The role of abdominal drainage in pancreatic resection - A multicenter validation study for early drain removal

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The role of abdominal drainage in pancreatic resection – A multicenter validation study for early drain removal

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ABSTRACT

Background: Abdominal drainage and the timing of drain removal in patients undergoing pancreatic resection are under debate. Early drain removal after pancreatic resection has been reported to be safe with a low risk for clinical relevant postoperative pancreatic fistula (CR-POPF) when drain amylase on POD1 is < 5000U/L. The aim of this study was to validate this algorithm in a large national cohort.
Methods: Patients registered in the Dutch Pancreatic Cancer Audit (2014–2016) who underwent pancreatoduodenectomy, distal pancreatectomy or enucleation were analysed. Data on post-operative drain amylase levels, drain removal, postoperative pancreatic fistulae were collected. Univariate and multivariate analysis using a logistic regression model were performed. The primary outcome measure was grade B/C pancreatic fistula (CR-POPF).
Results: Among 1402 included patients, 433 patients with a drain fluid amylase level of <5000U/L on POD1, 7% developed a CR-POPF. For patients with an amylase level >5000U/L the CR-POPF rate was 28%. When using a cut-off point of 2000U/L or 1000U/L during POD1-3, the CR-POPF rates were 6% and 5% respectively. For patients with an amylase level of >2000U/L and >1000UL during POD 1–3 the CR-POPF rates were 26% and 22% respectively (n = 223). Drain removal on POD4 or thereafter was associated with more complications (p = 0.004). Drain amylase level was shown to be the most statistically significant predicting factor for CR-POPF (Wald = 49.7; p < 0.001).
Conclusion: Our data support early drain removal after pancreatic resection. However, a cut-off of 5000U/L drain amylase on POD1 was associated with a relatively high CR-POPF rate of 7%. A cut-off point of 1000U/L during POD1-3 resulted in 5% CR-POPF and might be a safer alternative.

Introduction

Abdominal drains are used for early identification of haemorrhage, anastomotic dehiscence and fistula formation, allowing for a

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timely diagnosis and re-intervention when needed [1,2]. Abdominal drains are also used to drain intra-abdominal fluid and prevent further fluid accumulation [3]. Routine placement of intra-abdominal drains in general surgical procedures like appendectomy, cholecystectomy, minor hepatectomy, colectomy and gastrectomy has been largely abandoned as many studies have shown it does not reduce the complication rate and could even cause an increase in complications [2,4]. A common theory is that the drain serves as a porte d'entrée leading to a potential increase of postoperative infections and that the drain itself appears to act as a foreign body causing an inflammatory response and may interfere with the wound healing [2,3].

However, in pancreatic surgery the current practice in most centres worldwide is to routinely place abdominal drains after pancreatic resections [5]. This has been considered essential [6] to provide controlled external drainage of a pancreatic leak and to monitor pancreatic fistula formation.

Inadequate drainage of a pancreatic leak may lead to an intra-abdominal abscess, postpancreatectomy haemorrhage (PPH) or a pancreatic fistula, serious complications with an associated mortality risk. The preferred treatment option in case of a pancreatic fistula is drainage and if needed placement of extra percutaneous abdominal drains. Thus, the prophylactic drain placement at the time of surgery is concurrently also the treatment in case of a pancreatic fistula, which historically has been the main argument for the continuation of routine drain placement at the time of pancreatic surgery.

Although several studies have been conducted to investigate the value of routine intra-abdominal drainage after pancreatic surgery, the results are contradictive [2,3,7]. A number of recent studies showed that the use of drains after pancreatic surgery may not be beneficial and may even lead to an increase of complications [7–10]. On the other hand, a randomized multicentre trial provided evidence that refraining from routine drainage results in an increase in both the number of complications, the severity of these complications and an increase in mortality from 3% to 12% [11].

The debate *drain or no drain* resulted in an acceptance of the need for drainage after pancreatic surgery and deviated the focus to duration of drainage after pancreatic surgery. A recent meta-analysis concluded that a high drain amylase level on post-operative day one (POD1) was highly predictive for the development of a pancreatic fistula and would therefore require long-term drainage [12]. A landmark trial by Bassi et al. investigated the safety of early drain removal on post-operative day (POD) 3 versus late drain removal on POD5 [13]. They used a cut off amylase level of $\leq$5000 U/L on POD1, which the authors considered an acceptable indicator cut off point for the risk of clinically relevant pancreatic fistula formation [14]. The study suggested that early drain removal decreased the rate of pancreatic fistula and abdominal and pulmonary complications. As a result, the early removal of drains may be preferred in low risk patients with no evidence of fistula development [13]. The aim of this study was to verify retrospectively and possibly improve the algorithm proposed by Bassi et al. in a large cohort from the Dutch registry. The secondary aim was to identify risk factors for the development of pancreatic fistula after pancreatic surgery.

Material and methods

Since July 2013, all patients in the Netherlands who undergo a pancreatic resection are registered prospectively in the Dutch Pancreatic Cancer Audit (DPCA). This study is a retrospective cohort analysis using the national DPCA database including patients who underwent pancreatic resection between 2013 and August 2016 in 13 participating centres in the Netherlands. The primary aim of this study was to verify and improve the algorithm proposed by Bassi et al. [13] The secondary aim was to identify risk factors for the development of pancreatic fistula after pancreatic surgery.

Data collection

Pre-, intra- and postoperative variables were obtained from the DPCA database. Time of drain removal and amylase levels in the drain fluid are not routinely registered in the DPCA database. Therefore, all participating centres were visited to obtain the time of drain removal and the amylase levels in the drain fluid from patient files. In total, data of 2138 patients were collected, which were stored anonymously and matched with the national DPCA database by date of birth, sex, date of surgery and type of resection. The data collection was based on patient lists between 2013 and august 2016 provided by each participating hospital.

Outcome measures

Our primary outcome measure was grade B/C pancreatic fistula (CR-POPF) formation as defined by the 2005 ISGPS classification [15]. At the time these data were collected the new 2016 ISGPS definition was not yet published [16]. Secondary outcome measures included overall complications, postoperative haemorrhage (ISGPS classification), re-interventions, hospital readmission and 30-day mortality.

Inclusion

Adult patients who underwent a classic Whipple procedure, a pylorus preserving pancreatoduodenectomy (PPPD), a distal pancreatectomy or an enucleation procedure or a wedge resection were included in the study.

Exclusion

The DPCA database included 1972 patients. Patients who underwent a total pancreatectomy were excluded from our study. After excluding patients who did not receive a pancreatic resection and patients who underwent a total pancreatectomy, the database contained 1596 patients. A unique match was made by matching patients by variables like birth year, sex, date of surgery and hospital. After matching and combining the DPCA database with the collected data from each hospital there were 1402 patients in our research database left. See Consort diagram (Fig. 1).

Definitions

Time of drain removal was defined based on the post-operative day on which the surgical drain(s) were removed. If two surgical drains were left behind during surgery and the drains were removed separately, time of drain removal was defined by the post-operative day on which the last surgical/second surgical drain was removed. POD1 was defined as the first day after surgery. Early drain removal was defined as drain removal before or on the third post-operative day. Late drain removal was defined as drain removal from POD4 and beyond. CR-POPF (clinical relevant post-operative pancreatic fistula) was defined as Grade B and Grade C pancreatic fistula according to the 2005 ISGPS classification [15]. Complications were defined according to ISGPF definitions (2016) when applicable, all other complications were defined using th Clavien-Dindo classification [17].

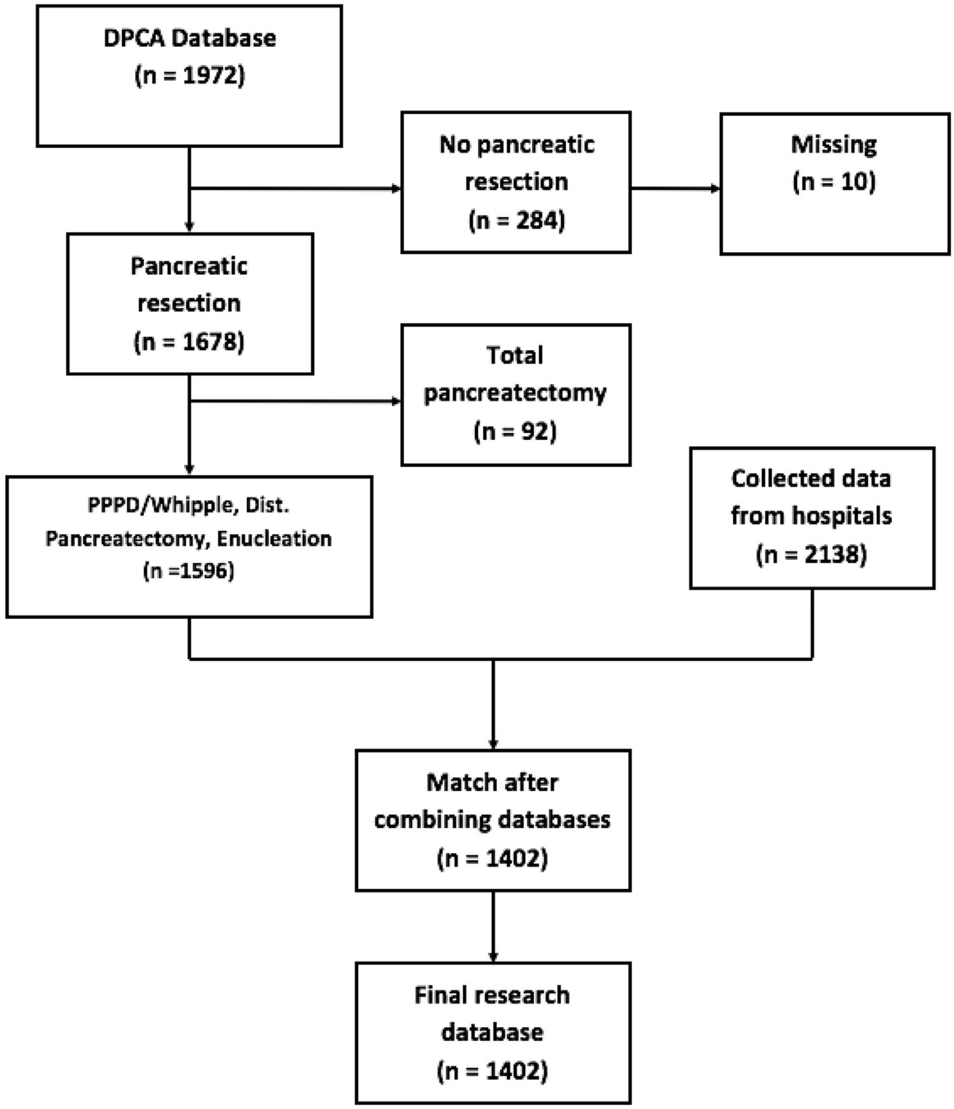


Fig. 1. Consort diagram.

Amylase analysis

In total 11 of the 13 participating hospitals used the Roche technique (Roche Molecular Systems Inc, Pleasanton, USA) for determining drain fluid amylase levels. The other 2 hospitals used the Siemens Dimension Vista technique (Siemens Healthcare GmbH, Erlangen, Germany). In total 7 hospitals maintained an upper limit for serum amylase of 107 U/L, 5 hospitals maintained an upper limit of 100 U/L, 1 hospital maintained an upper limit of 220 U/L and 1 hospital maintained an upper limit of 50 U/L.

Statistics

Data was collected in Microsoft Office Excel 2010 and later transferred to SPSS Statistics 22 (IBM, Somer, NY, USA) for statistical analysis. Descriptive statistics were calculated as percentages, median or mean as appropriate. Mann-Whitney test or Wilcoxon signed-rank test were used for univariate analysis of continuous variables if data were not normally distributed. In case the data were normally distributed an unpaired *t*-test or a logistic regression model was used. In case of nominal/categorical variables a Chi-squared test or a Fisher's exact test was used. For multivariate analysis, a multivariable logistic regression model (backward stepwise regression variable selection) was used. P values < 0.05 was considered significant. Analyses was performed in SPSS v.22 (IBM, Somer, NY, USA).

Ethics

All data were retrieved from an existing database from the Dutch Pancreatic Cancer Audit (DPCA). Since we used an existing anonymised database from the DPCA, no formal approval from the medical ethics committee was needed. The local ethics committees of all participating hospitals waived the need for informed consent.

Results

Post-operative drain fluid amylase levels

(see Table 1) Table 2a shows different cut-off points for drain fluid amylase levels on POD1. For different cut-off points ranging from 2500U/L up and till 7500U/L, the CR-POPF rates for patients

Table 1
Baseline characteristics.

	Study cohort (n = 1402)
Age, median, IQR	67 (58–73)
Sex (male), no. (%).	779 (55.6%)
BMI, median, IQR	24.8 (22.4–27.8)
ASA Score, no. (%)	
1	236 (16.8%)
2	864 (61.6%)
3	273 (19.5%)
4	3 (0.2%)
Unknown	26 (1.9%)
Type of resection, no. (%)	
Pylorus preserving pancreatoduodenectomy	784 (55.9%)
Whipple	384 (27.4%)
Distal pancreatectomy	220 (15.7%)
Wegde resection	7 (0.5%)
Enucleation	7 (0.5%)
Pancreatic texture, no. (%)	
Normal/soft	785 (56.0%)
Hard/fibrotic	373 (26.6%)
Unknown	244 (17.4%)
Location of tumor on CT/MRI, no. (%)	
Head of pancreas	546 (38.9%)
Body of pancreas	96 (6.8%)
Tail of pancreas	116 (8.3%)
Periampullary	101 (7.2%)
Duodenum	56 (4.0%)
Unknown	487 (34.7%)
Pathology, no. (%)	
Adenocarcinoma	967 (69.0%)
Neuroendocrine neoplasm	104 (7.4%)
Intraductal Papillary Mucinous Neoplasm	85 (6.1%)
Mucinous cystic neoplasm	20 (1.4%)
Adenoma	31 (2.2%)
Solid pseudopapillary neoplasm	9 (0.6%)
Serous cystadenoma	18 (1.3%)
Chronic pancreatitis	54 (3.9%)
Other	75 (5.3%)
Unknown	39 (2.8%)
Pancreatic fistula, no. (%)	
No	862 (61.5%)
Grade A	202 (14.4%)
Grade B	144 (10.3%)
Grade C	39 (2.8%)
Unknown	155 (11.1%)
Intra-abdominal drains, no. (%)	1355 (96.6%)
Mortality, no. (%)	40 (2.9%)

with a drain fluid amylase levels below the cut-off point were shown to be similar around 7–8%. The CR-POPF rates for patients with amylase levels above the cut-off point were ranging from 25 to 33% (AUC 0.592–0.637; PPV 25–33%; NPV 92–94%).

Table 3a shows different cut-off points for drain fluid amylase levels on POD1 ranging from 1000U/L up and till 5000U/L. Cut-off points for drain fluid amylase between 2000 and 5000U/L all showed similar results with CR-POPF rates for patients with a drain fluid amylase levels below the cut-off point of around 6–7%. The CR-POPF rates for patients with amylase levels above the cut-off point were ranging from approximately 25-29% (AUC 0.626–0.670; PPV 25–29%; NPV 93–94%). When drain fluid amylase levels were less than 1000U/L on POD1, no more than 5% of the patients developed a CR-POPF during their postoperative course. For patients with a drain fluid amylase levels of above 1000U/L the CR-POPF rate was 21% (AUC 0.687; PPV 21%; NPV 95%).

Tables 2b and 3b in the supplementary file section show comparable results for patients who underwent a pancreatoduodenectomy, excluding distal pancreatectomy and enucleation (Whipple/PPPD only).

We found a large variation between hospitals regarding the timing of measuring post-operative drain fluid amylase levels. Most of the patients (67.4%) did not have drain fluid amylase levels determined on POD1. Therefore, we also looked at the peak drain fluid amylase levels in a smaller selected cohort of patients (n = 223) who had drain fluid amylase determined daily during the first 3 post-operative days.

Table 4a shows different cut-off points for the peak drain fluid amylase levels during the first 3 post-operative days ranging from 1000 to 5000U/L.

Cut-off points for drain fluid amylase between 3000 and 5000U/L all showed similar results with CR-POPF rates for patients with a drain fluid amylase levels below the cut-off point of around 7–8%. The CR-POPF rates for patients with amylase levels above the cut-off point were ranging from approximately 25-29% (AUC 0.634–0.657; PPV 26–29%; NPV 92–93%).

Of 233 patients with a drain amylase level less than 2000U/L during the first 3 post-operative days, 6% developed a CR-POPF during their post-operative course. For patients with a drain fluid amylase levels of above 2000U/L the CR-POPF rate was 26% (AUC 0.701; PPV 26%; NPV 94%). In patients with a drain amylase level less than 1000U/L during the first 3 post-operative days only 5% developed a CR-POPF during their post-operative course. For patients with a drain fluid amylase levels of above 1000U/L the CR-POPF rate was 22% (AUC 0.707; PPV 22%; NPV 95%).

Fig. 2a shows ROC curves for different cut-off points for peak drain fluid amylase during first 3 post-operative days.

Table 4b and Fig. 2b in the supplementary file section shows comparable results for patients who underwent a pancreatoduodenectomy, excluding distal pancreatectomy and enucleation (Whipple/PPPD only).

Table 2a
Different cut-off points for drain fluid amylase on POD1 as predictor of CR-POPF.

CR-POPF N = 1295 Chi-squared test	No	Yes	Total	Missings	p-value (<0.05)	OR (95% CI)
POD1 Amylase					**<0.001***	**4.878 (2.521–9.440)**
<2500U/L	331 (93%)	23 (7%)	354			
>2500U/L	59 (75%)	20 (25%)	79			
Total	**390 (90%)**	**43 (10%)**	**433**	**862 (67%)**		
POD1 Amylase					**<0.001 ***	**4.962 (2.438–10.102)**
<5000 U/L	352 (93%)	28 (7%)	380			
>5000 U/L	38 (72%)	15 (28%)	53			
Total	**390 (90%)**	**43 (10%)**	**433**	**862 (67%)**		
POD1 Amylase					**<0.001 ***	**6.083 (2.517–14.703)**
<7500 U/L	365 (92%)	30 (8%)	395			
>7500 U/L	18 (67%)	9 (33%)	27			
Total	**383 (91%)**	**39 (9%)**	**422**	**873 (67%)**		

Table 3a
Different cut-off points for drain fluid amylase on POD1.

CR-POPF N = 1295 Chi-squared test	No	Yes	Total	Missings	p-value (<0.05)	OR (95% CI)
POD1 Amylase					**<0.001***	**4.960 (2.566–9.588)**
<1000 U/L	291 (95%)	16 (5%)	307			
>1000 U/L	99 (79%)	27 (21%)	126			
Total	**390 (90%)**	**43 (10%)**	**433**	**862 (67%)**		
POD1 Amylase					**<0.001***	**5.050 (2.628–9.706)**
<2000 U/L	323 (94%)	21 (6%)	344			
>2000 U/L	67 (75%)	22 (25%)	89			
Total	**390 (91%)**	**43 (10%)**	**433**	**862 (67%)**		
POD1 Amylase					**<0.001***	**5.034 (2.581–9.817)**
<3000 U/L	337 (93%)	24 (7%)	361			
>3000 U/L	53 (74%)	19 (26%)	72			
Total	**390 (90%)**	**43 (10%)**	**433**	**862 (67%)**		
POD1 Amylase					**<0.001***	**5.566 (2.787–11.115)**
<4000 U/L	349 (93%)	26 (7%)	375			
>4000 U/L	41 (71%)	17 (29%)	58			
Total	**390 (90%)**	**43 (10%)**	**433**	**862 (67%)**		
POD1 Amylase					**<0.001***	**4.962 (2.438–10.102)**
<5000 U/L	352 (93%)	28 (7%)	380			
>5000 U/L	38 (72%)	15 (28%)	53			
Total	**390 (90%)**	**43 (10%)**	**433**	**862 (67%)**		

Table 4a
Different cut-off points for peak drain fluid amylase during first 3 post-operative days.

CR-POPF N = 223 Chi-squared test	No	Yes	Total	Missings	p-value (<0.05)	OR (95% CI)
POD1-3 Amylase					**<0.001***	**5.952 (2.251–15.738)**
<1000 U/L	125(95%)	6 (5%)	131			
>1000 U/L	63 (78%)	18 (22%)	81			
Total	**188 (89%)**	**24 (11%)**	**212**	**11 (5%)**		
POD1-3 Amylase					**<0.001***	**5.794 (2.368–14.176)**
<2000 U/L	146 (94%)	9 (6%)	155			
>2000 U/L	42 (74%)	15 (26%)	57			
Total	**188 (89%)**	**24 (11%)**	**212**	**11 (5%)**		
POD1-3 Amylase					**<0.001***	**4.371 (1.812–10.543)**
<3000 U/L	153 (93%)	12 (7%)	165			
>3000 U/L	35 (74%)	12 (26%)	47			
Total	**188 (89%)**	**24 (11%)**	**212**	**11 (5%)**		
POD1-3 Amylase					**<0.001***	**5.267 (2.162–12.829)**
<4000 U/L	158 (93%)	12 (7%)	170			
>4000 U/L	30 (71%)	12 (29%)	42			
Total	**188 (89%)**	**24 (11%)**	**212**	**11 (5%)**		
POD1-3 Amylase					**<0.001***	**4.082 (1.651–10.094)**
<5000 U/L	160 (92%)	14 (8%)	174			
>5000 U/L	28 (74%)	10 (26%)	38			
Total	**188 (89%)**	**24 (11%)**	**212**	**11 (5%)**		

Early versus late removal

In a selected group of patients (n = 1078) late removal of abdominal drains was associated with a general complication rate of 60.2% versus 49.3% in the early drain removal group (p = 0.004). We found no significant effect of the timing of drain removal on delayed gastric emptying (22% vs 24%; p = 0.588). It appears that patients with late removal of drains have more post-operative bleedings, but the results were borderline significant (5% vs 2%; p = 0.059).

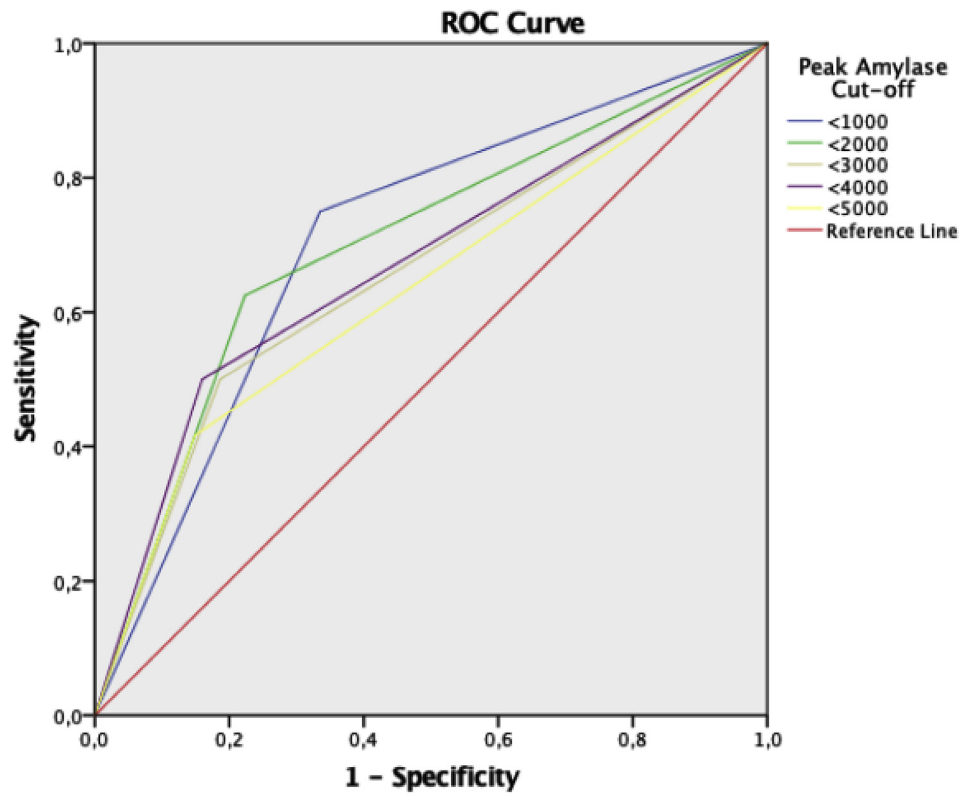
As expected, since pancreatic fistula formation requires the abdominal drains to be kept longer in situ, late removal of drains was associated with more CR-POPF (15% vs 6%; p < 0.001). We found no significant difference in mortality between early and late removal of abdominal drains (1% vs 1%; p = 0.389). Late removal of abdominal drains was significantly associated with more hospital re-admissions. In total 18% of the patients who had their drains removed on POD4 or later were readmitted to the hospital. For patients with drain removal before or on POD3 the re-admission rate was 10% (p = 0.006).

Patients who had a late removal of abdominal drains had more re-interventions in general (21% in the late group versus 13% in the early group, p = 0.016). It appears that patients with late removal of drains have more radiological re-interventions, but the results were borderline significant (13% vs 8%; p = 0.060). For re-operations (5% vs 4%; p = 0.449), endoscopic re-interventions (4% vs 3%; p = 0.494) and re-interventions under full anaesthesia (5% vs 4%; p = 0.602) as well as IC admissions (7% vs 6%; p = 0.712) we found no significant effect. Patients who had a late removal of abdominal drains had more blood transfusions (10% vs 5%; p = 0.022) (Table 5a).

Table 5b in the supplementary file section shows comparable results for patients who underwent a pancreatoduodenectomy, excluding distal pancreatectomy and enucleation (Whipple/PPPD only).

Risk factors for pancreatic fistula

Table 6a shows the results of the logistic regression model for



Peak Amylase POD 1-3	AUC	p-value (<0.05)	PPV	NPV
<1000	0.707	0.001*	22%	95%
<2000	0.701	0.001*	26%	94%
<3000	0.657	0.012*	26%	93%
<4000	0.670	0.007*	29%	93%
<5000	0.634	0.033*	26%	92%

Fig. 2a. ROC curves for different cut-off points for peak drain fluid amylase during first 3 post-operative days.

CR-POPF after backward stepwise regression variable selection (n = 852). Drain fluid amylase showed to be the most statistically significant predicting factor for the development of Grade B/C pancreatic fistula (Wald = 49.7; p < 0.001) followed by ASA score (Wald = 6.6; p = 0.036), BMI (Wald = 5.1; p = 0.023) and pancreatic texture (Wald = 4.8; p = 0.028).

Table 6b in the supplementary file section show comparable results for patients who underwent a pancreatoduodenectomy, excluding distal pancreatectomy and enucleation (Whipple/PPPD only).

Discussion

This nationwide retrospective cohort analysis demonstrates that different cut-off points for drain fluid amylase ranging from 2500 to 7500U/L on the first postoperative day after pancreatic resection had similar relatively high CR-POPF rates of around 7%. When applying a cut-off point of 5000U/L for the peak drain fluid amylase level during the first 3 post-operative days we still found a CR-POPF rate of 8%. A lower cut-off point of 1000U/L was associated with a CR-POPF rate of 5% and might therefore be a safer alternative, leading to less CR-POPF. Furthermore, this analysis demonstrates that late drain removal is associated with more complications and that the peak drain fluid amylase during the first 3 post-operative days is the most statistically significant predicting factor for the development of CR-POPF, followed by ASA score, BMI and pancreatic texture.

Analysis with pancreatoduodenectomy patients only, excluding distal pancreatectomy and enucleation showed comparable results.

Over the last decades, the use of abdominal drains in pancreatic surgery has been debated, and several studies have been published with contradictive results [2,3,7]. Some recent studies showed that the use of abdominal drains in pancreatic surgery may not be beneficial and may even lead to more complications [7–10]. A remarkable study in this regard is the study of Van Buren et al. [11] In this large multicentre trial, the omission of drains after pancreatoduodenectomy resulted in an increase in both the incidence as well as the severity of complications. The Data Monitoring Safety Board stopped this study because of an increase in mortality from 3% in the drain group versus 12% in the no-drain group [11]. They concluded that drain placement after pancreatoduodenectomy is strongly recommended. This is in accordance to current clinical practice in most pancreatic centres.

In 2013, a large multi-centre prospective randomised trial (the PANDA trial NTR3224) was started by the Dutch Pancreatic Cancer Group. This study compared drain placement versus no drain placement after pancreatoduodenectomy. After the publication of the study of Van Buren et al., in 2014, the PANDA trial was stopped

Table 5a
Early versus late drain removal complications.

N = 1078 (-bile leak −chylous leak) Chi-squared test	Early removal POD ≤ 3	Late removal POD ≥ 4	Total	Missings	p-value (<0.05)	OR (95% CI)
Complications					0.004*	1.555 (1.151–2.100)
-No	111 (50.7%)	314 (39.2%)	425 (42.2%)			
-Yes	108 (49.3%)	475 (60.2%)	583 (57.8%)			
Total	**219 (100%)**	**789 (100%)**	**1008 (100%)**	70 (6.5%)		
Delayed gastric emptying					0.588	0.907 (0.638–1.290)
-No	166 (76%)	611 (78%)	777 (77%)			
-Yes	53 (24%)	177 (22%)	230 (23%)			
Total	**219 (100%)**	**788 (100%)**	**1007 (100%)**	71 (7%)		
Bleeding					0.059	2.408 (0.941–6.163)
-No	213 (98%)	743 (95%)	956 (95%)			
-Yes	5 (2%)	42 (5%)	47 (5%)			
Total	**218 (100%)**	**785 (100%)**	**1003 (100%)**	75 (7%)		
CR-POPF					<0.001*	2.892 (1.598–5.233)
-No	206 (94%)	663 (85%)	869 (87%)			
-Yes	13 (6%)	121 (15%)	134 (13%)			
Total	**219 (100%)**	**784 (100%)**	**1003 (100%)**	75 (7%)		
Mortality					0.389	0.547 (0.136–2.205)
-No	213 (99%)	779 (99%)	992 (99%)			
-Yes	3 (1%)	6 (1%)	9 (1%)			
Total	**216 (100%)**	**785 (100%)**	**1001 (100%)**	77 (7%)		
Re-admission hospital					0.006*	1.933 (1.199–3.116)
-No	190 (90%)	630 (82%)	820 (83%)			
-Yes	22 (10%)	141 (18%)	163 (17%)			
Total	**212 (100%)**	**771 (100%)**	**983 (100%)**	95 (9%)		
Re-intervention					0.016*	1.681 (1.096–2.578)
-No	188 (87%)	621 (79%)	809 (81%)			
-Yes	29 (13%)	161 (21%)	190 (19%)			
Total	**217 (100%)**	**782 (100%)**	**999 (100%)**	79 (7%)		
Re-operation					0.449	1.349 (0.620–2.936)
-No	209 (96%)	736 (95%)	945 (95%)			
-Yes	8 (4%)	38 (5%)	46 (5%)			
Total	**217 (100%)**	**774 (100%)**	**991 (100%)**	87 (8%)		
Radiological re-intervention					0.060	1.651 (0.976–2.793)
-No	198 (92%)	673 (87%)	871 (88%)			
-Yes	18 (8%)	101 (13%)	119 (12%)			
Total	**216 (100%)**	**774 (100%)**	**990 (100%)**	88 (8%)		
Endoscopic re-intervention					0.484	1.343 (0.586–3.080)
-No	210 (97%)	737 (96%)	947 (96%)			
-Yes	7 (3%)	33 (4%)	40 (4%)			
Total	**217 (100%)**	**770 (100%)**	**987 (100%)**	91 (8%)		
Re-intervention under full anaesthesia					0.602	1.231 (0.563–2.695)
-No	208 (96%)	739 (95%)	947 (96%)			
-Yes	9 (4%)	35 (5%)	43 (4%)			
Total	**216 (100%)**	**774 (100%)**	**990 (100%)**	88 (8%)		
IC admission					0.712	1.121 (0.612–2.054)
-No	204 (94%)	728 (93%)	932 (93%)			
-Yes	14 (6%)	56 (7%)	70 (7%)			
Total	**218 (100%)**	**784 (100%)**	**1002 (100%)**	76 (7%)		
Blood transfusion					0.022*	2.101 (1.098–4.024)
-No	206 (95%)	704 (90%)	910 (91%)			
-Yes	11 (5%)	79 (10%)	90 (9%)			
Total	**217 (100%)**	**783 (100%)**	**1000 (100%)**	78 (7%)		

prematurely after 22 inclusions (personal communication).

A recent study from Witzigmann et al. renewed the debate 'to drain or not to drain' [18]. This multicentre randomised trial from two large centres in Germany showed that the omission of drains was not inferior to routine intra-abdominal drainage in terms of postoperative re-interventions. It also showed that no drain was superior in terms of clinically relevant (Grade B/C) pancreatic fistulae and fistula-associated complications. Therefore, Witzigmann et al. concluded that there is no need for routine prophylactic drainage after pancreatic resection with pancreaticojejunal anastomosis [14]. Despite this report, the clinical practice in most centres continued to favour routine drain placement. Obviously, more confirmatory evidence is needed before longstanding clinical practices will be changed.

Thus the question to drain or not to drain is still unanswered, but the high mortality in the no-drain group of Van Buren drives pancreatic surgeons to leave drains routinely after pancreatic resection. The optimal strategy may therefore be to drain all patients for a short period of time. Bassi et al. tried to develop an algorithm for drain removal. In a large prospective randomized trial, they showed that early drain removal may be safe in patients with a low risk for a pancreatic fistula. Low risk patients were defined as patients with an amylase level of ≤5000 U/L in the drain fluid on POD1 [13]. The cut-off point of ≤5000 was based on a previous study by the same group [14].

In our study, we intended to retrospectively verify this algorithm. Unfortunately, there seems to be a huge variation between hospitals in the timing and frequency of post-operative drain fluid amylase levels measurements. As a result, most of the patients in our database did not have drain fluid amylase levels determined

Table 6a
Logistic regression model CR-POPF with peak amylase during first 3 post-operative days.

CR-POPF N = 852 550 missings	B	S.E.	Wald	Df	P-value (<0.05)	OR (95% CI)
Early vs late removal						
Early (ref)						1
Late	0.557	0.385	2.089	1	0.148	1.746 (0.820–3.715)
Histological diagnosis						
Malign (ref)						1
Benign	0.149	0.267	0.314	1	0.575	1.161 (0.689–1.958)
BMI	0.060	0.027	5.143	1	0.023*	1.062 (1.008–1.119)
ASA	–	–	6.624	2	0.036*	–
ASA I (ref)						1
ASA II	−0.034	0.322	0.011	1	0.917	0.967 (0.514–1.818)
ASA III/IV	0.684	0.376	3.314	1	0.069	1.982 (0.949–4.140)
Texture of pancreas						
Normal/Soft (ref)						1
Hard/fibrotic	−0.684	0.311	4.826	1	0.028*	0.505 (0.274–0.929)
POD1-3 Amylase						
<1000 U/L (ref)						1
>1000 U/L	1.858	0.264	49.699	1	<0.001*	6.409 (3.824–10.743)
Constant	−3.906	0.975	16.033	1	0.000	0.020

Chi-square = 123.035 df = 18 p < 0.001 2 log likehood = 501.248 Nagelkerke R^2 = 0.259.
Hosmer and Lemeshow Test = 0.016 ROC = 0.804.

daily. Drain fluid amylase level data on POD1 were available in 433 patients. When using different cut-off points for drain amylase level on POD1 ranging from 2500U/L to 7500U/L all patients had comparable CR-POPF rates of around 7%.

Subsequently, we also looked at peak drain fluid amylase levels during the first 3 post-operative days. A cohort of 223 patients was selected who had drain fluid amylase determined daily during the first 3 post-operative days. This analysis showed that 8% of the patients in whom the drain fluid amylase level did not exceed 5000U/L during the first 3 post-operative days developed a CR-POPF. As the total number of CR-POPF in our entire cohort was 13.1%, we think this percentage of 8% is still too high to be applied as a useful cut off point. In our study, patients with drain fluid amylase levels of less than 2000U/L and less than 1000U/L had CR-POPF rates of respectively 6% and 5%. We therefore suggest that a lower cut-off point would be a safer alternative.

The most cited and most commonly used model for predicting POPF is the validated Fistula Risk Score (FRS) by Callery et al. [19] The FRS predicts POPF based on pancreatic texture, pancreatic duct diameter, intraoperative blood loss and definitive pathology. Blood loss is currently not registered in several audits including the DPCA. For this reason The Dutch Pancreatic Cancer Group recently developed the Alternative Fistula Risk Score (aFRS) in pancreatoduodenectomy based on pancreatic texture, pancreatic duct diameter and BMI [20]. When looking at risk factors for CR-POPF in our study we found results comparable to both the FRS and aFRS. In our study drain fluid amylase was the most statistically significant predicting factor for the development of Grade B/C pancreatic fistula followed by ASA score, BMI and pancreatic texture.

Based on the FRS and aFRS one could argue for a selective drainage in pancreatic surgery. Despite FRS and aFRS most pancreatic surgeons prefer routine drainage. It is unclear whether no drainage is beneficial for the patient compared to drainage for a short period of time (less than 4 days). A decision based on drain fluid amylase is probably more reassuring than peroperative risk modelling. In order to monitor drain fluid amylase an intra-abdominal drain will always be necessary. Based on our data, routine abdominal drainage after pancreatic resection with daily determination of drain fluid amylase levels and drain removal on POD 3 when the peak drain fluid amylase during the first three postoperative days does not exceed 1000U/L seems advisable.

Bassi et al. concluded in their study that late removal of abdominal drains was associated with a higher rate of post-operative complications with an increased hospital stay, hospital readmissions as well as hospital costs [13]. Our results correspond with these findings. We found that patients with late drain removal developed significantly more complications in general, had more hospital re-admissions and re-interventions as well as more blood transfusions. Also, it appeared that patients who had a late drain removal developed significantly more often a CR-POPF compared to patients who had their abdominal drains removed early. However, this may not be a causal relationship. The pancreatic fistula itself is most likely responsible for both late drain removal (which is the treatment for pancreatic fistula) and most additional associated complications.

Our study has a number of limitations. First, since this study is a retrospective observational study there could be confounding by indication, meaning that prognostic factors may have influenced treatment decisions. Therefore, the treatment effects could be biased. Second, the retrospective nature limits the availability of certain variables. In the majority of patients drain fluid amylase was not determined on the first post-operative day. Therefore, we also looked at the peak drain fluid amylase levels during the first 3 post-operative days to approximate the Bassi algorithm as close as possible. A retrospective setting is an as close as possible approximation of the ideal situation. A randomized controlled trial cohort with routine daily registration of drain fluid amylase levels would be needed to confirm our findings.

In conclusion, our data show that a cut-off point of 5000U/L for drain fluid amylase levels on POD1-3, is associated with a relatively high percentage of CR-POPF of 8%. We demonstrated that a cut-off point of 1000U/L for drain fluid amylase on POD1-3 might be a safer alternative to be applied in a clinical practise algorithm for early drain removal after pancreatic surgery, but a prospective study is needed to confirm these findings.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.07.041.

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