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ORIGINAL ARTICLE

Pancreatic resection in the pediatric, adolescent and young adult population: nationwide analysis on complications

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Abstract

Background: The aim of this study was to determine pancreatic surgery specific short- and long-term complications of pediatric, adolescent and young adult (PAYA) patients who underwent pancreatic resection, as compared to a comparator cohort of adults.

Methods: A nationwide retrospective cohort study was performed in PAYA patients who underwent pancreatic resection between 2007 and 2016. PAYA was defined as all patients <40 years at time of surgery. Pancreatic surgery-specific complications were assessed according to international definitions and textbook outcome was determined.

Results: A total of 230 patients were included in the PAYA cohort (112 distal pancreatectomies, 99 pancreatoduodenectomies), and 2526 patients in the comparator cohort. For pancreatoduodenectomy, severe morbidity (29.3% vs. 28.6%; P = 0.881), in-hospital mortality (1% vs. 4%; P = 0.179) and textbook outcome (62% vs. 58%; P = 0.572) were comparable between the PAYA and the comparator cohort. These outcomes were also similar for distal pancreatectomy. After pancreatoduodenectomy, new-onset diabetes mellitus (8% vs. 16%) and exocrine pancreatic insufficiency (27% vs. 73%) were lower in the PAYA cohort when compared to adult literature.

Conclusion: Pancreatic surgery-specific complications were comparable with patients ≥40 years. Development of endocrine and exocrine insufficiency in PAYA patients who underwent pancreatoduodenectomy, however, was substantially lower compared to adult literature.

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Introduction

Pancreatic resection in the pediatric, adolescent and young adult (PAYA) population is uncommon. Consequently, data on well-defined postoperative outcomes for this group, including postoperative pancreatic fistula, delayed gastric emptying and bile leakage, are scarce.[1] Pancreatic resection may also result in long-term endocrine and exocrine pancreatic insufficiency and data on these outcomes in the PAYA population are also limited.[2,3]

Currently, only several small retrospective case series were published on surgical outcomes and complications of pancreatic resection such as pancreatoduodenectomy in the PAYA population.[4,5,14,6–13] Furthermore, complications and surgical outcomes in these studies were not defined and scored according to the International Study Group of Pancreatic Surgery (ISGPS) and International Study Group of Liver Surgery (ISGLS).[15–18] Comparing results of previous research in PAYA patients with current outcomes is therefore challenging.

The aim of the PAPAYA (pancreatic resection in the PAYA population) study was to determine indications for surgery, pancreatic surgery-specific complications, as well as the development of pancreatic endocrine and exocrine insufficiency following pancreatic resection in PAYA patients in a nationwide cohort, compared to a contemporary comparator cohort of patients ≥40 years.

Methods

Study design

The nationwide, retrospective, multicenter cohort PAPAYA study was performed in PAYA patients who underwent pancreatic resection between January 1st 2007 and December 31st 2016 in one of the Dutch Pancreatic Cancer Group (DPCG) with at least five PAYA patients (n = 13 centers). The PAYA cohort was compared to a prospective cohort of control patients ≥40 years who underwent pancreatic resection between January 1st 2014 and December 31st 2016, derived from the Dutch Pancreatic Cancer Audit. The Dutch Pancreatic Cancer Audit includes all DPCG hospitals, each performing a minimum of 20 pancreatoduodenectomies annually.[19] Pancreatic resection included all types of resections (pancreatoduodenectomy, distal pancreatectomy, total pancreatectomy and pancreatic enucleation). Patients were excluded if essential data on the surgical procedure or outcomes were lacking. STROBE guidelines were adhered to von Elm et al.[20] The study protocol was approved by our center's institutional review board (METc 201700408), which granted a waiver of patient informed consent requirements.

Definitions short-term outcomes

PAYA was defined as all patients aged under 40 years at time of surgery. This is based on previous studies including pediatric, adolescent and young adult patients as a group.[21] All complications were defined and scored using the ISGPS definitions.[15–17] Leakage of the hepaticojejunostomy was scored using the ISGLS definition.[18] Complications were graded according to Clavien-Dindo grading system for surgical complications.[22] Complications with a Clavien-Dindo grade of III or higher were defined as major complications. Using the Clavien-Dindo classification the comprehensive classification index (CCI) was calculated for each patient.[23] Patients who were readmitted within 30 days after hospital discharge were recorded. Death during hospitalization was designated as mortality. Textbook outcome was defined as the absence of postoperative pancreatic fistula (POPF), bile leak, post-pancreatectomy hemorrhage (all grade B/C according to ISGPS or ISGLS), severe complications (Clavien-Dindo grade III or higher), readmission within 30 days after discharge, and in-hospital mortality.[24]

Definitions long-term outcomes

Pancreatic exocrine insufficiency was defined as still being on pancreatic enzyme replacement therapy after one year post-operatively.[25] New-onset diabetes after surgery was defined as the presence of any disruption of glucose hemostasis requiring new anti-hyperglycemic medication (oral hypoglycemic or insulin) upon medication review after discharge.[26]

Data collection

All participating centers were visited and the required data was collected from (digital) patient records and patient charts with daily notes. Records were screened for PAYA patients who had undergone pancreatic resection. Baseline parameters, intra-operative parameters, pathology parameters, postoperative complication, hospitalization parameters and follow-up data were recorded of PAYA patients who had undergone pancreatic resection.

Statistical analysis

Statistical analyses were performed using SPSS statistics for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). Dichotomous data were presented as proportions. Continuous data were presented as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were compared using the Fisher exact test or the Chi-square test. Continuous variables were compared using the Mann–Whitney U test or the Student's t-test. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The PAYA cohort comprised of 230 patients. 112 PAYA patients (49%) underwent distal pancreatectomy and 99 patients (43%) underwent pancreatoduodenectomy. Other surgical procedures included seven (3%) total pancreatectomies and 11 (5%) enucleations. Within the PAYA cohort, 18 patients (8%) were ≤18 years. In this subcohort, 12 patients underwent distal

pancreatectomy, five pancreatoduodenectomy and one patient an enucleation of a neuro-endocrine tumor (Fig. 1).

The comparator cohort initially comprised of 2586 patients, of which 60 patients were excluded from analysis because essential data on the surgical procedure or outcomes were lacking. Out of 2526 patients, 1969 (78%) underwent pancreatoduodenectomy and 469 patients (19%) underwent distal pancreatectomy. Other surgical procedures included 72 (3%) total pancreatectomies, and 16 enucleations (1%) (Fig. 1).

The PAYA and comparator cohorts had several differences in baseline characteristics. The PAYA cohort had a female predominance (62% vs 45%; P < 0.001) and American Society of Anesthesiologists (ASA) scores were substantially lower (P < 0.001). More than one fifth of all patients in the comparator cohort had preoperative diabetes mellitus compared to only four percent in the PAYA cohort (P < 0.001). Most patients in the PAYA cohort underwent distal pancreatectomy (49%) while most patients in the comparator cohort underwent pancreatoduodenectomy (77%; P < 0.001) (Table 1).

Pathology

The pathological characteristics are summarized in Fig. 2. More patients in the comparator cohort (76%) underwent pancreatic resection because of malignant disease, as compared with PAYA patients (51%) (P < 0.001). In contrast to the comparator cohort, adenocarcinoma (pancreatic ductal adenocarcinoma, duodenal carcinoma, distal cholangiocarcinoma, and ampullary adenocarcinoma) were less prevalent in the PAYA population (15% vs. 66%; P < 0.001). Most PAYA patients underwent pancreatic resection because of neuro-endocrine tumors (26%), as compared to 8% in the comparator cohort. Solid pseudopapillary neoplasms (SPN) were common in the PAYA population (12.5%), especially in the subgroup <18 years (44%) but rare in the comparator cohort (0.3%). In the PAYA cohort, 44 patients were classified as "other", which included gastrointestinal stroma cell tumor (n = 5), pseudocyst (n = 9), sarcoma (n = 4), neuroendocrine carcinoma (n = 1), pancreatoblastoma (n = 1), pancreatic acinar cell carcinoma (n = 1), colorectal adenocarcinoma (n = 3), nephroblastoma (n = 1), perihilar cholangiocarcinoma (n = 1), gastric signit ring cell carcinoma (n = 2), chronic inflammation or stenosis distal bile duct (n = 8), teratoma (n = 1), lymphangioma (n = 1), neurofibroma (n = 1), intrapancreatic accessory spleen (n = 1), metastasis of cervical cancer (n = 1), duodenal hamartomatous polyps (n = 2), and unclassifiable periampullary adenocarcinoma (n = 1).

Outcomes after pancreatoduodenectomy

The median age of PAYA patients who underwent pancreatoduodenectomy was 34 (IQR 28–37) years. Compared to the comparator cohort, the incidence of preoperative diabetes mellitus (6% vs 22%, P < 0.001) and ASA scores (P < 0.001) were lower in the PAYA cohort. Pancreatic surgery-specific complications after pancreatoduodenectomy of the PAYA cohort were similar to the comparator cohort. Only delayed gastric emptying (DGE) occurred more often in the PAYA cohort (P = 0.002) (Fig. 3). There was no difference in in-hospital mortality (1% vs. 3.9%, P = 0.179). Textbook outcome in the PAYA cohort (62%) was comparable to the comparator cohort (58%) (P = 0.572). In eight PAYA patients (8%) new onset diabetes mellitus occurred after pancreatoduodenectomy and 27 (27%) patients developed exocrine pancreatic insufficiency. These data were not available for the comparator cohort (Table 2).

Outcomes after distal pancreatectomy

The median age of PAYA patients who underwent distal pancreatectomy was 31 (IQR 22–36). In this cohort, there was a

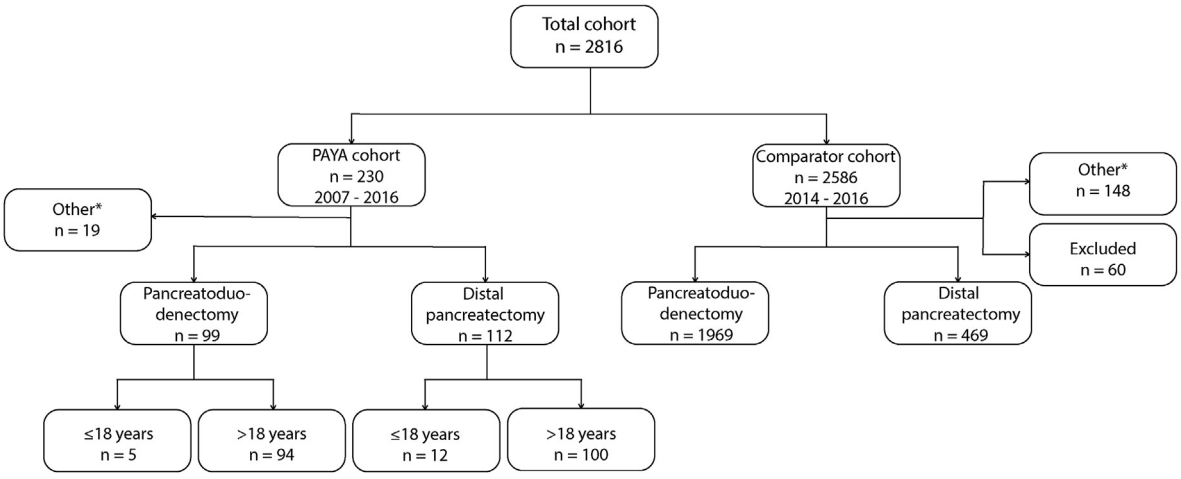

Figure 1 Flowchart of the surgical procedures in the PAYA and comparator cohorts. Within the PAYA cohort a subdivision was made for pediatric patients and for adolescent and young adult patients. *Other patients in the PAYA cohort include 11 enucleations and 7 total pancreatectomies. Other patients in the comparator cohort include 16 enucleations and 72 total pancreatectomies

Table 1 Clinical characteristics of the PAYA and comparator cohorts

Characteristic	Total cohort			PAYA cohort (<40 years)		
	PAYA (*n* = 230)	Comparator (*n* = 2526)	*P*	≤18 years (*n* = 18)	>18 years (*n* = 212)	*P*
Age at surgery (years), *median (IQR)*	32 (25–37)	68 (59–74)	**<0.001**	13 (9–14)	33 (27–37)	**<0.001**
Sex: females, *n (%)*	143 (62.2)	1168 (46.2)	**<0.001**	13 (72.2)	130 (61.3)	0.453
ASA fitness grade, *n (%)*			**<0.001**			0.740
Class I	100 (43.5)	393 (15.6)		8 (44.4)	92 (43.4)	
Class II	109 (47.4)	1583 (62.7)		5 (27.8)	104 (49.1)	
Class III	12 (5.2)	549 (21.7)		1 (5.6)	11 (5.2)	
Class IV	01 (0.4)	10 (0.4)		0 (0.0)	1 (0.4)	
missing	08 (3.5)	51 (2.0)		4 (22.2)	4 (1.9)	
BMI (kg/m^2), *median (IQR)*	24 (21–27)	25 (23–28)	**0.005**	20 (17–22)	24 (22–28)	**<0.001**
Preoperative diabetes mellitus (type 1 and 2), *n (%)*	9 (3.9)	540 (21.4)	**<0.001**	0 (0.0)	9 (4.2)	1.000
missing		586 (23.2)				
Use of somatostatin analogue, *n (%)*	134 (58.4)	1520 (60.2)	0.522	7 (38.9)	127 (59.9)	0.070
missing	3 (1.3)	108 (4.3)			3 (1.4)	
Neoadjuvant therapy, *n (%)*	4 (1.7)	90 (3.6)	**0.001**	0 (0.0)	4 (1.9)	1.000
missing	4 (1.7)			1 (5.6)	3 (1.4)	
Malignant disease, *n (%)*	117 (50.9)	1957 (75.7)	**<0.001**	7 (38.9)	110 (51.9)	0.290
Type of resection, *n (%)*			**<0.001**			0.449
Pancreatoduodenectomy	99 (43.0)	1969 (77.9)		5 (27.8)	94 (44.3)	
Distal pancreatectomy	112 (48.7)	469 (18.6)		12 (66.7)	100 (47.2)	
Total pancreatectomy	7 (3.0)	72 (2.9)		0 (0.0)	7 (3.3)	
Enucleation	11 (4.8)	16 (0.6)		1 (5.6)	10 (4.7)	
Other	1 (0.4)	0 (0.0)		0 (0.0)	1 (0.5)	

Data are given in numbers with percentages (%) or medians with interquartile ranges (IQR). For comparison between two groups Mann–Whitney *U* test were used for continuous variables and for binary variables Chi squared test or Fisher's exact test were used as appropriate. Abbreviations: ASA, American society of anesthesiologists; BMI, body mass index. Bold value indicates statistical significance.

predominance of females (77%). Compared to the comparator cohort, the incidence of preoperative diabetes mellitus (3% vs. 17%, P < 0.001) and ASA scores (P < 0.001) were lower in the PAYA cohort. Pancreatic surgery-specific complications after distal pancreatectomy between the PAYA cohort and comparator cohort were similar (Fig. 3). There was also no statistically significant difference in in-hospital mortality (0% vs. 1.7%, (P = 0.179)). Textbook outcome in the PAYA cohort (75%) was comparable to the comparator cohort (67%) (P = 0.102). In 17 PAYA patients (15%), new onset diabetes mellitus occurred after surgery and 18 (16%) patients developed exocrine pancreatic insufficiency (Table 3, Fig. 3).

Outcomes ≤18 years vs. 18–40 years

In the PAYA cohort, patients older than 18 years (*n* = 94) had similar clinical characteristics as patients of 18 years and younger (*n* = 5) who underwent pancreatoduodenectomy. Only the median BMI differed between both groups (19 vs 24 kg/m^2; P = 0.010). Postoperative pancreatic surgery-specific complications after pancreatoduodenectomy were comparable with the exception of bile leakage. Bile leakage occurred in patients (40%) of 18 years or younger compared to three (3%) patients older than 18 years (P = 0.019) (Table 2, Fig. 3).

In patients who underwent distal pancreatectomy, patients older than 18 years (*n* = 100) had higher ASA scores (P = 0.011), as compared with patients of 18 years and younger (*n* = 12). The median BMI differed between both groups (20 vs 24 kg/m^2; P < 0.001). Pancreatic surgery-specific complications after distal pancreatectomy were comparable (Table 3, Fig. 3).

Discussion

In this nationwide observational cohort study we demonstrated that pancreatic resection in PAYA patients is associated with comparable postoperative morbidity and mortality as in patients

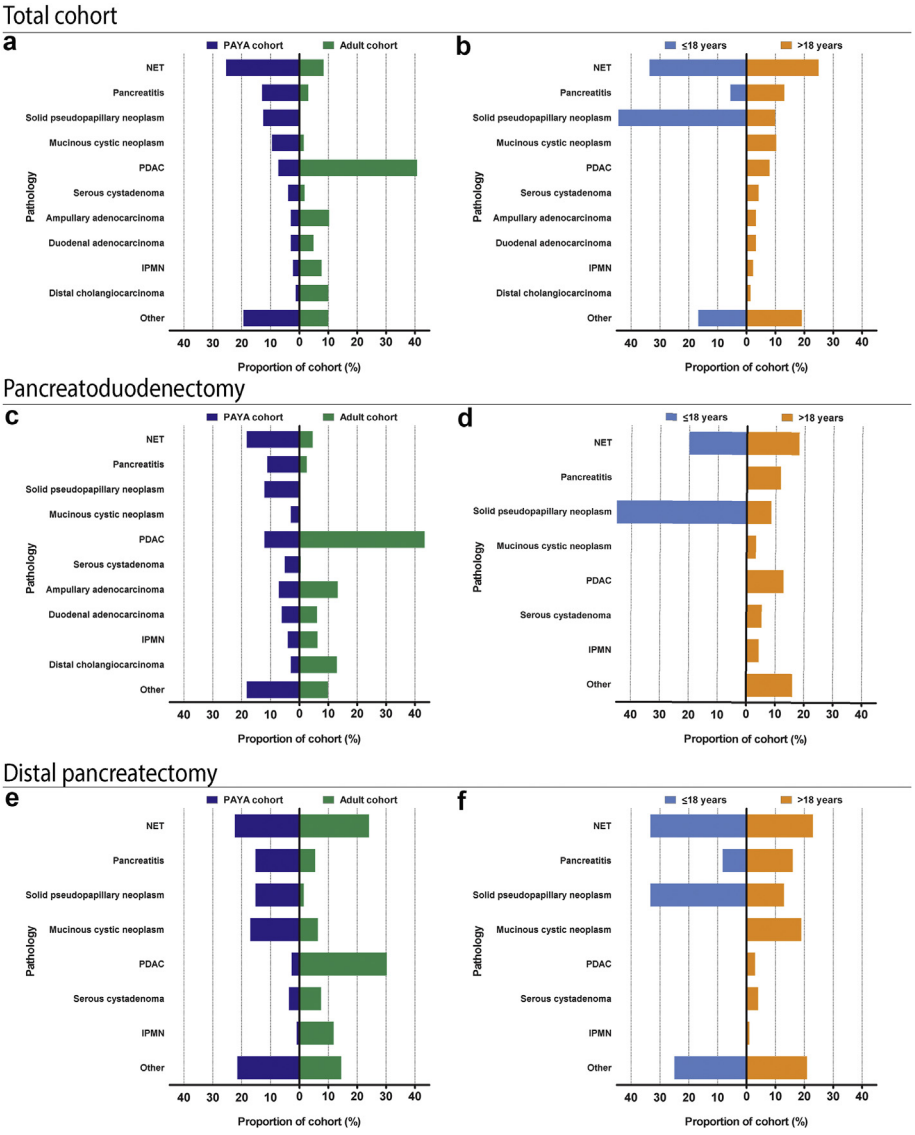

Figure 2 Histopathology after pancreatic resection a) the PAYA cohort compared to the comparator cohort. b) all PAYA patients ≤18 years compared to all PAYA patients >18 years. c) All PAYA patients and all patients ≥40 years who underwent pancreatoduodenectomy. d) all PAYA pat ≤18 years compared to all PAYA patients >18 years who underwent pancreatoduodenectomy. e) All PAYA patients and all patients ≥40 years who underwent distal pancreatectomy. f) all PAYA patients ≤18 years compared to all PAYA patients >18 years who underwent distal pancreatectomy. Abbreviations: NET, neuro endocrine tumor; PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal pancreatic mucinous neoplasm

≥40 years. Development of endocrine and exocrine insufficiency in PAYA patients, however, was substantially lower as compared with the adult literature.

Most previously published reports that described surgical outcomes and complications of pancreatic resection in PAYA patients were small, retrospective case series.[4,5,14,6–13] Because of the lack of published data on surgical outcomes in PAYA patients, it is challenging to properly discuss the risks and benefits of a pancreatic resection with patients and their caregivers. This is the first nationwide multicenter series of PAYA patients with pancreatic surgery-specific complications defined and scored using the Clavien-Dindo grading system,[22] ISGPS and ISGLS definitions, and Textbook Outcome.[15–17]

One of the aims of this study was to describe the indications of pancreatic resection in PAYA patients. Pancreatic ductal adenocarcinoma and distal cholangiocarcinoma were uncommon in the adolescent and young adult population and absent in pediatric patients. However, in the comparator cohort this was the most common indication for both pancreatoduodenectomy and distal pancreatectomy. A previous study which sought to define

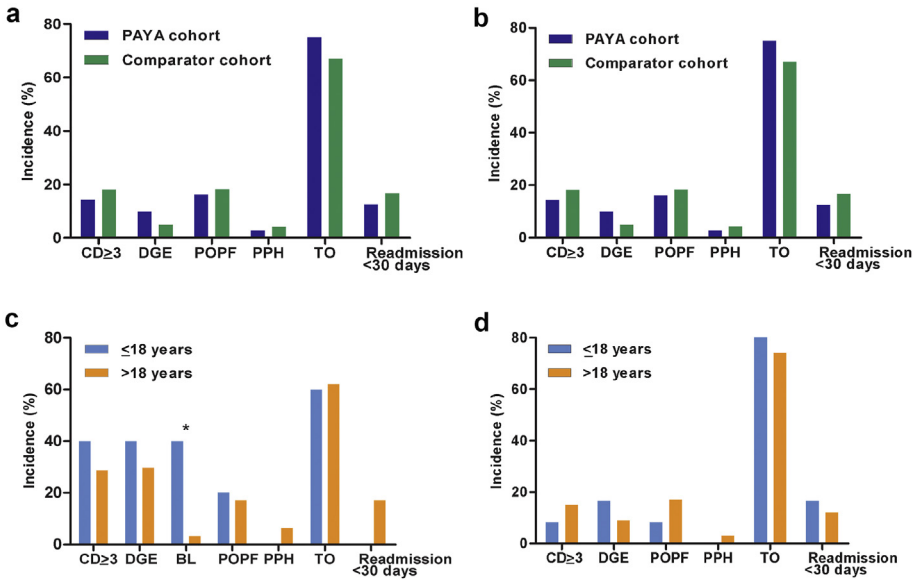

Figure 3 Postoperative complications, readmission rates and textbook outcome a) All PAYA patients and all patients ≥40 years who underwent pancreatoduodenectomy. b) All PAYA patients and all patients ≥40 years whounderwent distal pancreatectomy. c) All PAYA patients ≤18 years compared to all PAYA patients >18 years who underwent pancreatoduodenectomy. d) All PAYA patients ≤18 years compared to all PAYA patients >18 years who underwent distal pancreatectomy. *significant. Abbreviations: CD, Clavien Dindo; DGE, delayed gastric emptying; BL, bile leakage; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy hemorrhage. TO; textbook outcome

incidence trends for pediatric patients with pancreatic cancer based on the Surveillance, Epidemiology, and End Results registry identified only seven patients with ductal adenocarcinoma and four patients with acinar cell carcinoma between 1973 and 2004, which reflects the rarity of pancreatic neoplasms in this population.[28] SPN, pancreatitis and pancreatic neuro-endocrine tumors were relatively common in the PAYA population, especially in the subgroup <18 years. These results are comparable to previous findings in the literature.[14,27–29]

Our findings support previously published data on the safety of pancreatic resection in PAYA patients. Several small case series reported 0% 30-day mortality in pediatric patients who underwent pancreatoduodenectomy, which is in accordance with our results.[4,5,7–10,14] In the PAYA cohort, in-hospital mortality after pancreatoduodenectomy and distal pancreatectomy was not significantly different compared to the comparator cohort. During childhood, the volume of the pancreas increases and declines after the age of 40. This decline involves the pancreatic parenchyma and is associated with an increase in fibrosis and atrophy. Therefore, it is assumed that younger patients have a less fibrotic pancreas compared to adults although we did not see increased rates of clinically relevant POPF in the PAYA population. However, we did observe more delayed gastric emptying in PAYA patients who underwent pancreatoduodenectomy compared patients over 40 years of age. It is unclear what caused this difference. Other pancreatic surgery specific complications, complications requiring reintervention and length of hospital stay were comparable to the comparator cohort for both pancreatoduodenectomy and distal pancreatectomy.

Recently, a novel consensus-based definition of textbook outcome in pancreatic surgery was proposed. Textbook outcome is a composite outcome which attempts to cover the entire surgical process in a single indicator.[24] In the current study, textbook outcome was not significantly different between the comparator cohort and PAYA patients and between pediatric and adolescent and young adult patients. This finding further supports that pancreatic resection is safe in PAYA patients and outcomes are comparable to patients ≥40 years.

One of the long-term concerns after pancreatic resection is the occurrence of pancreatic endocrine or exocrine insufficiency. Steatorrhea, diabetes mellitus, and altered bowel function negatively influence quality of life.[28] This is especially a concern in the PAYA population since lifelong management and treatment of pancreatic endocrine and exocrine insufficiency is currently necessary. In our PAYA cohort, 8% of patients developed new onset diabetes mellitus after pancreatoduodenectomy and 27% of patients developed pancreatic insufficiency and used pancreatic enzyme replacement therapy the year after surgery. A systematic review and meta-analysis on new-onset diabetes after pancreatoduodenectomy found that the mean weighted overall proportion of new-onset diabetes mellitus after pancreatoduodenectomy was 16% (95% confidence interval, 12%–20%).[30] Reported rates on exocrine pancreatic insufficiency after pancreatoduodenectomy are also higher in the adult population.

Table 2 Clinical characteristics of patients who underwent pancreatoduodenectomy

Characteristic	Total cohort			PAYA cohort (<40 years)		
	PAYA (*n* = 99)	Comparator (*n* = 1969)	*P*	≤18 years (*n* = 5)	>18 years (*n* = 94)	*P*
Age at surgery (years), *median (IQR)*	34 (28–37)	68 (60–74)	**<0.001**	11 (9–14)	35 (29–37)	**<0.001**
Sex: females, *n (%)*	46 (46.5)	849 (43.1)	0.534	4 (80.0)	42 (44.7)	0.180
ASA fitness grade, *n (%)*			**<0.001**			0.669
Class I	40 (42.4)	288 (15.2)		2 (40.0)	40 (42.6)	
Class II	46 (46.5)	1225 (61.2)		2 (40.0)	44 (46.8)	
Class III	9 (9.1)	421 (21.2)		0 (0.0)	9 (9.6)	
Class IV	00 (0.0)	3 (0.4)		0 (0.0)	0 (0.0)	
missing	02 (2.0)	32 (2.0)		1 (20.0)	1 (1.1)	
BMI (kg/m^2), *median (IQR)*	25 (22–29)	25 (22–27)	0.741	19 (18–21)	24 (21–27)	**0.010**
Preoperative diabetes mellitus (type 1 and 2), *n (%)*	6 (6.1)	423 (21.5)	**<0.001**	0 (0.0)	6 (6.4)	1.000
missing		475 (24.1)				
Use of somatostatin analogue, *n (%)*	70 (70.7)	1216 (61.8)	0.132	1 (20.0)	69 (73.4)	**0.025**
missing		46 (2.3)				
Neoadjuvant therapy, *n (%)*	2 (2.0)	69 (3.5)	0.073	0 (0.0)	2 (2.1)	1.000
missing	1 (1.0)	927 (47.1)			1 (1.1)	
Procedure time, minutes, *median (IQR)*	300 (250–430)	n.a.	–	252 (199–295)	307 (257–439)	**0.045**
Blood loss, ml, *median (IQR)*	600 (400–950)	n.a.	–	300 (88–850)	600 (400–950)	0.128
Multivisceral resection, *n (%)*	10 (10.1)	163 (8.3)	0.645	1 (20.0)	9 (9.6)	0.423
missing		127 (6.4)			1 (1.1)	
Vascular resection, *n (%)*	5 (5.1)	296 (15.0)	**0.005**	1 (20.0)	4 (4 0.3)	0.195
missing		26 (1.3)		1 (20.0)	2 (2.1)	
Positive resection margins*, *n (%)*	5 (41.7)	349 (40.8)	0.998	n.a.	5 (41.7)	–
missing		18 (2.1)				
CCI-score, *median (IQR)*	12.2 (0.0–30.8)	n.a.	–	0 (0–41.0)	12.2 (6.5–28.4)	0.511
Textbook outcome, *n (%)*	61 (62)	1145 (58)	0.572	3 (60)	58 (62)	1.000
Length of hospital stay, days, *median (IQR)*	11 (9–17)	12 (9–18)	0.736	15 (10–27)	11 (9–16)	0.423
Adjuvant chemotherapy*, *n (%)*	10 (83.3)	536 (62.7)	0.526	n.a.	10 (83.3)	–
missing		88 (10.3)				
New-onset diabetes mellitus, *n (%)*	8 (8.1)	n.a.	–	0 (0.0)	6 (6.4)	1.000
Postoperative exocrine pancreatic insufficiency, *n (%)*	27 (27.3)	n.a.	–	1 (20.0)	26 (27.7)	1.000
In hospital mortality, *n (%)*	1 (1.0)	77 (3.9)	0.179	0 (0.0)	1 (1.1)	1.000

Data are given in numbers with percentages (%) or medians with interquartile ranges (IQR). For comparison between two groups Mann–Whitney *U* test were used for continuous variables and for binary variables Chi squared test or Fisher's exact test were used as appropriate. Abbreviations: ASA, American society of anesthesiologists; BMI, body mass index; CCI, comprehensive complication index. *Only patients with PDAC (pancreatic head resection). Bold value indicates statistical significance.

A systematic review by Tseng et al. found that 74% of patients after pancreatoduodenectomy developed exocrine pancreatic insufficiency.[25]

In PAYA patients who underwent distal pancreatectomy the occurrence of pancreatic endocrine and exocrine insufficiency was comparable to the literature. A total of 15% developed new-onset diabetes mellitus after surgery and 16% developed pancreatic exocrine insufficiency. De Bruijn et al. found that the average cumulative incidence of new-onset diabetes mellitus after distal pancreatectomy performed for chronic pancreatitis was 39% and for benign or (potentially) malignant lesions it was 14%.[31] A recent study found that 13% patients developed new-onset exocrine pancreatic insufficiency requiring pancreatic enzyme replacement therapy after distal pancreatectomy.[32]

The findings of the current study should be interpreted in light of some limitations. The sample size of this study is still relatively

Table 3 Clinical characteristics of patients who underwent distal pancreatectomy

Characteristic	Total cohort			PAYA cohort (<40 years)		
	PAYA (*n* = 112)	Comparator (*n* = 469)	*P*	≤18 years (*n* = 12)	>18 years (*n* = 100)	*P*
Age at surgery (years), *median (IQR)*	31 (22–36)	66 (56–73)	**<0.001**	13 (9–14)	32 (25–37)	**<0.001**
Sex: females, *n (%)*	86 (76.8)	250 (53.3)	**<0.001**	8 (66.7)	78 (78.0)	0.469
ASA fitness grade, *n (%)*			**<0.001**			**0.011**
Class I	53 (47.3)	87 (18.6)		6 (50.0)	47 (47.0)	
Class II	49 (43.8)	277 (59.0)		2 (16.7)	47 (47.0)	
Class III	3 (2.7)	95 (20.2)		1 (8.3)	2 (2.0)	
Class IV	01 (0.9)	5 (1.1)		0 (0.0)	1 (1.0)	
missing	06 (5.3)	5 (1.1)		3 (25.0)	3 (3.0)	
BMI (kg/m^2), *median (IQR)*	24 (21–27)	26 (23–29)	**<0.001**	20 (15–23)	24 (22–28)	**<0.001**
Preoperative diabetes mellitus (type 1 and 2), *n (%)*	3 (2.7)	78 (16.6)	**<0.001**	0 (0.0)	3 (3.0)	1.000
missing		76 (16.2)				
Use of somatostatin analogue, *n (%)*	57 (50.9)	247 (52.7)	0.413	5 (41.7)	52 (52.0)	0.677
missing	3 (2.7)	33 (7.0)			3 (3.0)	
Neoadjuvant therapy, *n (%)*	2 (1.8)	15 (3.2)	**0.007**	0 (0.0)	2 (2.2)	0.369
missing	2 (1.8)	323 (68.9)		1 (8.3)	1 (1.1)	
Procedure time, minutes, *median (IQR)*	200 (155–278)	n.a.	–	259 (157–304)	200 (155–278)	0.406
Blood loss, ml, *median (IQR)*	300 (138–925)	n.a.	–	210 (125–740)	300 (113–1075)	0.381
Multivisceral resection, *n (%)*	53 (47.3)	304 (64.8)	**<0.001**	5 (41.7)	48 (48.0)	0.766
Vessel resection, *n (%)*	0 (0.0)	46 (9.8)	**0.001**	0 (0.0)	0 (0.0)	–
missing		6 (1.3)				
Positive resection margins*, *n (%)*	1 (33.3)	51 (35.9)	1.000	n.a.	1 (33.3)	–
missing		5 (3.5)				
CCI-score, *median (IQR)*	0 (0–22.2)	n.a.	–	0 (0–20.9)	0 (0–22.6)	0.607
Textbook outcome, *n (%)*	84 (75)	313 (67)	0.102	10 (83)	74 (74)	0.727
Length of hospital stay, days, *median (IQR)*	7 (6–10)	8 (6–12)	**0.008**	7 (6–9)	7 (6–10)	0.975
Adjuvant chemotherapy*, n *(%)*	3 (100.0)	78 (55.0)	0.283	n.a.	3 (100.0)	–
missing		13 (9.2)				
New-onset diabetes mellitus, *n (%)*	17 (15.2)	n.a.	–	1 (8.3)	16 (16.0)	0.689
Postoperative exocrine pancreatic insufficiency, *n (%)*	18 (16.1)	n.a.	–	0 (0.0)	18 (18.0)	0.209
In hospital mortality, *n (%)*	0 (0.0)	8 (1.7)	0.364	0 (0.0)	0 (0.0)	–

Data are given in numbers with percentages (%) or medians with interquartile ranges (IQR). For comparison between two groups Mann–Whitney *U* test were used for continuous variables and for binary variables Chi squared test or Fisher's exact test were used as appropriate. Abbreviations: ASA, American society of anesthesiologists; BMI, body mass index; CCI, comprehensive complication index. *Only patients with PDAC. Bold value indicates statistical significance.

small which is clearly related to the rarity of pancreatic resections in the PAYA population. Perez et al. found an overall incidence of malignant pancreatic tumors in children of 0.18 case per million people in the United states.[33] Similar numbers were seen in Italy with an annual incidence estimated to be 0.20 case per million people in the 0–19 year old group.[6] The retrospective design has its known limitations. Complications were only assessed based on the available medical records. Major complications were surely noted, but minor complications may have been missed. We remain confident that especially pancreatic surgery-specific complications were adequately reported. We compared the PAYA data with a comparator cohort from the Dutch Pancreatic Cancer Audit. In a nationwide registry not all parameters are recorded, or recorded with sufficient detail.[19] The PAYA patients included in this study underwent resection between 2007 and 2017 while the comparator cohort from the Dutch Pancreatic

Cancer Audit is from 2014 up until 2016. Furthermore, we did not use a coefficient of fat absorption test, the reference standard, or the fecal elastase-1 test or the fecal chymotrypsin test to assess pancreatic exocrine insufficiency but relied on medication use. Finally, we did not correct for potential variation in postoperative strategy between the centers included in this study.

Our study aim was to bridge the knowledge gap on the indications and short- and long-term surgical outcomes in PAYA patients. The results of the nationwide PAPAYA cohort study demonstrate that 51% of pancreatic resections in the PAYA population is performed for malignant disease, in contrast to 76% of pancreatic resections in patients over 40 years of age. Pancreatic surgery-specific complications in PAYA patients were comparable with patients $\geq$40 years for both pancreatoduodenectomy and distal pancreatectomy. Development of endocrine and exocrine insufficiency in PAYA patients who underwent pancreatoduodenectomy, however, was substantially lower compared to adult literature.

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Author contributions

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Conflict of interest

None to declared.

References

1. Cameron JL, He J. (2015) Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 220:530–536.
2. Ishikawa O, Ohigashi H, Eguchi H, Yokoyama S, Yamada T, Takachi K *et al*. (2004) Long-term follow-up of glucose tolerance function after pancreaticoduodenectomy: comparison between pancreaticogastrostomy and pancreaticojejunostomy. *Surgery* 136: 617–623.
3. Nakamura H, Murakami Y, Uemure K, Hayashidani Y, Sudo T, Ohge H *et al*. (2009) Predictive factors for exocrine pancreatic insufficiency after pancreatoduodenectomy with pancreaticogastrostomy. *J Gastrointest Surg* 13:1321–1327.
4. Dasgupta R, Kim PCW. (2005) Relationship between surgical volume and clinical outcome: should pediatric surgeons be doing pancreaticoduodenectomies? *J Pediatr Surg* 40:793–796.
5. Choi SH, Kim SM, Oh JT, Park JY, Seo JM, Lee SK. (2006) Solid pseudopapillary tumor of the pancreas: a multicenter study of 23 pediatric cases. *J Pediatr Surg* 41:1992–1995.
6. Dall'igna P, Cecchetto G, Bisogno G, Conte M, Chiesa PL, D'Angelo P *et al*. (2010) Pancreatic tumors in children and adolescents: the Italian TREP project experience. *Pediatr Blood Canc* 54:675–680.
7. Muller CO, Guérin F, Goldzmidt D, Fouquet V, Franchi-Abella S, Fabre M *et al*. (2012) Pancreatic resections for solid or cystic pancreatic masses in children. *J Pediatr Gastroenterol Nutr* 54:369–373.
8. Speer AL, Barthel ER, Patel MM, Grikscheit TC. (2012) Solid pseudopapillary tumor of the pancreas: a single-institution 20-year series of pediatric patients. *J Pediatr Surg* 47:1217–1222.
9. Sugito K, Furuya T, Kaneda H, Masuko T, Ohashi K, Inoue M *et al*. (2012) Long-term follow-up of nutritional status, pancreatic function, and morphological changes of the pancreatic remnant after pancreatic tumor resection in children. *Pancreas* 41:554–559.
10. D'Ambrosio G, Del Prete C, Grimaldi C, Bertocchini A, Lo Zupone C, Monti L *et al*. (2014) Pancreaticoduodenectomy for malignancies in children. *J Pediatr Surg* 49:534–538.
11. Park HH, Kim HY, Jung SE, Lee SC, Park KW. (2016) Long-term functional outcomes of PPPD in children - nutritional status, pancreatic function, GI function and QOL. *J Pediatr Surg* 51:398–402.
12. Mahida JB, Thakkar RK, Walker J *et al*. (2015) Solid pseudopapillary neoplasm of the pancreas in pediatric patients: a case report and institutional case series. *J Pediatr Surg Case Rep* 3:149–153.
13. Mansfield SA, Mahida JB, Dillhoff M, Porter K, Conwell D, Ranalli M *et al*. (2016) Pancreaticoduodenectomy outcomes in the pediatric, adolescent, and young adult population. *J Surg Res* 204:232–236.
14. Lindholm EB, Alkattan AK, Abramson SJ, Price AP, Heaton TE, Balachandran VP *et al*. (2016) Pancreaticoduodenectomy for pediatric and adolescent pancreatic malignancy: a single-center retrospective analysis. *J Pediatr Surg* 52:299–303.
15. Bassi C, Dervenis C, Butturini G *et al*. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138: 8–13.
16. Wente MN, Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C *et al*. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 142:761–768.
17. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ *et al*. (2007) Postpancreatectomy hemorrhage (PPH): an international study group of pancreatic surgery (ISGPS) definition. *Surgery* 142:20–25.
18. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L *et al*. (2011) Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 149:680–688.
19. van Rijssen LB, Koerkamp B, Zwart MJ, Bonsing BA, Bosscha K, van Dam RM *et al*. (2017) Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit. *HPB* 19:919–926.
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 4e296.
21. Bleyer A, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B. (2008) The distinctive biology of cancer in adolescents and young adults. *Nat Rev Canc* 8:288–298.
22. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications. *Ann Surg* 240:205–213.

23. Slankamenac K, Graf R, Barkun J, Clavien PA. (2013) The comprehensive complication index. *Ann Surg* 258:1–7.

24. van Roessel S, Macky TM, van Dieren S, van der Schelling GP, Nieuwenhuijs VP, Bosscha K *et al*. (2020) Textbook outcome: nationwide analysis of a novel quality measure in pancreatic surgery. *Ann Surg* 271: 115–172.

25. Tseng DSJ, Molenaar IQ, Besselink MG, van Eijck CH, Borel Rinkes IH, van Santvoort HC. (2016) Pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer: a systematic review. *Pancreas* 45:325–330.

26. Burkhart RA, Gerber SM, Tholey RM, Lamb KM, Somasundaram A, McIntyre CA *et al*. (2015) Incidence and severity of pancreatogenic diabetes after pancreatic resection. *J Gastrointest Surg* 19:217–225.

27. Waters AM, Maizlin II, Russell RT, Dellinger M, Gow KW, Goldin A *et al*. (2019) Pancreatic islet cell tumors in adolescents and young adults. *J Pediatr Surg* 54:2103–2106.

28. Armstrong T, Walters E, Varshney S, Johnson CD. (2002) Deficiencies of micronutrients, altered bowel function, and quality of life during late follow-up after pancreaticoduodenectomy for malignancy. *Pancreatology* 2:528–534.

29. de Castro SMM, Singhal D, Aronson DC, Busch ORC, van Gulik TM, Obertop H *et al*. (2007) Management of solid-pseudopapillary neoplasms of the pancreas: a comparison with standard pancreatic neoplasms. *World J Surg* 31:1130–1135.

30. Scholten L, Mungroop TH, Haiijtink SAL, Issa Y, van Rijssen LB, Koerkamp BG *et al*. (2018) New-onset diabetes after pancreatoduodenectomy: a systematic review and meta-analysis. *Surgery* 164:6–16.

31. De Bruijn KMJ, van Eijck CHJ. (2015) New-onset diabetes after distal pancreatectomy: a systematic review. *Ann Surg* 261:854–861.

32. Hallac A, Aleassa EM, Rogers M, Falk GA, Morris-Stiff G. (2019) *Exocrine pancreatic insufficiency in distal pancreatectomy: incidence and risk factors*. Oxford: HPB.

33. Perez EA, Gutierrez JC, Koniaris LG, Neville HL, Thompson WR, Sola JE. (2009) Malignant pancreatic tumors: incidence and outcome in 58 pediatric patients. *J Pediatr Surg* 44:197–203.

