuizen waar pancreaschirurgie wordt verricht. Het doel van de studie: voorkomen van levensbedreigende complicaties en mortaliteit. Een studie van dergelijke omvang moet beoordeeld worden door een onafhankelijke commissie. Daarom legden we de studie eerst voor aan de medisch-ethische toetsingscommissie (METC) in het coördinerende ziekenhuis om te beoordelen of de studie onder de reikwijdte van de WMO valt. Deze METC nodigde ons uit om de studie toe te lichten. Tijdens twee bezoeken aan de METC hebben wij, samen met een toegewijde epidemioloog, alle ethische en praktische vragen van de commissie beantwoord. Hierna hebben wij het studieprotocol ingediend voor beoordeling, voorzien van een aanbiedingsbrief en een ingevuld centrumspecifiek formulier met elf vragen over de WMO-plicht van de studie. De commissie oordeelde in 33 dagen (één vergadering) dat de studie niet onder de WMO valt. Bij hun oordeel maakten ze het voorbehoud dat de studie nog wel moest worden voorgelegd aan de lokale commissies van de deelnemende ziekenhuizen om een verklaring van geen bezwaar voor het uitvoeren van de studie te verkrijgen.

De toetsingsprocedures in de achttien participerende centra varieerden sterk. De uitersten: een centrum dat ons nadrukkelijk vroeg hen niet te informeren over deze studie, een ander centrum verlangde maar liefst negen verschillende studiedocumenten. De procedure in dit laatste centrum beschrijven wij als voorbeeld. Dit centrum vroeg ons naast de gebruikelijke documenten, ook om een lijst van deelnemende centra, een samenwerkingsovereenkomst tussen het initiërend en het participerend centrum, een begroting van de studiekosten, een bewijs van afsluiten van een aansprakelijkheidsverzekering en het getekende cv en BROK-certificaat van de lokale hoofdonderzoeker.

Voordat er duidelijkheid was over de toetsingsprocedure in dit centrum, is er 24 keer contact geweest tussen de coördinerend onderzoeker en de lokale wetenschappelijke commissie. Het gehele toetsingsproces in dit centrum nam 140 dagen in beslag, waarna er zonder aanvullende vragen of aanpassingen aan de studiedocumenten een verklaring van geen bezwaar voor het uitvoeren van de studie werd afgegeven.

Tabel 1: overzicht van toetsingen per centrum

Centrum	(Hernieuwde) toetsing op WMO-plicht door METC	Toetsing lokale uitvoerbaarheid door RvB	Toetsing door ander lokale commissie	Aantal verschillende ingediende documenten	Duur beoordelings-procedure (dagen)
1*	Ja	Ja	-	9	80
2	Ja	Ja	-	4	58
3	Ja	-	Ja‡	2	136
4	Ja	-	Ja†	4	55
5	Ja	-	-	4	19
6	Ja	-	-	3	17
7	Ja	-	-	3	31
8	-	Ja	-	9	57
9	-	Ja	-	7	0 ¶
10	-	Ja	-	7	44
11	-	Ja	-	6	43
12	-	Ja	-	5	0 ¶
13	-	Ja	-	5	0 ¶
14	-	Ja	-	5	7
15	-	Ja	-	3	22
16	-	-	Ja#	9	67
17	-	-	-	1	0 ‖
18	-	-	-	0	0 ‖

* Primair oordelende METC
‡ Toetsing door twee onafhankelijke wetenschappelijke commissies die het studieprotocol hebben beoordeeld
† Toetsing door privacyfunctionaris
# Toetsing door wetenschapsbureau
¶ Goedkeuring per ommegaande
‖ Geen enkele toetsing vereist

Tabel 1 en 2 geven een overzicht van de toetsingsprocedures en de vereiste documenten in de achttien ziekenhuizen. Zes METC's hebben de studie, na het initiële oordeel dat de studie niet-WMO-plichtig is, opnieuw getoetst op WMO-plicht. Hiervoor vroegen vier METC's ons een centrumspecifiek vragenformulier gericht op WMO-toetsing in te vullen. Het merendeel van deze vragen hield geen verband met de criteria voor WMO-plicht. In tien ziekenhuizen heeft de raad van bestuur de studie formeel getoetst op lokale uitvoerbaarheid. In twee ziekenhuizen was helemaal geen toetsing vereist. In totaal waren er, ná beoordeling door de initieel oordelende METC, 43 verschillende documenten nodig voor lokale toetsing in achttien ziekenhuizen (mediaan vijf documenten per centrum). In veertien ziekenhuizen moesten we een of meer centrumspecifieke formulieren invullen, met in totaal 385 verschillende vragen. De vragen hadden vaak overlap met de inhoud van het studieprotocol, maar er waren ook vragen over de afspraken rondom publicatie van de resultaten, de toestemmingsprocedure en de lokale haalbaarheid van de studie. Gedurende de gehele toetsingsprocedure was er 280 keer contact tussen de lokale commissies en de coördinerend onderzoeker. Per centrum was er gemiddeld negen keer e-mailcontact en drie keer telefonisch contact en bracht het studieteam twee bezoeken aan de ziekenhuizen. Het voorbereiden van de indiening kostte gemiddeld 39 dagen per centrum. De toetsing kostte gemiddeld 27 dagen per centrum. De gehele toetsingsprocedure van deze studie duurde bijna acht maanden. Alle METC's oordeelden – conform de initieel oordelende METC – dat de studie niet onder de reikwijdte van de WMO valt. De studie werd door 21 verschillende commissies getoetst waarna geen enkele inhoudelijke of tekstuele aanpassing in een van de studiedocumenten werd gevraagd.

Tabel 2: Verschillende documenten vereist voor toetsing van een multicentrische niet WMO-plichtige studie

Document	Toelichting	Aantal ziekenhuizen waarin vereist[†]
Aanbiedingsbrief	Uitleg over rationale en ontwerp van het onderzoek en overwegingen rondom individuele toestemmings-procedure. Opgesteld door studieteam op verzoek van initieel oordelend METC.	10/18
Aanmeldingsformulier	Uniek voor ieder centrum; bevat centrum specifieke vragen omtrent de inhoud van de studie, ethische aspecten en lokale afspraken.	14/18
Verklaring initieel oordelend METC	De verklaring van de initieel oordelend METC heeft geoordeeld dat de studie niet onder de WMO valt*	15/17[‡]
Studieprotocol	Hierin wordt de achtergrond van de studie beschreven, het plan van aanpak met onder andere de patiënten inclusie- en -exclusiecriteria, de primaire en secundaire uitkomstmaten en de statistische analyses.	15/18
Lijst deelnemende ziekenhuizen	Lijst van alle ziekenhuizen die deelnemen aan het onderzoek	6/18
Curriculum Vitae (CV)	Volledige CV's van 1) de centrale hoofdonderzoeker en 2) de lokale hoofdonderzoeker	6/18

BROK certificaat hoofdonderzoeker	Bewijs van actieve registratie in het Basiscursus Regelgeving en Organisatie Klinisch onderzoek	3/18
Samenwerkingsovereenkomst	Met daarin afspraken over o.a. eigendom van data, afspraken rondom communicatie tussen deelnemende partijen en verantwoordelijkheden van de hoofdonderzoekers. Wordt afgesloten tussen het initiërende centrum en één deelnemend centrum	9/18
Begroting	Uniek voor ieder centrum	6/18
Verzekeringscertificaat	Certificaat van de aansprakelijkheidsverzekering van een deelnemend centrum	1/18

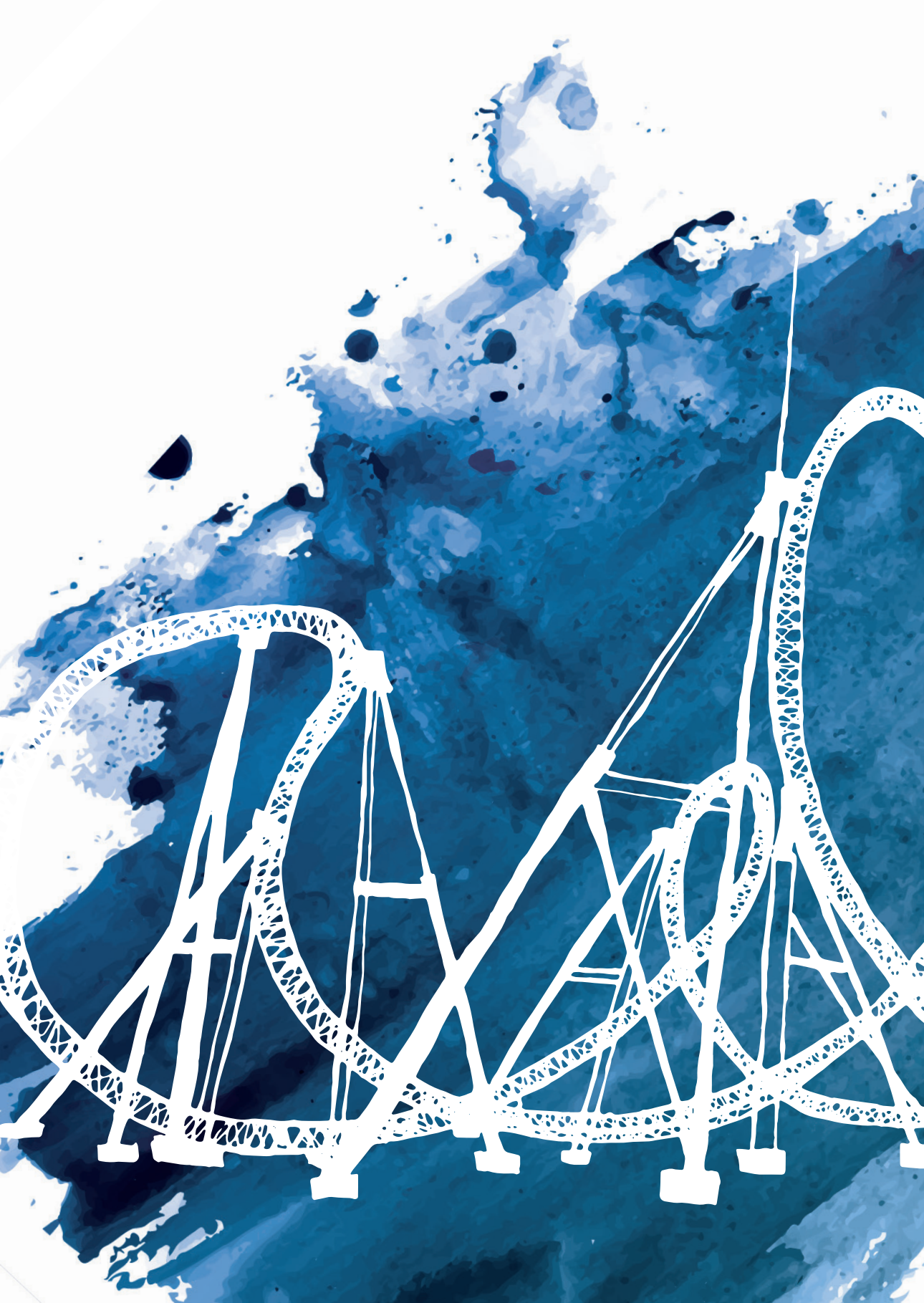
* Wet Medisch Wetenschappelijk Onderzoek met mensen
† Exclusief beoordeling initieel oordelend METC, inclusief toets op lokale uitvoerbaarheid in dat centrum
‡ Over 17 ziekenhuizen waarin de studie beoordeeld werd na oordeel van de initieel oordelend METC

We concluderen dat het verkrijgen van goedkeuring voor een niet-WMO-plichtige multicenterstudie onoverzichtelijk en inefficiënt is. Dat komt vooral door onduidelijkheid over en grote verschillen tussen de lokale toetsingsprocedures. De procedures zijn behalve erg tijdrovend, ook frustrerend voor de onderzoekers en voor de leden van de 21 commissies die deze studie hebben getoetst, zonder dat dit tot kwalitatief beter onderzoek heeft geleid. Het opnieuw toetsen van een studie die al eerder is beoordeeld door een METC – wat bij deze studie zes keer is gedaan – leidt bovendien tot potentieel conflicterende oordelen tussen CCMO-erkende METC's. Daarom pleiten wij voor landelijke afspraken over de toetsing van niet WMO-plichtige studies en we richten ons daarvoor met name tot de CCMO. Over de inhoud van een dergelijke richtlijn doen we de volgende aanbevelingen:

- Er zijn afspraken nodig over de rol van de METC's bij het beoordelen van een studie die al eerder door een CCMO-erkende METC als niet-WMO-plichtig is beoordeeld. Wij stellen voor om – conform de Richtlijn Externe Toetsing van de CCMO – deze toetsing te beperken tot slechts één METC en dat dit oordeel wordt overgenomen door de METC's van de participerende ziekenhuizen.

- Prospectieve niet-WMO-plichtige studies moeten worden geregistreerd in een erkend register. Er worden zaken geregistreerd als studiepopulatie, toestemmingsprocedure, dataverzameling, studieontwerp (evt. inclusief interventie), dataverzameling en -opslag, participerende ziekenhuizen, duur van de studie en financiële afspraken.

- Er zijn landelijke afspraken nodig over de niveaus waarop een niet-WMO-plichtige studie wordt beoordeeld in de participerende ziekenhuizen. Ons voorstel is om een gestandaardiseerde toets te doen op basis van het voorgestelde register.



PART V

Discussion, summary and appendices

Summary

Pancreatic surgery is complex and remains associated with a high risk of complications. A single complication may provoke a potentially lethal cascade of associated complications. In **chapter 1** the impact of individual complications on unfavorable outcomes like mortality and organ failure was assessed in 2620 patients undergoing pancreatoduodenectomy. Population attributable fractions (PAFs) were used to quantify the impact, while adjusting for confounders and other complications. This analysis showed mortality (3.6% in this cohort) was mostly attributed to postoperative pancreatic fistula (PAF 25.7%) and postpancreatectomy hemorrhage (PAF 32.8%), as was organ failure (7.6% in this cohort; PAF 21.8% and 22.1%, respectively). We concluded that quality improvement initiatives aiming to improve clinical outcomes after pancreatoduodenectomy should focus on postoperative pancreatic fistula and postpancreatectomy hemorrhage. As literature suggests postpancreatectomy hemorrhage is often caused by postoperative pancreatic fistula through vessel erosion, we focused primarily on postoperative pancreatic fistula in this thesis.

In the second part of this thesis, the prevention of postoperative pancreatic fistula was evaluated. As pancreatic fistula appears to be a failure of the pancreatic anastomosis, addition of material to strengthen the anastomosis was evaluated in **chapter 2**. Six studies on the use of matrix-bound sealants were evaluated. Reported rates of pancreatic fistula were comparable between patients treated with and without sealants. We concluded that the current data do not support the routine use of sealants in pancreatic surgery. In **chapter 3**, a comprehensive overview of all pancreatic anastomosis techniques described in literature is presented. A total of 61 different techniques were found and summarized in 19 subgroups. All techniques were illustrated and published on www.pancreatic-anastomosis.com, which can be used for uniformity in reporting and for educational purposes. A meta-analysis showed comparable rates of clinically relevant pancreatic fistula in RCTs on different subtypes of pancreatic anastomoses.

In the third part, the efforts made to define the 'best practice' in both recognition and management of complications after pancreatic resection is described. **Chapter 4** includes an overview of all clinical, biochemical and radiologic variables for early recognition of clinically relevant postoperative pancreatic fistula described in literature. Identified variables were: non-serous drain efflux; positive drain culture; elevated temperature; elevated C-Reactive Protein (CRP); elevated white blood cell (WBC) count and peripancreatic collections on computed tomography. In **chapter 5** we compared the diagnostic accuracy of CRP to WBC for early detection of complications after pancreatoduodenectomy in a multicenter cohort. CRP was superior to WBC in detecting major complications on postoperative day (POD) 3 (area under the curve [AUC]:0.74 vs. 0.54, $P < 0.001$) and POD 5 (AUC:0.77 vs. 0.68, P=0.031), however not on POD 7 (AUC:0.77 vs. 0.76, P=0.773). Results were confirmed in a validation cohort. In addition, the accuracy of CRP vs. WBC was also evaluated for detecting

postoperative pancreatic fistula. In this comparison, CRP was also superior to WBC on POD 3 (AUC: 0.78 vs. 0.54, P<0.001) and POD 5 (AUC: 0.83 vs. 0.71, P<0.001).

The first study we performed on the management of pancreatic fistula is described in **chapter 6**. In a multicenter propensity-matched cohort, clinical outcome of patients undergoing catheter drainage was compared with relaparotomy as primary treatment for pancreatic fistula after pancreatoduodenectomy. In-hospital mortality in the 309 included patients was 17.8%. In the matched cohort, mortality was lower in patients undergoing primary catheter drainage (14.1% vs 35.9%; P = .007). The rate of new-onset single-organ failure (4.7% vs 20.3%; P = .007) and new-onset multiple-organ failure (15.6% vs 39.1%; P = .008) was also lower after primary catheter drainage. It was concluded that, when minimally invasive drainage is feasible, primary catheter drainage should be the first step in treatment of severe pancreatic fistula. In **chapter 7** we evaluated if we could identify a specific subgroup in whom minimally invasive catheter drainage might not be successful (i.e. survival without relaparotomy) after pancreatoduodenectomy. Primary catheter drainage was successful in 175 of 227 included patients (77%). Multivariable logistic regression revealed that male sex, higher age and respiratory failure at time of catheter drainage were negative prognostic factors for success. We believe clinical outcomes could be improved through implementation of an intensified postoperative monitor strategy focused on early detection and early catheter drainage for pancreatic fistula before the phase of respiratory failure.

Minimally invasive drainage appears to be successful in most patients. For some patients however, relaparotomy might still be necessary. In **chapter 8** different treatment strategies during relaparotomy for pancreatic fistula are compared in a multicenter cohort and meta-analysis. A total of 162 patients undergoing relaparotomy for pancreatic fistula were compared: completion relaparotomy (22%) vs. a pancreas-preserving procedure (78%). Mortality was higher after completion pancreatectomy (56% vs. 32%), even after adjustment for confounders (adjusted OR 2.55, 95% CI 1.07 to 6.08). Meta-analysis confirmed the association between completion pancreatectomy and mortality. It was therefore concluded that a pancreas-preserving procedure was preferable over completion pancreatectomy in these patients.

Another severe complication, as identified in chapter 1, is postpancreatectomy hemorrhage. An overview of literature on both diagnosis and management of this complication is presented in **chapter 9**. The incidence of late postpancreatectomy hemorrhage ranged from 3% to 16% (weighted mean: 5%). CT-scan and diagnostic angiography were able to identify the source of hemorrhage in 67% (66/98) and 69% (114/166) of patients, respectively. The most frequently identified origin of the hemorrhage was the gastroduodenal artery stump (79/275; 29%), followed by the common hepatic artery (51/275; 19%) and splenic artery (32/275; 12%). Overall mortality was 21% (98/464 patients; range 0% - 38%). Mortality was lower after primary interventional angiography compared to primary relaparotomy (16% vs 37%

respectively). It was concluded that CT-scan and diagnostic angiography are equally sensitive in detecting the bleeding source and that interventional angiography appears to be superior to relaparotomy and endoscopy as first intervention to stop the bleeding.

In the fourth part of this thesis, the implementation of best practice is described. Based on the before mentioned chapters, we designed a multimodal algorithm for early recognition and minimally invasive management of postoperative complications after pancreatic resection. We hypothesized that implementation of this multimodal algorithm would result in better clinical outcomes than usual care. This hypothesis was tested in the nationwide stepped-wedge cluster randomized trial (PORSCH trial, **chapter 10**). In this trial design, all 17 centers were randomized for time to crossover from usual care (control group) to treatment according to a multimodal, multidisciplinary algorithm (intervention group). A smartphone application was designed incorporating the algorithm, which included daily evaluation of clinical and biochemical markers. The smartphone application determined when to perform abdominal computed tomography and radiologic drainage, when to start antibiotic treatment and when to remove abdominal drains. The primary outcome was assessed by a blinded adjudication committee and was a composite of bleeding requiring invasive intervention, organ failure, and 90-day mortality. In 22 months, a total of 1748 patients were included. The primary outcome occurred in 8.5% in the intervention group vs. 14.0% in the control group (adjusted risk ratio [RR] 0.48; 95% CI 0.38-0.61; P<0.0001). All individual components of the primary outcome were decreased in the intervention group: bleeding requiring intervention (5.4% vs. 5.8%; adjusted RR 0.65; 95% CI 0.42-0.99; P=0.046); organ failure (4.5% vs. 10.3%; adjusted RR 0.35; 90%CI 0.20-0.60; P0.00013); 90-day mortality (2.7% vs. 5.0%; adjusted RR 0.42; 95%CI 0.19-0.92; P=0.029). We concluded that the implementation of this multimodal algorithm improved clinical outcomes compared to usual care, including an approximate 50% reduction of nationwide mortality.

In **chapter 11**, we performed a prospective evaluation of procedures to obtain medical ethical and local approval in all 18 centers participating in the PORSCH trial. In the Netherlands, medical research is divided into two categories. For research in which patients are subjected to (experimental) treatments or specific rules of conduct, extensive regulations are described in the WMO (Wet Medisch-wetenschappelijk Onderzoek met mensen). Medical ethical committees (MEC) can decide if studies fall into this first category or not. The PORSCH trial was evaluated and it was judged that this study did not meet the criteria of the WMO. For this second category, only little regulations apply. The local procedures differed considerably, ranging from two centers who did not handle any medical ethical or local approval procedures and urged us not to inform them on this study in any way, to one center that asked us to submit nine different documents. After obtaining initial approval of the first testing MEC, a total of six MEC's re-assessed if the trial met the criteria of the WMO. All of them judged it did not. 21 different committees evaluated the study documents. 43 different study

documents were needed (average of 5 documents per center). 385 different questions on the study were answered. 280 emails and calls were conducted in the 8 months it took to obtain approval in all centers. None of the committees deemed it necessary to change anything in the study material after evaluation. We concluded that this process is complex and insufficient and requires a considerable investment of time and resources, and we emphasize the difference in procedures between the centers.

Main study questions and answers in this thesis

Chapter

1. What is the impact of individual complications on mortality, organ failure, hospital stay and readmission after pancreatoduodenectomy?

   Postoperative pancreatic fistula and postpancreatectomy hemorrhage attributed considerable to all unfavorable outcomes and accounted for 26% and 33% of the total in-hospital mortality, respectively. Delayed gastric emptying had the greatest impact on prolonged hospital stay. The impact of evaluated complications on readmission was relatively small (maximum risk adjusted attribution of 11%).

2. Do matrix-bound sealants prevent or ameliorate the course of post-operative pancreatic fistula after a pancreatic resection according to available literature?

   The pooled data in this systematic review do not show an advantage of the use of sealants after pancreatic resection, for there was no statistically significant decrease in the incidence of clinically relevant fistula (i.e. ISGPF POPF grade B/C). With regard to the other postoperative complications, time to drain removal, hospital stay and mortality, no major differences between the sealants and control group were found.

3. What pancreatic anastomosis techniques have been described in peer-reviewed articles on patients undergoing pancreatoduodenectomy and is one technique superior to others in terms of the incidence of clinically relevant postoperative pancreatic fistula when all randomized controlled trials are evaluated?

   A complete overview of 61 major pancreatic anastomotic techniques reported in peer-reviewed publications, summarized on www.pancreatic-anastomosis.com. The meta-analysis of six randomized trials comparing pancreaticogastrostomy with pancreaticojejunostomy demonstrated a clinically relevant POPF rate of 12% versus 20%, respectively. This difference was favorable for pancreaticogastrostomy, although not significant (P = 0.05).

4. What is the accuracy of postoperative clinical, biochemical and radiologic variables for early recognition of clinically relevant pancreatic fistula after pancreatic resection as described in available literature?

   A non-serous drain output, positive drain culture, elevated temperature or CRP or WBC and peripancreatic collections on abdominal CT scan appear to be the most reliable variables for early detection of clinically relevant pancreatic fistula, although proposed cut-off values and timing varies leading to a wide range in diagnostic indices. In addition, it should be noted that early elevation in amylase in serum

or drain fluid appears to be an important predictor for the occurrence of clinically relevant pancreatic fistula.

5. Is C-reactive protein (CRP) superior to white blood cell count (WBC) in the detection of major complications in the first seven days after pancreatoduodenectomy?

   CRP appears to be superior to WBC in the early postoperative phase (i.e. postoperative day 3 and 5). Patients with continuous elevation of CRP levels were consistently at a higher risk of developing major complications and POPF. While, WBC only demonstrated to have a similar diagnostic value on postoperative day 7.

6. Are clinical outcomes of patients undergoing catheter drainage superior to those undergoing relaparotomy as the primary treatment for severe pancreatic fistula after pancreatoduodenectomy?

   Primary catheter drainage as the first intervention for severe pancreatic fistula after pancreatoduodenectomy is associated with a better clinical outcome, including lower mortality, less organ failure, fewer additional relaparotomies, and less new-onset diabetes compared with direct relaparotomy.

7. What predictors can be identified for successful minimally invasive catheter drainage as first invasive intervention in the treatment of postoperative pancreatic fistula after pancreatoduodenectomy?

   In this multicenter cohort of patients undergoing minimally invasive drainage for pancreatic fistula after pancreatoduodenectomy, male sex, higher age and the presence of respiratory failure were negatively associated with the success of catheter drainage (i.e. survival without the need for relaparotomy). For respiratory failure is the only independent predictor that can be influenced, we believe clinical outcomes could be improved through implementation of an intensified postoperative monitor strategy focused on early detection and early catheter drainage for pancreatic fistula before the phase of respiratory failure.

8. When performing relaparotomy for pancreatic fistula after pancreatoduodenectomy, is completion pancreatectomy superior to pancreas-preserving procedures when evaluating both Dutch data and available literature in terms of clinical outcomes?

   Completion pancreatectomy was independently associated with a doubling of mortality rate, compared with a pancreas-preserving 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.

9. What is the available evidence on the incidence, detection, management and clinical outcomes of treatment strategies for late postpancreatectomy hemorrhage?

   According to the current literature, late postpancreatectomy hemorrhage remains a relatively uncommon complication with a mean incidence of 5%. However, overall mortality continues to be high at 21%. This review showed that sensitivity of angiography (69%) to identify the source of the hemorrhage was comparable to the CT-scan (67%). Endoscopy failed to identify the location of bleeding in 31% of patients with an overt luminal bleeding. The mortality rate was lower after a primary endovascular approach as compared to primary relaparotomy and primary endoscopy (i.e. 15%, 37%, and 24%, respectively).

10. Can major complications and death be prevented by the nationwide implementation of an algorithm for early recognition and minimally invasive management of complications in patients undergoing pancreatic resection as compared to usual care?

    This randomized trial demonstrated that the use of a novel algorithm for early recognition and management of postoperative complications in patients undergoing pancreatic resection greatly improved clinical outcomes. This included an approximate 50% reduction of mortality nationwide. Our findings support a strategy in which all patients undergo a structured daily evaluation to identify and treat complications before they become clinically relevant. The smartphone application that was designed for bed-side use of the algorithm can be used for this purpose.

11. What procedures have to be performed to obtain both medical ethical and local approval before the start of the PORSCH trial, and what are the differences between participating centers?

    The local procedures differed considerably, ranging two center who did not handle any medical ethical or local approval procedure and urged us not to inform them on this study in any way, to one center asked us to submit nine different study documents. A total of 21 different committees evaluated the study documents. 385 different questions on the study were answered during the 8 months it took to obtain approval in all centers. None of the committees deemed it necessary to change anything in the study material after evaluation.

General discussion and future perspectives

This thesis provides answers on several important questions adding to the improvement of clinical outcomes of patients in pancreatic surgery. In the following paragraphs, the implications for clinical practice and future research are presented per main topic.

Prevention of Postoperative Pancreatic Fistula

Postoperative pancreatic fistula is addressed as the Achilles heel in pancreatic surgery. Although the exact pathophysiologic mechanism remains unknown, it appears to be primary failure of the pancreatic anastomosis. Many different pancreatic anastomotic techniques have been described. The most well-known types are the pancreaticogastrostomy and pancreaticojejunostomy. Within these two groups, however, many different subtypes can be identified (i.e. end-to-end vs. end-to-side, one-layered vs. multiple-layered, with or without invagination). As there are many different techniques published in peer-reviewed journals, we created a comprehensive and illustrated online overview on www.pancreatic-anastomosis.com. The online platform is being used for education by residents, HPB fellows and surgeons, and is incorporated in international registries to increase uniformity in reporting anastomotic techniques. Although many authors believe their own technique to be superior, we found that clinical outcomes are comparable between all techniques. We therefore concluded that extensive experience or relative unfamiliarity with one technique determines the success of the anastomosis, and that surgeons should focus on perfecting one or two different techniques. Also, the addition of matrix-bound sealants showed no benefit in terms of pancreatic fistula. Overall, it was concluded from the first part of this thesis that despite many efforts, pancreatic fistula cannot be eliminated entirely.

Defining best practice in pancreatic surgery

A nationwide Dutch study showed that not only the prevention of complications, but more importantly the adequate management of complications is essential in order to improve clinical outcomes.[1] We therefore further focused on defining and implementing best practice in management of complications in pancreatic surgery. Postoperative pancreatic fistula may lead to a cascade of complications which could lead to sepsis and death.[2,3] As with any form of sepsis, early recognition and early intervention might prevent further deterioration.[4] In this part of this thesis, the process of establishing a 'best practice' algorithm for 1) early detection and 2) adequate management of postoperative pancreatic fistula is described.

An extensive literature search was performed to identify all variables measured at any time after pancreatic resection associated with postoperative pancreatic fistula. In addition, the diagnostic ability of C-reactive protein (CRP) was compared to white blood cell count (WBC) in terms of detecting complications after pancreatoduodenectomy in a large Dutch cohort. The first part of the algorithm focused on early recognition of

postoperative pancreatic fistula and was based on the clinical, biochemical and radiologic variables identified in these two studies.

Once pancreatic fistula is suspected and the patient is showing signs of inflammation, management should be prompt. Relaparotomy used to be the standard form of treatment, but over the past years minimally invasive treatment strategies have become more popular.[5,6] In a large propensity-matched cohort, minimally invasive drainage as first intervention for pancreatic fistula after pancreatoduodenectomy, compared to primary relaparotomy, was associated with a better clinical outcome, including lower mortality. The majority of patients underwent primary catheter drainage, but still a considerable proportion (27%) was treated primarily through relaparotomy. It was remarkable that treatment strategies differed considerably between centers, with the proportion of patients primarily treated with relaparotomy ranging from 12 to 67%. Another study in the same cohort showed minimally invasive drainage is successful in 77% of patients. The only predictor associated with the success of minimally invasive drainage that could potentially be influenced, was respiratory failure. This underlined the importance of early (i.e. before organ failure was developed) management of postoperative pancreatic fistula.

In a small number of patients, relaparotomy might be inescapable for several good and less good reasons (e.g. inability to access a peripancreatic collection by interventional radiology, personal preference of the surgeon, or patients' deterioration).[7] One of the reasons relaparotomy might be appealing is the opportunity to perform a completion pancreatectomy and entirely remove the source of inflammation.[3] When comparing completion pancreatectomy with pancreas-preserving procedures during relaparotomy, the latter appears to be preferable because pancreas preserving procedures are associated with lower mortality, even after correction for confounders. The difference in mortality might be explained by more severe tissue injury and more inflammatory response in these often critically ill patients, as was observed in patients with necrotizing pancreatitis.[8] All available evidence on management strategies for pancreatic fistula was obtained from prospective and retrospective cohort studies. With the current evidence, we believed it would be unethical to perform a randomized trial with a direct head-to-head comparison for different invasive interventions for pancreatic fistula. Furthermore, we showed that the real profit might be in a combination of both early and adequate management of complications. We therefore designed a randomized stepped-wedge cluster trial testing the added value of a multilevel algorithm for both early detection and minimally invasive management for postoperative pancreatic fistula. The studies included in this part of thesis form the basis on which the first version of this algorithm was designed. The final algorithm is presented in chapter 10 of this thesis.

Implementing best practice in pancreatic surgery

The PORSCH trial is a nationwide stepped-wedge cluster randomized trial. All patients undergoing pancreatic resection over a 22-month period in The Netherlands were

included. In this trial design, all 17 centers were randomized for time to crossover from usual care (control group) to treatment according to a multimodal, multidisciplinary algorithm for early recognition and minimally invasive management of postoperative complications (intervention group). The algorithm considerably improved clinical outcomes of patients undergoing pancreatic resection compared to usual care, including an approximate 50% reduction of nationwide mortality. Because only parameters that are already being used in daily practice are included in the algorithm, it is cheap, easy to use and safe.

The rationale for the algorithm is based on two concepts. The first is that complications can be identified before they become clinically relevant, by using a structured daily evaluation. The algorithm recommends abdominal CT scan at a relatively low threshold of subtle changes in vital signs and inflammatory markers. This resulted in a higher number of CT scans in the intervention group, but more importantly the first CT scan was performed two days earlier in the intervention group. This might be in contrast with the old surgical concept that the patient's clinical condition should be leading in the decision to perform an invasive intervention, but supports the efficacy of the algorithm in terms of timely identification of complications. The second concept is timely treatment of complications. Patients in the intervention group underwent treatment with antibiotics and radiologic drainage more often and earlier. Relaparotomy was less often performed in the intervention group, and as a result less patients were exposed to the pro-inflammatory 'second-hit' of surgical trauma. This supports both the efficacy of timely treatment of complications and the superiority of minimally invasive treatment strategies over relaparotomy in these patients.

We evaluated a combined effect of the algorithm and did not investigate the beneficial effect of each individual component, including the increased general awareness for the patient's wellbeing. Future research might be focused on identifying the most effective parts of the algorithm, potentially using modern technologies like artificial intelligence, aiming to create a leaner version of the algorithm. Also, the use of similar algorithms might be useful in other types of surgery (e.g. in hepatectomy or esophagectomy).

In the last chapter of this thesis, a prospective evaluation of procedures was performed to obtain ethical and local approval to start the PORSCH trial. The main finding in this study was that the process was unclear and there were major differences in procedures between the 18 participating centers. Some centers urged us not to inform them in any way on this study that would start in their center. The entire process included evaluation of 43 different study documents and 385 different questions by 21 different committees, after which not one amendment to the study material was required. This topic has attracted the attention of the Dutch Ministery of Health. Partly due to our efforts, the legislation is being revised, with the aim of increasing the uniformity in local testing procedures for these types of studies.[9,10]

This thesis presents 10 years of research on pancreatic surgery. Important discoveries have been presented and clinical practice has already changed because of these findings. Our ancestors recognized the necessity to drain fluid or pus from infected sites using hollow feather-quills, and today we continue to do so. At the same time however, another old surgical concept may have shifted. Traditionally, clinical assessment of your patients is the most important factor in determining whether or not to perform a (surgical) intervention. Findings in this thesis show, however, that in patients undergoing pancreatic resection, further steps in management of complications should not be delayed, even if the patient is in good clinical condition. Clinical deterioration and even mortality can be prevented by early complication management. This concept might be extrapolated to other types of major (abdominal) surgery, for example hepatectomy or esophagectomy. There are still many new ideas to be developed and many more studies to be performed. The Dutch Pancreatic Cancer Group continues to expand the boundaries in order to improve outcomes of patients with pancreatic disease.

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Dutch summary (Nederlandse samenvatting)

Complicaties na chirurgie komen voor bij ongeveer 20% van patiënten, bij operaties aan de alvleesklier ligt dit percentage zelfs op circa 50%. Wanneer complicaties niet adequaat herkend en behandeld worden, kan dit ervoor zorgen dat er een cascade van opeenvolgende complicaties ontstaat wat uiteindelijk zelfs kan leiden tot orgaanfalen, IC opname of overlijden. Zelfs met de continue verbeteringen in de zorg zijn complicaties van grote operaties niet altijd te voorkomen. Om die reden is het gesuggereerd dat onderzoek naar op het verbeteren van uitkomsten van deze patiënten niet alleen gericht zou moeten zijn op het voorkomen van complicaties, maar juist ook het vroeg detecteren en behandelen van complicaties. Het vroeg herkennen van complicaties kan echter moeilijk zijn, omdat de operatie op zichzelf ook al een ontstekingsreactie in het lichaam op gang brengt waardoor het lastig kan zijn om subtiele veranderingen in de vitale parameters (zoals hartslag, bloeddruk, temperatuur, ademfrequentie) en ontstekingswaarden in het bloed op te merken.

De meest uitgevoerde pancreasoperatie is een Whipple operatie, waarbij de kop van de alvleesklier samen met de twaalfvingerige darm en de galblaas verwijderd wordt. Deze operatie is complex en geassocieerd met een hoge kans op complicaties. Een van de meest gevreesde complicaties is het ontstaan van lekkage van alvleeskliersappen in de vrije buikholte. Deze sappen zijn eroderend en kunnen daardoor leiden tot een ontstekingsreactie in het lichaam, wat kan leiden tot orgaan falen, maar ook tot erosie van grote bloedvaten, waardoor er grote bloedingen kunnen ontstaan. In **hoofdstuk 1** onderzochten we de impact van individuele complicaties op de meest ernstige uitkomsten zoals orgaanfalen en sterfte. Uit dit hoofdstuk bleek dat lekkage van alvleeskliersappen en ernstige bloedingen de grootste impact hadden op sterfte na een Whipple operatie (aan deze complicaties kon respectievelijk 25% en 33% van de sterfte worden toegeschreven). Hetzelfde gold voor orgaanfalen, waarvan 22% toegeschreven kon worden aan lekkage van alvleeskliersappen en 22% aan bloedingen. We concludeerden dat toekomstig onderzoek zich met name zou moeten richten op deze twee complicaties. Omdat er aanwijzingen zijn in de literatuur dat een deel van de bloedingen veroorzaakt wordt door lekkage van alvleeskliersappen, hebben wij ons in dit proefschrift met name gericht op deze laatste complicatie.

In het tweede deel van dit proefschrift hebben we geëvalueerd of er methoden zijn om lekkage van alvleeskliersappen te voorkomen. Voor **hoofdstuk 2** bekeken wij de studies waarin het gedeelte van de alvleesklier waar deze doorgenomen werd verstevigd werd met een patch. Deze studies lieten geen verbetering zien in het aantal patiënten of de ernst van lekkage van alvleeskliersappen. In **hoofdstuk 3** bekeken wij alle verschillende hechttechnieken voor het maken van de verbinding tussen de alvleesklier en de dunne darm. Er werden 61 verschillende technieken geëvalueerd en samengevat op www.pancreatic-anastomosis.com. Ook hiervoor gold dat er geen techniek geïdentificeerd kon worden die minder vaak of minder ernstige lekkage van alvleeskliersappen gaf.

In het derde deel van dit proefschrift hebben wij ons gericht op het vroeg detecteren en adequaat behandelen van complicaties, om uiteindelijk te komen tot een '*best practice*'. In **hoofdstuk 4** beschrijven wij een overzicht van alle verschenen literatuur over het vroeg herkennen van lekkage van alvleeskliersappen, hierin beschrijven we klinische parameters, bloedwaarden en karakteristieken op CT-scans. In **hoofdstuk 5** vergeleken wij de accuraatheid van twee verschillende bloedtesten voor het herkennen van complicaties na een Whipple operatie. Deze analyse liet zien dat de bepaling CRP superieur was aan witte bloedcellen. Beide tests worden wereldwijd veel gebruikt. Bevindingen uit deze twee studies vormden de basis van het algoritme zoals beschreven in hoofdstuk 10.

Wanneer er het vermoeden bestaat op lekkage van alvleeskliersappen, moet de behandeling prompt zijn. Behandeling bestond vanuit oudsher altijd uit een reoperatie, waarbij de buik opnieuw geopend werd en de verbinding gepoogd werd te repareren of waarbij er drains (slangen) vlak bij het lek achtergelaten werden. Dit is echter weer een grote belasting op het lichaam en brengt weer een ontstekingsreactie op gang. Daarom is er de afgelopen jaren een voorkeur voor een meer minimaal-invasieve behandelstrategie, waarbij door de radioloog via de huid drains geplaatst worden vlak bij het lek. In **hoofdstuk 6** worden deze twee behandelstrategieën vergeleken in een cohort van patiënten met lekkage van alvleeskliersappen na een Whipple operatie. Omdat er destijds waarschijnlijk een reden was om voor de ene of andere behandeling te kiezen (patiënten die een reoperatie ondergingen waren bijvoorbeeld op dat moment vaker ernstig ziek), werd er gebruik gemaakt van propensity score matching. Op deze manier werd een patiënt die een reoperatie onderging '*gematcht*' aan een patiënt die een vergelijkbare score had (en dus ongeveer even ziek was). Deze studie liet zien dat in patiënten die primair behandeld werden met minimaal invasieve drainage sterfte lager was (14% versus 36%), en dat er minder vaak orgaan falen optrad. In **hoofdstuk 7** lieten wij zien dat minimaal-invasieve drainage een succesvolle behandeling was in 77% van de patiënten met lekkage van alvleeskliersappen na een Whipple operatie. Voorspellers voor het falen van minimaal invasieve drainage waren mannelijk geslacht, hogere leeftijd en pulmonaal falen. Minimaal-invasieve drainage lijkt in het merendeel, maar niet in alle patiënten, succesvol lijkt te zijn. Een aantal patiënten zal toch nog een reoperatie ondergaan. In **hoofdstuk 8** bekeken we de verschillende behandelstrategieën tijdens reoperatie. Hierbij werd er onderscheid gemaakt tussen het totaal verwijderen van de alvleesklier, en strategieën waarbij de alvleesklier gespaard bleef (zoals het repareren of opnieuw aanleggen van de verbinding met de darm, of het plaatsten van drains bij het lek). Sterfte was hoger na het totaal verwijderen van de alvleesklier dan wanneer er een alvleesklier-sparende techniek werd gebruikt (56% versus 32%). Geconcludeerd werd dat de eerste stap in de behandeling van lekkage van alvleeskliersappen via minimaal-invasieve drainage zou moeten zijn, het liefst voor er orgaan falen optreedt. Wanneer dit niet mogelijk is, zou er bij een reoperatie gepoogd moeten worden de alvleesklier te sparen.

In **hoofdstuk 9** bekeken we ernstige bloedingen. Dit is de complicatie die, naast lekkage van alvleeskliersappen, als meest ernstig werd geïdentificeerd in hoofdstuk 1 van dit proefschrift. Op basis van literatuur over deze complicatie werd er inzicht verkregen in hoe vaak er ernstige bloedingen voorkwamen (circa 5% van de patiënten), wat de eerste stap was in het identificeren van de bron van de bloeding (CT-scan of angiografie) en wat de meest effectieve behandelstrategie was. Angiografie met plaatsen van stent of coils was geassocieerd met een lagere mortaliteit dan een reoperatie (16% versus 37%).

Alle bevindingen uit bovenstaande studies werden gecombineerd in een multilevel '*best practice*' algoritme voor vroege herkenning en minimaal-invasieve behandeling van complicaties na alvleesklierchirurgie. In het vierde deel van dit proefschrift testten we de hypothese dat door implementatie van dit algoritme in alle Nederlandse ziekenhuizen waar alvleesklieroperaties uitgevoerd worden de uitkomsten voor patiënten (met name het aantal patiënten met een ernstige bloeding, orgaanfalen of sterfte) zou verbeteren. Dit testten we in de PORSCH-trial, een landelijke *stepped wedge* gerandomiseerde studie die in **hoofdstuk 10** wordt beschreven. In deze studie startten alle ziekenhuizen in de controlegroep, waarin ze de zorg voor hun patiënten organiseerden zoals ze dat altijd deden. Gedurende de studie werd het algoritme stapsgewijs geïmplementeerd in 17 ziekenhuizen in Nederland. De volgorde waarin dit gebeurde was at random. Uiteindelijk werden de uitkomsten van patiënten die geopereerd werden in de controle fase vergeleken met de uitkomsten van patiënten de geopereerd werden na implementatie van het algoritme. Het algoritme zelf was complex, en bestond uit een dagelijkse evaluatie van diverse klinische parameters en bloedwaarden (zoals bijvoorbeeld koorts en CRP). Om het gebruik in de dagelijkse praktijk te vergemakkelijken werd het algoritme verwerkt in een smartphone applicatie die gratis te downloaden is. De studie duurde 22 maanden en in die tijd werden 1748 patiënten geïncludeerd in de studie. Het gecombineerde primaire eindpunt van ernstige bloedingen, orgaanfalen en sterfte kwam minder vaak voor na implementatie van het algoritme (9% vs. 14%). Hetzelfde gold voor orgaan falen (5% vs. 10%) en sterfte (3% vs. 5%). Wij concludeerden dat de implementatie van het multilevel algoritme zorgde voor een verbetering van klinische uitkomsten, met name een bijna 50% vermindering in sterfte, op een landelijke schaal.

In **hoofdstuk 11** beschreven wij het proces wat wij doorliepen om goedkeuring te krijgen voor start van de PORSCH-trial in alle centra. Deze studie valt niet onder de Wet Medisch Wetenschappelijk Onderzoek (WMO), wat betekent dat er maar weinig wet- en regelgeving is voor de toetsingsprocedure. Dit leidde ertoe dat lokale procedures significant verschilden van elkaar, waarbij er twee centra waren die ons expliciet vroegen hen niet te informeren over deze studie, en één centrum dat ons vroeg negen verschillende studiedocumenten in te dienen. Zes medisch ethische toetsingscommissies (METC's) toetsten opnieuw (nadat de initiële METC hier reeds over had geoordeeld) of de studie wel of niet onder de WMO viel, en concludeerden allen dat dat niet het geval was. Eenentwintig verschillende commissies beoordeelden 43 verschillende studiedocumenten met daarin 385 unieke vragen. Tweehonderdtachtig

e-mails en telefoontjes werden uitgewisseld tussen de coördinerend onderzoeker en de verschillende toetsende commissies in de acht maanden die het duurde om uiteindelijk goedkeuring te krijgen in alle centra. Geen van de toetsende commissies vond het nodig dat wij iets veranderden in de studiedocumenten of procedures. Deze studie heeft ertoe geleid dat er een kamerstuk is geschreven waarin er opgeroepen wordt tot uniformiteit in toetsingsprocedures van studies die niet onder de WMO vallen, waarin de aanbevelingen die wij deden in het artikel overgenomen zijn.

In dit proefschrift wordt 10 jaar van onderzoek naar complicaties na alvleesklieroperaties weergegeven. De bevindingen die worden gepresenteerd hebben al geleid tot een verandering in huidige zorg en zal de zorg mogelijk nog verder gaan veranderen. Een traditioneel chirurgisch concept is dat de kliniek van de patiënt leidend is. Wanneer een patiënt bijvoorbeeld een hoog CRP heeft, maar zich niet ziek voelt en er niet ziek uitziet, wordt ons geleerd dat er tijd is om af te wachten. Bevindingen in dit proefschrift laten echter zien dat er in bepaalde patiëntengroepen deze ruimte wellicht niet is, en dat je juist moet handelen vóór dat een patiënt klinische tekenen van ziek zijn laat zien. Bij alvleesklierchirurgie lijkt dit het geval. Dit concept moet verder getoetst worden bij andere soorten grote buikoperaties zoals bijvoorbeeld leverchirurgie, slokdarmchirurgie en operaties aan de blaas. Samen met de landelijke consortia gaan wij door met het verleggen van grenzen met als doel de kwaliteit van zorg voor patiënten te verbeteren.

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Curriculum vitae auctoris

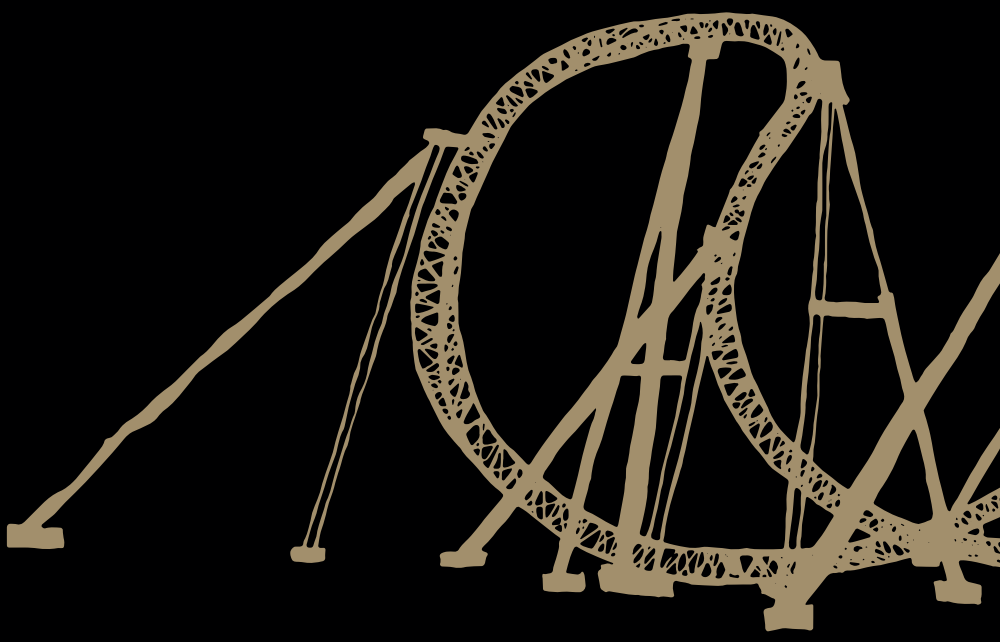
Jasmijn Smits was born on July 28th 1991 in Groningen, the Netherlands. After moving to Oss with her brother Hidde, sister Josien and parents Taco and Anne-Margot, she graduated from the Titus Brandsma Lyceum in 2009. Most winters she went skiing in Italy with her family. She started medical school at the Utrecht University in the same year.

After her first internship in 2012 she joined the pancreatic research group at the Department of Surgery in the University Medical Center Utrecht, under supervision of prof. dr. Quintus Molenaar. She started her research investigating the prevention of postoperative pancreatic fistula, and thereafter she focussed on the management of this complication as well as other complications after pancreatic resection. She initiated and finished the nationwide randomized PORSCH trial providing the ultimate prove for the hypothesis formed in the early years of her research career. During her time as medical student and PhD candidate she actively participated in the organization of the Dutch Pancreatic Cancer Group.

After graduating medical school in 2016, she continued doing research under supervision of prof. dr. Quintus Molenaar and prof. dr. Hjalmar van Santvoort. She received different grants for her research, amongst others a personal grant (the Alexandre Suerman Stipend) for 3 years of research including semi-annual masterclasses, and a grant by the Dutch Cancer Society. She was given the opportunity to visit many different conferences around the world to present her work, and received awards for presentations at these meetings.

In 2019 she started working as resident at the Department of Surgery at the Diakonessenhuis in Utrecht, which she combined with coordination of the PORSCH trial. In 2021 she started surgical training in Utrecht, first at the University Medical Center in Utrecht under the supervision of prof. dr. Menno Vriens and dr. Marijn Houwert. After one year she continued surgical training at the Diakonessenhuis Utrecht under supervision of dr. Mark van Heijl.

Besides working in the hospital, Jasmijn enjoys swimming, field hockey, running, sailing, and skiing. Preferably with family, friends and her boyfriend Okke-Jaap. Also, she has a small business in designing and making leather bags.



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