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Pancreatic

The use and clinical outcome of total pancreatectomy in the United States, Germany, the Netherlands, and Sweden

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ABSTRACT

Background: Total pancreatectomy has high morbidity and mortality and differences among countries are currently unknown. This study compared the use and postoperative outcomes of total pancreatectomy among 4 Western countries.

Methods: Patients who underwent one-stage total pancreatectomy were included from registries in the United States, Germany, the Netherlands, and Sweden (2014–2018). Use of total pancreatectomy was assessed by calculating the ratio total pancreatectomy to pancreatoduodenectomy. Primary outcomes were major morbidity (Clavien Dindo ≥3) and in-hospital mortality. Predictors for the primary outcomes were assessed in multivariable logistic regression analyses. Sensitivity analysis assessed the impact of volume (low-volume <40 or high-volume ≥40 pancreatoduodenectomies annually; data available for the Netherlands and Germany).

Results: In total, 1,579 patients underwent one-stage total pancreatectomy. The relative use of total pancreatectomy to pancreatoduodenectomy varied up to fivefold (United States 0.03, Germany 0.15, the Netherlands 0.03, and Sweden 0.15; $P < .001$). Both the indication and several baseline characteristics differed significantly among countries. Major morbidity occurred in 423 patients (26.8%) and differed (22.3%, 34.9%, 38.3%, and 15.9%, respectively; $P < .001$). In-hospital mortality occurred in 85 patients (5.4%) and also differed (1.8%, 10.2%, 10.8%, 1.9%, respectively; $P < .001$). Country, age ≥75, and vascular resection were predictors for in-hospital mortality. In-hospital mortality was lower in high-volume centers in the Netherlands (4.9% vs 23.1%; $P = .002$), but not in Germany (9.8% vs 10.6%; $P = .733$).

Conclusion: Considerable differences in the use of total pancreatectomy, patient characteristics, and postoperative outcome were noted among 4 Western countries with better outcomes in the United States and Sweden. These large, yet unexplained, differences require further research to ultimately improve patient outcome.

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Introduction

Total pancreatectomy (TP) is a relatively uncommon operation, which is mostly performed for pancreatic cancer, chronic pancreatitis, or main duct intraductal papillary mucinous neoplasm (IPMN).[1–4] Most surgeons are reluctant to perform TP because of the resulting lifelong endocrine and exocrine pancreatic insufficiency.[5] However, it is unknown whether the threshold to perform TP differs between surgeons and centers. For instance, some surgeons may consider a TP in the case of a very challenging pancreatic anastomosis, whereas others view this as a relative contraindication for TP. To what extent such differences could even exist between countries is unclear since nationwide data are lacking.

A recent study with 329 patients from 2 very high-volume centers reported a low 30-day mortality of 2.1% after TP.[6] In contrast, a recent pan-European snapshot study reported an in-hospital mortality of 5% after TP.[7] The latter study also showed that high-volume centers had better outcomes after TP. Next to hospital volume, patient characteristics may also affect postoperative outcomes. A previous comparison of 20,000 pancreatoduodenectomies from 4 Western registries demonstrated considerable differences in patient and tumor characteristics in the period 2014 to 2017.[8] It is unclear to what extent such differences also exist between patients undergoing TP.

The aim of this study is to assess differences in the use of TP, patient baseline characteristics, and in short-term postoperative outcomes after one-stage TP among 4 Western registries of pancreatic surgery.

Methods

Patients and design

This cohort study combined data on patients undergoing one-stage TP from 4 registries on pancreatic surgery: United States (American College of Surgeons National Surgical Quality Improvement Program [NSQIP], multicenter, 142 centers in 2017, including several Canadian hospitals), Germany (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie - Studien-, Dokumentations- und Qualitätszentrum [StuDoQ], multicenter, 54 centers in 2017), the Netherlands (Dutch Pancreatic Cancer Audit, nationwide, 17 centers in 2017), and Sweden (Swedish National Pancreatic and Periampullary Cancer Registry, nationwide, 6 centers in 2017).[9–12] The national coverage of these registries was reported as 66%, 20%, 93%, and 86%, respectively.[9–11,13] All patients who underwent one-stage TP from 2014 to 2018, and were registered in 1 of the registries, were included. From the StuDoQ database patients were included between 2014 and 2017. The study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[14]

Data collection

Baseline characteristics and postoperative and pathological outcomes were collected according to the previously described methods for the comparison of pancreatoduodenectomies (PDs) from the 4 registries by this study group.[8] The use of TP per country/registry was assessed by calculating the ratio of TP to PD. Postoperative outcomes were registered during initial hospital admission, until 30 days after surgery, or until discharge if longer than 30 days. Additionally, failure-to-rescue rates (ie, mortality after a major complication) were calculated, assuming that all patients with in-hospital mortality died from a major complication.[15] The failure-to-rescue rate is calculated by dividing the number of deaths by the number of patients with a major complication and reflects the management of complications. Annual center volume was based on the annual volume of PDs during the last year, which was extracted from the registration and could only be assessed for Germany and the Netherlands. Low- and high-volume centers were defined based on a previously used cutoff value of <40 (low-volume) or ≥40 (high-volume) PDs annually.[16]

Statistical analysis

Baseline characteristics and postoperative and pathological outcomes were presented using descriptive statistics. Normally distributed continuous data were compared using the one-way analysis of variance and presented as means with standard deviations. Non-normally distributed continuous data were compared using the Kruskal-Wallis test and presented as medians with interquartile ranges (IQR). Categorical data are presented as frequency with percentages and were compared using the χ^2 test. Missing data were described and not imputed, and complete case analyses were performed (missing data <5% in multivariable analyses). Sensitivity analyses for major morbidity and in-hospital mortality were performed for patients with IPMN and for patients operated in high-volume versus low-volume centers to observe the impact of volume on postoperative outcomes. In addition, postoperative outcomes were described for patients who died. Potential independent predictors for major morbidity and in-hospital mortality within patient, preoperative, and histopathological diagnosis characteristics were identified in univariable logistic regression models. Variables with a P value < .10 in univariable analyses were entered in the multivariable regression models, and backward step selection was used. Results were reported as the odds ratio (OR) with corresponding 95% confidence interval (CI). All P values were based on a 2-sided test, and P values of < .05 were considered statistically significant. P values of < .001 were considered statistically significant due to a Bonferroni correction for multiple comparisons in the analyses of baseline characteristics and postoperative and pathological outcomes. Data were analyzed using IBM SPSS Statistics for Windows, version 26 (IBM Corp, Armonk, NY).

Results

Overall, 1,579 patients after one-stage TP met the inclusion criteria. There were 663 patients from the United States (mean number per center: 5), 538 from Germany (mean: 10), 120 from the Netherlands (mean: 7), and 258 from Sweden (mean: 43). The relative use of TP differed up to fivefold among countries (ratio TP to PD: 0.03, 0.15, 0.03, and 0.15, respectively; P < .001).

The median age at operation was 66 years (IQR 57–73), and 732 patients (46.4%) were female (Table I). Laparoscopic and robotic TP, including those converted to open procedures, was performed in 68 (4.3%) and 29 patients (1.8%), respectively. Venous resections (ie, portal vein or superior mesenteric vein) were performed in 345 patients (21.8%), arterial resections in 15 (0.9%), and venous and arterial resections in 54 (3.4%). On final histopathological diagnosis, 836 patients (52.9%) were diagnosed with a pancreatic adenocarcinoma, followed by 229 patients (14.5%) with IPMN without invasive cancer, and 176 patients (11.1%) with chronic pancreatitis. Major morbidity occurred in 423 patients (26.8%) and in-hospital mortality in 85 patients (5.4%).

Patient, preoperative, and intraoperative characteristics

Patient, preoperative, and intraoperative characteristics for each country are displayed in Table I. Patients in the United States were younger (63 years old) compared to 68, 65, and 68 years in Germany, the Netherlands, and Sweden, respectively (P < .001).

Table I
Patient, preoperative and intraoperative characteristics

	Total N = 1,579	NSQIP United States n = 663	StuDoQ Germany n = 538	DPCA The Netherlands n = 120	SNPPCR Sweden n = 258	P value
Age at operation, median (IQR), y	66 (57–73)	63 (54–71)	68 (59–75)	65 (58–72)	68 (60–73)	< **.001**
Missing	5 (0.3%)			5 (4.2%)		
Female patients	732 (46.4%)	333 (50.2%)	228 (42.6%)	59 (49.2%)	112 (43.4%)	.028
Missing	3 (0.2%)			3 (2.5%)		
BMI, median (IQR), kg/m^2	25.0 (22.6–28.6)	25.8 (22.8–29.8)	24.8 (22.6–27.7)	23.9 (21.8–27.9)	24.8 (22.6–27.5)	< **.001**
Missing	17 (1.1%)	5 (0.8%)	4 (0.7%)	2 (1.7%)	6 (2.3%)	
≥10% weight loss 6 mon preoperatively	376 (23.8%)	107 (16.1%)	112 (20.8%)	36 (30.0%)	121 (46.9%)	< **.001**
Missing	42 (2.7%)		21 (3.9%)	18 (15.0%)	3 (1.2%)	
Functional health status						< **.001**
Independent	1,508 (95.5%)	652 (98.3%)	497 (92.4%)	105 (87.5%)	254 (98.4%)	
Partially dependent	45 (2.8%)	9 (1.4%)	32 (5.9%)	2 (1.7%)	2 (0.8%)	
Totally dependent	5 (0.3%)	-	4 (0.7%)	1 (0.8%)	-	
Missing	21 (1.3%)	2 (0.3%)	5 (0.9%)	12 (10.0%)	2 (0.8%)	
ASA score						< **.001**
1	64 (4.1%)	1 (0.2%)	19 (3.5%)	9 (7.5%)	35 (13.6%)	
2	571 (36.2%)	130 (19.6%)	232 (43.1%)	72 (60.0%)	137 (53.1%)	
3	869 (55.0%)	473 (71.3%)	277 (51.5%)	37 (30.8%)	82 (31.8%)	
4	72 (4.6%)	58 (8.7%)	9 (1.7%)	2 (1.7%)	3 (1.2%)	
5	1 (0.1%)	1 (0.2%)	-	-	-	
Missing	2 (0.1%)		1 (0.2%)		1 (0.4%)	
Diabetes mellitus	594 (37.6%)	272 (41%)	200 (37.2%)	49 (40.8%)	73 (28.3%)	.004
Missing	6 (0.4%)		2 (0.4%)	2 (1.7%)	2 (0.8%)	
COPD	78 (4.9%)	18 (2.7%)	37 (6.9%)	14 (11.7%)	9 (3.5%)	< **.001**
Missing	9 (0.6%)		2 (0.4%)	4 (3.3%)	3 (1.2%)	
Heart failure	51 (8.6%)	3 (0.5%)	46 (8.6%)	2 (1.7%)	NA	< **.001**
Missing	13 (1.0%)		7 (1.3%)	6 (5.0%)		
Hypertension	798 (50.5%)	331 (49.9%)	311 (57.8%)	31 (25.8%)	125 (48.4%)	< **.001**
Missing	21 (1.3%)		2 (0.4%)	10 (8.3%)	9 (3.5%)	
Dialysis	10 (0.8%)	5 (0.8%)	5 (0.9%)	-	NA	.587
Missing	10 (0.8)		2 (0.4%)	8 (6.7%)		
Albumin, median (IQR), g/L	39 (33–43)	38.0 (31.0–42.0)	39.3 (34.6–43.4)	39.0 (31.5–43.5)	NA	.001
Missing	436 (33%)	95 (14.3%)	250 (46.5%)	91 (75.8%)		
Biliary stent placement						< **.001**
No	1,108 (70.2%)	468 (70.6%)	401 (74.5%)	75 (62.5%)	164 (63.6%)	
Yes–ERCP	379 (24.0%)	121 (18.3%)	133 (24.7%)	34 (28.3%)	91 (35.3%)	
Yes–PTCD	8 (0.5%)	6 (0.9%)	-	2 (1.7%)	-	
Yes–type unknown	12 (0.8%)	12 (1.8%)	-	-	-	
Missing	72 (4.6%)	56 (8.4%)	4 (0.7%)	9 (7.5%)	3 (1.2%)	
Neoadjuvant chemotherapy*	196 (12.4%)	110 (34.7%)	34 (10.6%)	7 (9.2%)	20 (16.3%)	< **.001**
Missing	59 (3.7%)		1 (0.3%)	29 (38.2%)		
Neoadjuvant radiotherapy*	53 (7.4%)	45 (14.2%)	5 (1.6%)	3 (3.9%)	NA	< **.001**
Missing	31 (4.3%)	1 (0.3%)	1 (0.3%)	29 (38.2%)		
Y of surgery						< **.001**
2014	257 (16.3%)	114 (17.2%)	98 (18.2%)	26 (21.7%)	19 (7.4%)	
2015	312 (19.8%)	137 (20.7%)	110 (20.4%)	28 (23.3%)	37 (14.3%)	
2016	326 (20.6%)	126 (19.0%)	112 (20.8%)	23 (19.2%)	65 (25%)	
2017	465 (29.4%)	154 (23.2%)	218 (40.5%)	23 (19.2%)	70 (27.1%)	
2018	219 (13.9%)	132 (19.9%)	-	20 (16.7%)	67 (26.0%)	
Operative approach						< **.001**
Open (excluding conversion)	1,477 (93.5%)	591 (89.1%)	519 (96.5%)	113 (94.2%)	254 (98.4%)	
Laparoscopic without conversion	33 (2.1%)	24 (3.6%)	5 (0.9%)	2 (1.7%)	2 (0.8%)	
Laparoscopic with conversion	35 (2.2%)	19 (2.9%)	10 (1.9%)	4 (3.3%)	2 (0.8%)	
Robotic without conversion	20 (1.3%)	20 (3.0%)	-	-	-	
Robotic with conversion	9 (0.6%)	9 (1.4%)	-	-	-	
Missing	5 (0.3%)		4 (0.7%)	1 (0.8%)		
Vascular resection						< **.001**
No	1,143 (72.4%)	489 (73.8%)	412 (76.6%)	80 (66.7%)	162 (62.8%)	
Venous (portal or SMV)	345 (21.8%)	111 (16.7%)	121 (22.5%)	34 (28.3%)	79 (30.6%)	
Arterial (celiac, hepatic, or SMA)	15 (0.9%)	11 (1.7%)	1 (0.2%)	-	3 (1.2%)	
Venous and arterial	54 (3.4%)	35 (5.3%)	4 (0.7%)	3 (2.5%)	12 (4.7%)	
Missing	22 (1.4%)	17 (2.6%)		3 (2.5%)	2 (0.8%)	
Spleen resection	582 (44.1%)	324 (48.9%)	209 (38.8%)	49 (40.8%)	NA	< **.001**
Missing	127 (9.6%)	119 (17.9%)		8 (6.7%)		
Colon resection	54 (4.1%)	18 (2.7%)	28 (5.2%)	8 (6.7%)	NA	.082
Missing	137 (10.4%)	119 (17.9%)		18 (15.0%)		
Partial gastrectomy	156 (11.8%)	79 (11.9%)	73 (13.6%)	4 (3.3%)	NA	0.015
Missing	138 (10.4%)	119 (17.9%)		19 (15.8%)		
Abdominal drain placed	767 (73.7%)	438 (66.1%)	NA	110 (91.7%)	219 (84.9%)	< **.001**

(*continued on next page*)

Multiple significant differences also were observed for other patient characteristics, comorbidities, biliary stent placement, and use of neoadjuvant chemotherapy (Table I). The proportion of patients with pancreatic adenocarcinoma as indication for TP was the lowest in the United States and Sweden (47.8%, 59.5%, 63.3%, 47.7%; $P < .001$; Table II). The proportion of patients with IPMN was the

Table I (*continued*)

	Total N = 1,579	NSQIP United States n = 663	StuDoQ Germany n = 538	DPCA The Netherlands n = 120	SNPPCR Sweden n = 258	P value
Missing	27 (2.6%)			6 (5.0%)	17 (6.6%)	
Days in situ, median (IQR), d[†]	6.0 (4.0–9.0)	6.0 (4.0–9.0)		6 (4.5–15.5)	6.0 (4.0–8.0)	.083
Missing	164/767 (21.4%)	83/438 (18.9%)		81/110 (73.6%)		

Values are numbers with percentages within parentheses unless indicated otherwise.
Bold numbers indicate statistical significance after Bonferroni correction ($P < .001$).
ASA, American Society of Anesthesiologist; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *DPCA*, Dutch Pancreatic Cancer Audit; *ERCP*, endoscopic retrograde cholangiopancreatography; *IQR*, interquartile range; *NA*, not applicable; *NSQIP*, National Surgical Quality Improvement Program; *PTCD*, percutaneous transhepatic cholangiography drainage; *SMA*, superior mesenteric artery; *SMV*, superior mesenteric vein; *SNPPCR*, Swedish National Pancreatic and Periampullary Cancer Registry; *StuDoQ*, Studien-, Dokumentations- und Qualitätszentrum.
[*] Patients with pancreatic adenocarcinoma, respectively 317, 320, 76, and 123 patients.
[†] Number of d until drain removal from resection to removal.

lowest in Germany (15.5%, 9.3%, 16.7%, 21.7%; $P < .001$). Surgery for chronic pancreatitis was performed most often in the United States and Germany (14.5%, 11.9%, 4.2%, and 4.3%; $P < .001$). The vascular resection rate was highest in Sweden with 23.6%, 23.4%, 30.8%, and 36.4%; $P < .001$. Differences were shown for spleen, colon, and gastric resection as well as drain placement (Table I).

Postoperative outcomes

Major morbidity rates differed among the countries with 22.3%, 34.9%, 38.3%, and 15.9% for United States, Germany, the Netherlands, and Sweden, respectively ($P < .001$). As described in Table II, pancreatectomy specific complications also differed among the countries. The reoperation rate was highest in Germany (8.9%, 20.3%, 13.3%, 10.5%; $P < .001$), while the readmission rate was the highest in the United States (20.7%, 5.9%, 13.3%, 2.7%, respectively; $P < .001$). In-hospital mortality was highest in Germany and the Netherlands (1.8%, 10.2%, 10.8%, 1.9%, respectively; $P < .001$; Fig 1, *A*). The same was found for failure-to-rescue rates, which were 8.1%, 29.3%, 28.3%, and 12.2%, respectively ($P < .001$; Fig 1, *B*).

Multivariable analysis

Patients from Germany and the Netherlands, but not from Sweden, had higher odds of major morbidity compared to patients from the United States (Germany: OR 2.07, 95% CI 1.57–2.74; $P < .001$; the Netherlands: OR 3.10, 95% CI 1.96–4.90; $P < .001$; Sweden: OR 0.85, 95% CI 0.56–1.28; $P = .426$; Table III). Other predictors of major morbidity were American Society of Anesthesiologists score $\geq$3 (OR 1.65, 95% CI 1.27–2.15; $P < .001$), vascular resection (OR 1.70, 95% CI 1.30–2.23; $P < .001$), and periampullary cancer (reference: pancreatic ductal adenocarcinoma; OR 2.91, 95% CI 1.58–5.36; $P = .001$). This pattern for countries was also identified for in-hospital mortality (United States: reference; Germany: OR 5.19, 95% CI 2.73–9.89; $P < .001$; the Netherlands: OR 6.41, 95% CI 2.82–14.61; $P < .001$; Sweden: OR 0.94, 95% CI 0.33–2.71; $P = .911$; Table III). In addition, age $\geq$75 (OR 2.67, 95% CI 1.67–4.28; $P < .001$) and vascular resection (OR 1.94, 95% CI 1.21–3.12; $P = .006$) were associated with in-hospital mortality. Pathological diagnosis (ie, pancreatic adenocarcinoma, IPMN, and chronic pancreatitis) was not a predictor for in-hospital mortality.

Sensitivity analysis

In 229 patients with IPMN, major morbidity was 21.0% and in-hospital mortality was 3.1% (mortality after TP for IPMN in the United States 1.0% [1/103], Germany 6.0% [3/50], the Netherlands 10.0% [2/20], and Sweden 1.8% [1/55]). In total, 246 patients underwent TP in high-volume centers in Germany (8 centers) and 81 patients in the Netherlands (9 centers, Supplementary Table 1). Median center volume for Germany in 2017 was 15 PDs (IQR 5–29) and in the 8 high-volume centers 47 PDs (IQR 43–52). In the Netherlands, median center volume was 40 PDs (IQR 24–60) and in the 9 high-volume centers 58 PDs (IQR 42–78). In Germany, major morbidity was 33.6% in low-volume centers compared to 36.6% in high-volume ($P = .537$) and in the Netherlands 51.3% vs 32.1% ($P = .095$), respectively. In-hospital mortality was not higher in low-volume centers in Germany (10.6% vs 9.8%; $P = .733$, respectively). In the Netherlands, in-hospital mortality was higher in low-volume centers (23.1% vs 4.9%; $P = .002$).

Supplementary Table S2 shows that the percentages of organ failure, pneumonia, and postpancreatic hemorrhage were relatively high in patients who died.

Discussion

This largest international analysis in 1,579 patients after one-stage TP found a major morbidity rate of 26.8% and an in-hospital mortality rate of 5.4%. The relative use of TP differed up to five-fold among the 4 countries. Differences were also noted for patient characteristics, surgical indications, and clinical outcomes among the 4 countries. Outcomes were better in the United States and Sweden as compared to Germany and the Netherlands. Although partly explained by surgical volume, many of these differences remain unexplained. In multivariable analyses, country and vascular resection were predictors of both major morbidity and in-hospital mortality. Evaluation of the mechanisms behind these differences may improve outcomes of patients undergoing TP.

Before attempting to interpret these results, it should be noted that these registries differ in design, and some variables had to be recoded to enable comparisons among countries. As concluded in the previous comparison between these 4 registries, implementation of key parameters with identical definitions in the separate registries is required.[8] The Dutch and Swedish registries are nationwide with very high coverage, whereas the NSQIP and German StuDoQ registries are multicenter with a two-third and one-fifth nationwide coverage, respectively. The NQSIP has a high presence of high-volume centers, which could partly explain the high rate of neoadjuvant therapy and improved postoperative outcomes in the United States.[17] The nationwide coverage of the StuDoQ registry should be improved and is currently expanding. Currently, harmonization of the registries is one of the main tasks of the Global Audits on Pancreatic Surgery Group. The number of TPs per center differed widely among the countries and was especially high in Sweden with good outcomes. This could be explained by the extensive centralization of pancreatic surgery in Sweden in 6 university hospitals (ie, 5 of which performed at least 60 PDs in 2018).[9,18] However, Sweden included more than double the number of TPs compared to the Netherlands, whereas their population is 10 million in 2018 as compared to 17 million in the Netherlands. This

Table II
Postoperative and pathological outcomes

	Total N = 1,579	NSQIP United States n = 663	StuDoQ Germany n = 538	DPCA The Netherlands n = 120	SNPPCR Sweden n = 258	P value
Postoperative outcomes						
Clavien-Dindo classification						< .001
No complications or Clavien Dindo <3	1,127 (71.4%)	515 (77.7%)	346 (64.3%)	64 (53.3%)	202 (78.3%)	
Clavien Dindo ≥3	423 (26.8%)	148 (22.3%)	188 (34.9%)	46 (38.3%)	41 (15.9%)	
Missing	29 (1.8%)		4 (0.7%)	10 (8.3%)	15 (5.8%)	
Surgical site infection	142 (9.0%)	45 (6.8%)	66 (12.3%)	7 (5.8%)	24 (9.3%)	.008
Missing	67 (4.2%)		16 (3.0%)	37 (30.8%)	14 (5.4%)	
Pneumonia	130 (8.2%)	45 (6.8%)	48 (8.9%)	6 (5.0%)	31 (12.0%)	**< .001**
Missing	116 (7.3%)		5 (0.9%)	38 (31.7%)	73 (28.3%)	
Postpancreatectomy hemorrhage, grade B/C	78 (8.5%)	NA	35 (6.5%)	6 (5.0%)	37 (14.3%)	**< .001**
Missing	22 (2.4%)		4 (0.7%)	4 (3.3%)	14 (5.4%)	
Delayed gastric emptying, grade B/C	205 (13.0%)	104 (15.7%)	61 (11.3%)	22 (18.3%)	18 (7.0%)	.001
Missing	36 (2.3%)	13 (2.0%)	4 (0.7%)	3 (2.5%)	16 (6.2%)	
Bile leak, grade B/C	55 (3.5%)	6 (0.9%)	34 (6.3%)	7 (5.8%)	8 (3.1%)	**< .001**
Missing	147 (9.3%)	132 (19.9%)		1 (0.8%)	14 (5.4%)	
Radiologic intervention performed	77 (9.8%)	59 (8.9%)	NA	18 (15.0%)	NA	.012
Missing	19 (2.4%)	6 (0.9%)		13 (10.8%)		
Organ failure	176 (11.1%)	60 (9.0%)	87 (16.2%)	19 (15.8%)	10 (3.9%)	**< .001**
Missing	15 (0.9%)		4 (0.7%)	11 (9.2%)		
ICU admission	186 (11.8%)	NA	87 (16.2%)	23 (19.2%)	21 (8.1%)	.003
Missing	161 (10.2%)		4 (0.7%)	11 (9.2%)	14 (5.4%)	
Reoperation	211 (13.4%)	59 (8.9%)	109 (20.3%)	16 (13.3%)	27 (10.5%)	**< .001**
Missing	54 (3.4%)		10 (1.9%)	11 (9.2%)	33 (12.8%)	
Duration of stay, median (IQR), d[*]	14.0 (9.0–20.0)	9.0 (7.0–14.0)	20.0 (15.0–27.0)	15.0 (11.0–21.0)	12.0 (8.8–17.0)	**< .001**
Missing	16 (1.0%)	9 (1.4%)		1 (0.8%)	6 (2.3%)	
Readmission	192 (12.2%)	137 (20.7%)	32 (5.9%)	16 (13.3%)	7 (10.4%)[†]	**< .001**
Missing	229 (14.5%)		9 (1.7%)	12 (10.0%)	17 (25.4%)	
In-hospital mortality	85 (5.4%)	12 (1.8%)	55 (10.2%)	13 (10.8%)	5 (1.9%)	**< .001**
Missing	11 (0.7%)		1 (0.2%)	1 (0.8%)	9 (3.5%)	
Time between resection and in-hospital mortality, median (IQR), d[‡]	14.0 (3.0–23.5)	16.5 (3.5–20.5)	13.0 (4.0–24.0)	10.0 (1.5–23.5)	26.0 (1.0–63.0)	.686
Failure to rescue	85/423 (20.1%)	12/148 (8.1%)	55/188 (29.3%)	13/46 (28.3%)	5/41 (12.2%)	**< .001**
Pathological outcomes						
Histopathological diagnosis						**< .001**
Pancreatic adenocarcinoma	836 (52.9%)	317 (47.8%)	320 (59.5%)	76 (63.3%)	123 (47.7%)	
Periampullary cancer	50 (3.2%)	7 (1.1%)	30 (5.6%)	1 (0.8%)	12 (4.7%)	
Neuroendocrine tumor	90 (5.7%)	58 (8.7%)	16 (3.0%)	5 (4.2%)	11 (4.3%)	
IPMN	229 (14.5%)	103 (15.5%)	50 (9.3%)	20 (16.7%)	56 (21.7%)	
Chronic pancreatitis	176 (11.1%)	96 (14.5%)	64 (11.9%)	5 (4.2%)	11 (4.3%)	
Other	168 (10.6%)	71 (10.7%)	52 (9.7%)	12 (10.0%)	33 (12.8%)	
Missing	30 (1.9%)	11 (1.7%)	6 (1.1%)	1 (0.8%)	12 (4.7%)	
T-stage[§]						.004
Tis/T0	11 (1.2%)	6 (1.9%)	4 (1.1%)	-	1 (0.7%)	
T1	76 (8.6%)	38 (11.7%)	29 (8.3%)	1 (1.3%)[‖]	8 (5.9%)	
T2	156 (17.6%)	57 (17.6%)	63 (18.0%)	17 (22.1%)	19 (14.1%)	
T3	560 (63.2%)	203 (62.7%)	221 (63.1%)	45 (58.4%)	91 (67.4%)	
T4	55 (6.2%)	8 (2.5%)	27 (7.7%)	6 (7.8%)	14 (10.4%)	
Tx	3 (0.3%)	1 (0.3%)	-	-	2 (1.5%)	
Missing	25 (2.8%)	11 (3.4%)	6 (1.7%)	8 (10.4%)		
N-stage[§]						**< .001**
N0	308 (34.8%)	143 (44.1%)	123 (35.1%)	21 (27.3%)	21 (15.6%)	
N+	553 (62.4%)	164 (50.6%)	222 (63.4%)	54 (70.1%)	113 (83.7%)	
Nx	3 (0.3%)	2 (0.6%)	-	-	1 (0.7%)	
Missing	22 (2.5%)	15 (4.6%)	5 (1.4%)	2 (2.6%)		
M-stage[§]						.001
M0/Mx	738 (83.3%)	225 (69.4%)	321 (91.7%)	72 (93.5%)	120 (88.9%)	
M1	38 (4.3%)	5 (1.5%)	13 (3.7%)	5 (6.5%)	15 (11.1%)	
Missing	110 (12.4%)	94 (29.0%)	16 (4.6%)			
Tumor stage[§]						**< .001**
0	9 (1.0%)	4 (1.2%)	4 (1.1%)	9 (11.7%)[¶]	1 (0.7%)	
I	110 (12.4%)	44 (13.6%)	49 (14.0%)	41 (53.2%)	8 (5.9%)	
II	509 (57.4%)	163 (50.3%)	210 (60.0%)	13 (16.9%)	95 (70.4%)	
III	90 (10.2%)	7 (2.2%)	56 (16.0%)	5 (6.5%)	14 (10.4%)	
IV	38 (4.3%)	5 (1.5%)	13 (3.7%)	9 (11.7%)	15 (11.1%)	
Missing	130 (14.7%)	101 (31.2%)	18 (5.1%)		2 (1.5%)	
Resection margin[§]		NA				**< .001**
R0	329 (58.5%)		246 (70.3%)	35 (45.5%)	48 (35.6%)	
R1	208 (37.0%)		92 (26.3%)	36 (46.8%)	80 (59.3%)	
Missing	25 (4.4%)		12 (3.4%)	6 (7.8%)	7 (5.2%)	

(*continued on next page*)

Table II (*continued*)

	Total N = 1,579	NSQIP United States n = 663	StuDoQ Germany n = 538	DPCA The Netherlands n = 120	SNPPCR Sweden n = 258	P value
Tumor size for benign tumors[#]			NA			.078
<2 cm	37 (10.7%)	26 (14.8%)		3 (10.7%)	8 (11.8%)	
2–5 cm	61 (17.6%)	36 (20.5%)		6 (21.4%)	19 (27.9%)	
>5 cm	64 (18.4%)	27 (15.3%)		11 (39.3%)	26 (38.2%)	
Missing	185 (53.3%)	89 (49.4%)		8 (28.6%)	15 (22.1%)	

Values are numbers with percentages within parentheses unless indicated otherwise.
Bold numbers indicate statistical significance after Bonferroni correction ($P < .001$).
DPCA, Dutch Pancreatic Cancer Audit; *ICU,* intensive care unit; *IPMN,* intraductal papillary mucinous neoplasm; *IQR,* interquartile range; *MCN,* mucinous cystic neoplasm; *NA,* not applicable; *NSQIP,* National Surgical Quality Improvement Program; *SNPPCR,* Swedish National Pancreatic and Periampullary Cancer Registry; *StuDoQ,* Studien-, Dokumentations- und Qualitätszentrum; *Surgical site infection:* superficial, deep incisional, and wound disruption.
[*] In patients without in-hospital mortality.
[†] Only in patients operated in 2018.
[‡] In patients with in-hospital mortality.
[§] In patients with pancreatic or periampullary adenocarcinoma, respectively 324, 350, 77, and 135 patients.
[‖] Patients operated in 2018 ($n = 14$) were staged according to the TNM8 classification: 7 patients had stage T2, 5 patients stage T3, 1 patient stage T4, and in 1 patient the stage was missing.
[¶] Patients operated in 2018 ($n = 14$) were staged according to the TNM8 classification: 1 patient had stage I, 5 patients stage II, and 8 patients stage III.
[#] Benign and neuroendocrine tumors (excluding chronic pancreatitis), respectively 176, 75, 28, and 75 patients.

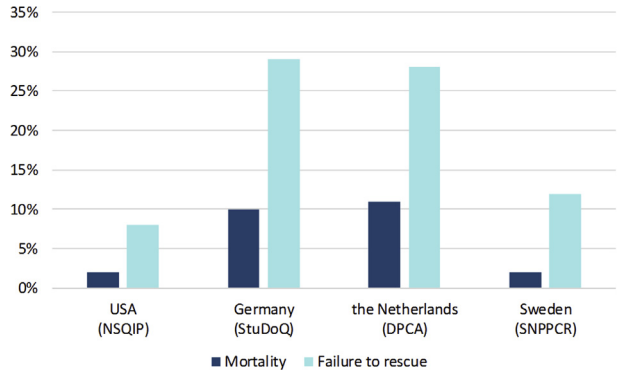

Fig. 1. Mortality and failure to rescue among the 4 countries.

difference was also reflected in the TP to PD ratio, which was lower for the United States and the Netherlands compared to Germany and Sweden. This suggests a higher threshold for TP in the United States and the Netherlands, but reasons for these differences are unclear.

In line with our findings, a recent pan-European snapshot study of 277 patients after TP demonstrated rates of major morbidity of 25% and in-hospital mortality of 5%.[7] Also, a systematic review of cohorts with at least 100 TPs found outcomes comparable to the current study: major complications 27% vs 23% to 32% (current study versus systematic review), post-pancreatectomy hemorrhage 9% vs 4% to 14%, bile leak 4% vs 2% to 6%, delayed gastric emptying 13% vs 7% to 18%, and in-hospital mortality 5% vs 5% to 9%.[7] However, in a series describing 12-year results of 2 very high-volume centers, 30-day and 90-day mortality rates were lower with 2% and 3%, respectively.[6] These results are in line with the results from the United States and Sweden, which both had an in-hospital mortality of 2%, yet are in contrast with the high mortality rates in both Germany (10%) and the Netherlands (11%). The difference in mortality rates is interesting, and, next to age ≥75 and vascular resection, country was identified as a predictor. Understanding the causes of death in patients after TP would be informative. The main reason for mortality after PD is a postoperative pancreatic fistula with or without subsequent intra-abdominal bleeding, but pancreatic fistula does not occur after TP. Unfortunately, the registries lack cause of death as a variable, and therefore, differences are very difficult to explain. Analyzing the postoperative outcomes in patients who died suggest organ failure, pneumonia (ie, pulmonary sepsis with organ failure), and postpancreatic hemorrhage as causes of death. The relation between mortality after partial pancreatectomy and center volume is also well-established and was recently demonstrated for TP.[7,19–21] A future study could aim to develop a case-mix adjustment model to more properly compare morbidity and mortality in patients after TP, as was recently done for patients who underwent liver resection for colorectal liver metastases.[22] Case-mix factors for patients who underwent pancreatic surgery were already identified from a systematic literature search, and the most important factors were selected after multidisciplinary and international discussions.[10]

The presence of high-volume centers in the United States and advanced centralization in Sweden could explain the lower in-hospital mortality.[9,17,18] The sensitivity analysis showed that in-hospital mortality was lower in the Netherlands in 9 centers performing more than 40 PDs annually, confirming the effect of volume. Interestingly, sensitivity analyses in the German cohort did not show different outcomes for high volume (≥40 PDs annually), although the volume per center was lower than in the Netherlands. Higher-volume centers may have superior failure-to-rescue rates due to more developed perioperative care, such as improved preoperative patient selection, protocolized care, intensive care, interventional radiology, and nurse-to-patient ratio.[15] The lower failure-to-rescue rates as seen the United States and Sweden probably contributed to the lower in-hospital mortality rates.[23–25]

Major morbidity also was higher in Germany and the Netherlands and much lower in Sweden. The low major morbidity rate after TP in Sweden is similar to the previously published results from the Swedish registry.[9] This low rate might be partially based on the indication for TP (ie, planned versus unplanned), a lower threshold for TP (ie, thus also including less complicated patients), or on a registration bias.[26] Surgical morbidity was higher in patients with malignant compared to benign disease (eg, IPMN or chronic pancreatitis), whereas 30-day and in-hospital mortality was not related to pathological diagnoses.[4,7,27] In this study, patients with IPMN had an acceptable major morbidity of 21.0% and in-hospital mortality of 3.1%. In multivariable analysis, patients with periampullary cancer had significantly higher odds for major morbidity when compared to pancreatic ductal adenocarcinoma, but histopathological diagnosis was not a predictor for in-hospital mortality. Considering these results, the indication for TP should be well considered in all patients, but a shared decision-making program is feasible for patients with a benign disease. For example, the prophylactic total pancreatectomy

Table III
Multivariable regression analyses to assess predictors for major morbidity and mortality

	Major morbidity				Mortality			
	Univariable analysis OR (95% CI)	P value	Multivariable analysis* OR (95% CI)	P value	Univariable analysis OR (95% CI)	P value	Multivariable analysis† OR (95% CI)	P value
Country								
United States	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Germany	**1.89 (1.46–2.44)**	**< .001**	**2.07 (1.57–2.74)**	**< .001**	**6.19 (3.28–11.69)**	**< .001**	**5.19 (2.73–9.89)**	**< .001**
The Netherlands	**2.50 (1.64–3.81)**	**< .001**	**3.10 (1.96–4.90)**	**< .001**	**6.65 (2.96–14.97)**	**< .001**	**6.41 (2.82–14.61)**	**< .001**
Sweden	0.71 (0.48–1.04)	.075	0.85 (0.56–1.28)	.426	0.84 (0.39–3.19)	.844	0.94 (0.33–2.71)	.911
Age ≥75	**1.34 (1.02–1.77)**	**.036**			**3.20 (2.04–5.04)**	**< .001**	**2.67 (1.67–4.28)**	**< .001**
Male patients	**1.27 (1.01–1.59)**	**.041**			1.26 (0.81–1.96)	.317		
BMI	1.00 (0.97–1.02)	.681			1.01 (0.97–1.04)	.681		
ASA score ≥3	**1.39 (1.10–1.75)**	**.006**	**1.65 (1.27–2.15)**	**< .001**	1.39 (1.10–1.75)	.774		
Comorbidities	0.95 (0.76–1.20)	.677			1.26 (0.81–1.96)	.299		
Preoperative biliary drainage	0.88 (0.68–1.15)	.359			0.89 (0.53–1.49)	.659		
Neoadjuvant chemotherapy	0.90 (0.63–1.27)	.536			0.75 (0.36–1.59)	.459		
Minimally invasive surgery	0.92 (0.58–1.47)	.723			0.54 (0.17–1.74)	.300		
Vascular resection	**1.51 (1.18–1.93)**	**.001**	**1.70 (1.30–2.23)**	**< .001**	**1.74 (1.11–2.74)**	**.017**	**1.94 (1.21–3.12)**	**.006**
Histopathological diagnosis								
Pancreatic adenocarcinoma	1.00 (reference)		1.00 (reference)		1.00 (reference)			
Periampullary cancer	**2.73 (1.52–4.90)**	**.001**	**2.91 (1.58–5.36)**	**.001**	**2.39 (1.03–5.58)**	**.043**		
Neuroendocrine tumor	0.93 (0.57–1.52)	.760	1.27 (0.76–2.11)	.364	0.12 (0.33–1.36)	.124		
IPMN	**0.67 (0.47–0.96)**	**.028**	0.93 (0.63–1.35)	.685	0.46 (0.20–1.01)	.054		
Chronic pancreatitis	0.87 (0.60–1.26)	.456	1.10 (0.75–1.64)	.620	0.42 (0.17–1.07)	.068		
Other	0.87 (0.60–1.27)	.470	1.08 (0.73–1.60)	.709	0.81 (0.39–1.68)	.575		

Bold numbers in univariable analysis indicates variables that were entered in multivariable analysis ($P < .10$).
Bold numbers in multivariable analysis indicates statistical significance ($P < .05$).
ASA, American Society of Anesthesiologists; *BMI,* body mass index; *CI,* confidence interval; *IPMN,* intraductal papillary mucinous neoplasm; *OR,* odds ratio.
* Multivariable analysis after backward step selection in 1,507 patients.
† Multivariable analysis after backward step selection in 1,541 patients.

program for patients with a very high risk of developing pancreatic cancer (ie, main-duct IPMN).[28] In patients with benign disease, an important role is reserved for islet autotransplantation.

Another significant difference among the countries was the rate of reoperation. Similar to our analyses of patients who underwent PD, Germany had the highest reoperation rate.[8] The high reoperation rate was surprising given the fact that no pancreatic fistula would have been present after surgery, and it is common practice to use a step-up approach before performing a reoperation. Other complications such as postpancreatectomy hemorrhage, bile leak, and organ space surgical site infections are potential indications for reoperation. This possibility is supported by a report from a very high-volume German center in which the relaparotomy rate in 434 consecutive TPs was 17.1%.[4]

The readmission rate was the highest in the United States. In the literature, increasing age, comorbidity, preoperative therapy, extensive surgery, and complications were described as predictors for readmission in pancreatic surgery.[29–32] These predictors do not completely explain our results. For example, median age in the United States was lower than in the other countries, and the major morbidity rate in the United States was lower than in Germany. Likely, the shorter duration of stay observed in the US cohort contributed to readmission rates. In addition, readmission and duration of hospital stay might also be largely influenced by cultural differences, for example by temporary housing with family or referral to a nursing home.

The ultimate question is how to improve outcomes after TP. As described above, multiple factors might be related to differences in outcomes, but we have yet to identify specific factors. Improving outcomes will therefore require a multidimensional, multidisciplinary program improving all hospital processes around pancreatic surgery. These processes could include preoperative patient selection (based on risk factors as described in this study), protocolized care, up-to-date intensive care, high-volume surgical care, broad experience in interventional radiology, and a high nurse-to-patient ratio. To successfully optimize these processes, centralization of pancreatic surgery will be required to reduce morbidity, mortality, and costs.

The present study has several limitations that must be considered when interpreting the results. First, baseline characteristics differed among countries. These differences may not explain the findings since the differences do not seem to benefit countries with good outcomes (eg, high body mass index, American Society of Anesthesiologists in the United States). Second, the exact use of TP could not be calculated for each of the 4 countries because only the registries of the Netherlands and Sweden include all procedures nationwide. However, the ratio TP to PD is expected to give a rather good insight in the relative use of TP per country. Third, the indication for TP was not included in the registries, which could add substantially to explaining the intercountry differences. Fourth, information about center volume of pancreatic resections was not available for the United States and Sweden. Therefore, outcomes could not be related to center volume, which could have been a partial and potentially large explanation for differences among countries.

In conclusion, this transatlantic cohort study showed that one-stage TP is associated with substantial major morbidity and in-hospital mortality. Use of TP widely varied among countries. Although this analysis is one of the largest cohorts over a relatively short time period, overall results of this contemporary experience were not improved compared to earlier reports. Outcomes were better in the United States and Sweden, but the comparison between countries remains difficult due to differences in use of TP and designs of the registries. One of the main challenges of the Global Audits on Pancreatic Surgery Group will be to harmonize the key parameters registered. The observed differences among countries require further research to ultimately improve patient outcomes.

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Conflicts of interest/Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [https://doi.org/10.1016/j.surg.2021.02.001].

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