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## Surgical approach and short-term outcomes in adults and children undergoing total pancreatectomy with islet autotransplantation: A report from the Prospective Observational Study of TPIAT

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## ABSTRACT

**Background:** Total pancreatectomy with islet autotransplantation (TPIAT) is a viable option for treating debilitating recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) in adults and children. No data is currently available regarding variation in approach to operation.

**Methods:** We evaluated surgical techniques, islet isolation and infusion approaches, and outcomes and complications, comparing children (n = 84) with adults (n = 195) enrolled between January 2017 and April 2020 by 11 centers in the United States in the Prospective Observational Study of TPIAT (POST), which was launched in 2017 to collect standard history and outcomes data from patients undergoing TPIAT for RAP or CP.

**Results:** Children more commonly underwent splenectomy (100% versus 91%, p = 0.002), pylorus preservation (93% versus 67%; p < 0.0001), Roux-en-Y duodenojejunostomy reconstruction (92% versus 35%; p < 0.0001), and enteral feeding tube placement (93% versus 63%; p < 0.0001). Median islet equivalents/kg transplanted was higher in children (4577; IQR 2816-6517) than adults (2909; IQR 1555-

**Abbreviations:** Chronic pancreatitis, CP; endoscopic retrograde cholangiopancreatography, ERCP; islet equivalents per kilogram body weight, IEQ/kg; islet number per kilogram body weight, IN/kg; Prospective Observational Study of TPIAT, POST; recurrent acute pancreatitis, RAP; total pancreatectomy with islet autotransplantation, TPIAT.

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Total pancreatectomy with islet autotransplantation

4479;  $p < 0.0001$ ), with COBE purification less common in children (4% versus 15%;  $p = 0.0068$ ). Median length of hospital stay was higher in children (15 days; IQR 14–22 versus 11 days; IQR 8–14;  $p < 0.0001$ ), but 30-day readmissions were lower in children (13% versus 26%,  $p = 0.018$ ). Rate of portal vein thrombosis was significantly lower in children than in adults (2% versus 10%,  $p = 0.028$ ). There were no mortalities in the first 90 days post-TPIAT.

**Conclusions:** Pancreatectomy techniques differ between children and adults, with islet yields higher in children. The rates of portal vein thrombosis and early readmission are lower in children.

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## 1. Introduction

For children and adults with recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) refractory to standard medical and endoscopic interventions, surgery may be considered to relieve pain and improve quality of life [1,2]. Conventional surgical options in patients with debilitating pancreatitis include both partial resections (e.g., Whipple procedure), surgical drainage procedures (e.g., modified Puestow procedure), and combination drainage-resection (e.g., Beger procedure, Berne procedure, Frey procedure). However, many patients do not have the anatomy (e.g., uniformly adequately dilated main pancreatic duct or inflammatory mass in head of pancreas) of disease to consider such conventional operations. Total pancreatectomy with islet autotransplantation (TPIAT) has gained traction in the United States for managing many of these cases [3–6], particularly for children [7–11] and those with pancreatitis genetic risk factors [12,13] or a small (non-dilated) pancreatic duct [14]. To date, most research in TPIAT has been reported from single institutions and retrospective in nature. Thus, in 2017, the multicenter Prospective Observational Study of TPIAT (POST) was launched to collect standard history and outcomes data from patients undergoing TPIAT for RAP or CP [15].

One aspect that has not been a focus of study to date is variation in approaches to operation. After total pancreatectomy is performed, continuity of the gastrointestinal and biliary tracts must be restored, and various approaches may be used to achieve this. For example, gastrointestinal reconstruction has been described with or without pylorus preservation, and early reports described end-to-end duodenoduodenostomy, while more recent literature largely describes Roux-en-Y reconstruction of the alimentary tract [3,9]. Surgical reconstruction may vary depending on the surgeon, the surgical center, and patient anatomy (e.g., if prior pancreatic or gastrointestinal surgery was performed). Splenectomy is most common, but not universal [16,17]. Overall, predominant approaches and variations have not been formally studied.

TPIAT is often preferred for children with debilitating RAP and CP who fail medical and endoscopic therapies [7–9]. Children have distinct considerations, including a high rate of pancreatitis genetic risk factors compared to adults, smaller body size, greater technical challenges in islet isolation, and higher caloric needs for growth [18–22]. These considerations may impact TPIAT approach or early post-operative course and complications.

Herein, we report surgical approaches to TPIAT and early post-operative course in patients enrolled in the multicenter POST study and undergoing TPIAT. The aims of these interim analyses were: (1) to describe surgical approaches to TPIAT used across major centers performing this procedure in POST; and (2) to compare TPIAT surgical approaches and early (30-day) surgical outcomes and complications in children and adult patients.

## 2. Methods

### 2.1. POST study

The Prospective Observational Study of TPIAT is a multicenter study with 13 centers performing TPIAT in the United States (11 centers contributing surgical data to these analyses). Patients are eligible if undergoing total or completion pancreatectomy for CP or RAP at a participating center. The decision to proceed to TPIAT is based on clinical criteria defined by each participating institution. Individuals undergoing only partial pancreatectomy with islet autotransplantation, total pancreatectomy without islet autotransplantation, or TPIAT for disease other than pancreatitis (e.g., tumor) are excluded. The POST study protocol has been described in detail elsewhere [15]. It was reviewed and approved by the Institutional Review Board at each site. Informed consent, or parental consent and patient assent as age appropriate, was obtained for each participant.

### 2.2. Patient population for current analyses

POST is in process with continuing enrollment [15]. This report includes participants who had completed TPIAT operation and had baseline and TPIAT surgical procedure data available in the POST database on April 14, 2020. The distribution of adults and children included in the current report is shown in [Supplemental Table 1](#). This interim analysis was designed to describe pancreatectomy and islet infusion procedures and 30 day post-TPIAT surgical course in POST's first 279 participants, emphasizing adult ( $\geq 18$  years of age) and pediatric ( $< 18$  years of age) subgroups.

### 2.3. Descriptive data

We collected descriptive data including demographics (age, sex, race) and pancreatitis history, including indications for TPIAT (CP and/or RAP), pancreatitis risk factors defined by the TIGAR-O criteria (Toxic/Metabolic, Idiopathic, Genetic, Autoimmune, Recurrent Pancreatitis, and/or Obstructive), and prior procedural interventions to treat pancreatitis including endoscopic retrograde cholangiopancreatography (ERCP), celiac or splanchnic nerve blocks, cholecystectomy, or other operations for CP (any of open sphincterotomy/sphincteroplasty, distal pancreatectomy, longitudinal pancreaticojejunostomy or variant (Frey), duodenum-preserving pancreatic head resection (Beger, Berne) or Whipple pancreatoduodenectomy).

### 2.4. Surgical procedure of TPIAT and data collection

Generally, total pancreatectomy involves resecting the entire pancreas while preserving blood supply to it as long as possible to reduce ischemia time, along with duodenectomy with variable

approaches to gastrointestinal reconstruction, reconstruction of the biliary tract, and (usually) splenectomy. The approach to certain aspects of the procedure, including reconstruction of gastrointestinal and biliary anastomoses, varies across institutions and surgeons performing the operation. Islets are isolated by enzymatic and mechanical digestion, with or without a COBE purification step [23], and are transplanted intraportally, with secondary sites used based on the surgical team's clinical discretion, usually when concerns about tissue volume or elevated portal venous pressure prevent infusion of all islets intraportally.

We collected standardized data on surgical approach for each participant, including whether the operation was performed by open laparotomy versus laparoscopic, laparoscopic-assisted, or robotic approaches; whether splenectomy was performed; the approach to gastrointestinal reconstruction and whether TPIAT was pylorus-preserving; the approach to biliary reconstruction; and whether an enteral feeding tube was placed as part of the operation.

We also collected details on islet processing and isolation results including whether COBE purification was performed, number and mass of islets, tissue volume, and site(s) of islet infusion. Islet mass is quantified as islet equivalents (IEQ), a measure that accounts for islet number and islet size, standardizing islet size to 150  $\mu\text{m}$ . Islet number (IN) is the raw number of islets without adjusting for islet size/volume.

Post-operatively, we collected details on length of hospital stay, 30-day hospital readmission, and reoperation within 30 days. We also collected details on complications of interest after TPIAT agreed upon by the investigators before enrollment began. These included episodes of abdominal or wound infection requiring

procedural intervention, post-operative bleeding, thrombosis (any portal vein thrombosis, pulmonary emboli, and deep venous thrombosis), bile duct obstruction or leak, severe hypoglycemia (defined by loss of consciousness or seizure), and prolonged use of mechanical ventilation or vasopressors for blood pressure support more than 24 h after completion of TPIAT operation.

## 2.5. Statistical analyses

Summary data are summarized as median and interquartile range (IQR). Children and adults were compared using Fisher's exact test for categorical characteristics (e.g., sex, presence/absence of a given risk factor for pancreatitis) and two-sample t-tests for characteristics on continuous scales (e.g., age, final tissue volume). Statistical analyses were performed in R (version 3.6.2). In adult cohort subanalysis, outcomes were compared by type of gastrointestinal reconstruction using Fisher's exact test for categorical characteristics and one-way ANOVA for characteristics on continuous scales.

## 3. Results

### 3.1. Baseline characteristics

At the time of analyses, 279 patients enrolled in POST had completed the TPIAT operation (N = 195 adults; N = 84 children) (Table 1). Sex, race, and ethnicity were similar in adults and children. Indications for proceeding with TPIAT reported by the surgical center were RAP (67% of children, 53% of adults;  $p = 0.035$ ) and/or chronic pancreatitis (87% of children, 85% of adults), with

**Table 1**  
Demographic characteristics and pancreatitis history before TPIAT.

Variables	Adults ( $\geq 18$ years)	Children ( $< 18$ y)	P-value
N	195	84	
Age, mean $\pm$ sd	38.2 $\pm$ 12.9	11.4 $\pm$ 4.1	<b>&lt;0.0001</b>
Sex, n (%)			0.79
Male	74 (38%)	30 (36%)	
Female	121 (62%)	54 (64%)	
Race, n (%)			0.39
White/Caucasian	177 (91%)	79 (94%)	
Asian	4 (2%)	1 (1%)	
Black/African American	6 (3%)	1 (1%)	
Native Hawaiian/Pacific Islander	2 (1%)	0 (0%)	
American Indian/Alaska Native	0 (0%)	1 (1%)	
Mixed race	6 (3%)	1 (1%)	
Don't know/declined to answer	0 (0%)	1 (1%)	
Hispanic or Latino, n (%)	16 (8%)	7 (8%)	1.0
Indication(s) for TPIAT, n (%)			
Recurrent Acute Pancreatitis	102 (53%)	56 (67%)	<b>0.035</b>
Chronic Pancreatitis	165 (85%)	73 (87%)	0.85
Risk Factors for Pancreatitis, n (%)			
Toxic/Metabolic	40 (21%)	1 (1%)	<b>&lt;0.0001</b>
Idiopathic	30 (16%)	1 (1%)	<b>0.0001</b>
Genetic <sup>a</sup>	94 (48%)	70 (83%)	<b>&lt;0.0001</b>
Autoimmune	2 (1%)	2 (2%)	0.59
Recurrent or Severe AP	135 (70%)	73 (87%)	<b>0.0024</b>
Obstructive	57 (30%)	19 (23%)	0.31
Prior Procedures for Pancreatitis, n (%)			
ERCP	150 (77%)	65 (77%)	1.0
Celiac or Splanchnic Nerve Block	76 (39%)	5 (6%)	<b>&lt;0.0001</b>
Cholecystectomy	123 (63%)	20 (24%)	<b>&lt;0.0001</b>
Open sphincterotomy	8 (4%)	2 (2%)	0.73
Open pseudocyst drainage	5 (2.6%)	1 (1.2%)	0.67
Lateral pancreaticojejunostomy	8 (4%)	2 (2%)	0.73
Whipple procedure	14 (7%)	0 (0%)	<b>0.007</b>
Distal pancreatectomy	11 (6%)	0 (0%)	<b>0.038</b>

Abbreviations: TPIAT = total pancreatectomy with islet autotransplantation; AP = acute pancreatitis; CP = chronic pancreatitis; ERCP = endoscopic retrograde cholangiopancreatography.

<sup>a</sup> 30% of adults did not have any genetic testing; all children had genetic testing.

many patients having both. Risk factors for pancreatitis were identified for most participants, with genetic risk factors (per the providers' testing) or prior recurrent or severe AP more often identified in children ( $p < 0.0001$  and  $p = 0.0024$ , respectively) and toxic/metabolic risk factors being more common in adults ( $p < 0.0001$ ). Pancreatic disease was reported as "idiopathic" more commonly in adults (16%) than in children (1%;  $p = 0.0001$ ). However, genetic testing was not performed in 30% of adults. Prior ERCP was common in both children and adults, but adults were more likely to have a history of celiac or splanchnic nerve blocks ( $p < 0.0001$ ) or cholecystectomy ( $p < 0.0001$ ). Although prior pancreatic operations were uncommon overall, adults were also more likely to have undergone a prior pancreatic operation for CP ( $p < 0.003$ ); specifically, adults more frequently had undergone a Whipple procedure (14 (7%) adults vs 0 children,  $p = 0.007$ ) or distal pancreatectomy (11 (6%) adults vs 0 children,  $p = 0.038$ ) before TPIAT.

### 3.2. Surgical approach to total or completion pancreatectomy

Table 2 reports details of the pancreatectomy. Most procedures in adults and children were described as open pancreatectomy with small but statistically significant differences ( $p = 0.029$ ) in the approach to pancreatectomy in children and adults, with slightly more laparoscopic-assisted procedures in children, and with robotic procedures, though uncommon overall, performed only in adults. Completion pancreatectomy was more common in adults, reflecting greater likelihood of prior resection procedures than in children ( $p = 0.036$ ). In total pancreatectomy, the pancreas was more often resected in continuity (compared to split *in situ*) in adults ( $p = 0.0007$ ). Splenectomy was performed in 91% of adults and in 100% of children ( $p = 0.002$ ). The pylorus was preserved more often in pediatric procedures (93% vs 67% of adults,  $p < 0.0001$ ).

Reconstruction of the gastrointestinal tract was more varied in adult patients compared to children. Gastrointestinal continuity was restored by Roux-en-Y duodenojejunostomy in 92% of children, vs 35% of adults ( $p < 0.0001$ ). Biliary reconstruction was most often by choledochojejunostomy (74% of adults, 64% of children) or by hepaticojejunostomy (22% of adults, 35% of children) ( $p = 0.04$ ). Children more often had enteral feeding tubes placed during surgery (93% vs 63% of adults,  $p < 0.0001$ ), with gastrojejunal tubes more common in children ( $p < 0.0001$ ).

### 3.3. Islet isolation and transplant in children and adults

Children and adults had similar total islet equivalents transplanted ( $p = 0.37$ ) (Table 3). However, children had a higher unadjusted islet number (IN,  $p = 0.009$ ) and greater islet mass and islet number relative to size (IEQ/kg and IN/kg) ( $p < 0.0001$  for both) compared to adults. COBE purification was rare but more common in adults (15% vs 4% of children,  $p = 0.0068$ ), and the median final pellet tissue volume (ml/kg body weight) did not differ between adults and children. All islets were transplanted exclusively intraportally in most participants (86% of adults, 85% of children,  $p = 0.85$ ), with part of the islet graft transplanted elsewhere in the abdominal cavity in the remainder. Microbial growth in the islet preparation was common and similar in both groups (35% of children, 42% of adults,  $p = 0.43$ ).

### 3.4. Post-TPIAT length of hospital stay and complications

The median post-operative hospital stay was 15 days (IQR 14–22) for children and 11 days (IQR 8–14) for adults ( $p < 0.0001$ ) (Table 4). However, children were less likely to be readmitted than

adults (13% vs 26% of adults) ( $p = 0.018$ ). One or more reoperations were performed within 30 days after the TPIAT in 11% of adults and 7% of children ( $p = 0.39$ ). Complication profiles of the groups were similar except portal vein thrombosis occurred more often in adults (10% versus 2% of children,  $p = 0.028$ ). In subanalysis of adult patients, we found no significant differences between the four types of GI reconstruction, in terms of need for reoperation within 30 days, primary reason for reoperation, or length of hospital stay post-TPIAT. There were no mortalities in the first 90 days post-TPIAT.

## 4. Discussion

Total pancreatectomy with islet autotransplantation has become a viable and effective therapy for both children and adults with CP or RAP who suffer debilitating pain and impaired quality of life despite maximal medical and endoscopic treatment in the absence of pancreatic anatomy and morphology to consider a conventional surgical option. To date, most studies of TPIAT have been single center retrospective reports, and no studies have been published describing variations in technical approaches to operation. Furthermore, we hypothesized that surgical approaches and outcomes and complications would differ between children and adults undergoing TPIAT, due to distinctive characteristics of pediatric patients. This is the first multicenter prospective study to report surgical approaches to TPIAT and the early post-operative course, with important differences identified between adults and children in pancreatectomy techniques, islet isolation approaches, and outcomes and complications. We found significant differences between adults and children in risk factors for pancreatitis and in prior procedures for managing CP and RAP. We also found that children more commonly underwent splenectomy, pylorus preservation, Roux-en-Y duodenojejunostomy reconstruction, and enteral feeding tube placement. Children had higher islet mass transplanted compared to adults. Finally, regarding early post-operative outcomes, while children had a longer median length of hospital stay for the index surgical admission, they were less often readmitted within 30 days and had a lower rate of portal vein thrombosis.

Risk factors for RAP and CP are known to differ between adult and pediatric patients, with genetic risk factors (e.g., *PRSS1*, *SPINK1*, *CFTR*, *CTRC*) more commonly reported in children. Over 80% of children in POST had at least one genetic risk factor for pancreatitis, which is consistent with the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) cohort, in which 73% of children with CP had at least one mutation in a pancreatitis-related gene [18]. Toxic/metabolic risk factors were much more frequently identified in our adults (21%) than in our children (1%), which is consistent with the high incidence (42–77%) of heavy alcohol use reported as the etiology of CP in adult studies [24]. Note that while idiopathic CP has been reported commonly in adult studies [24] and we too report significantly more adults (16%) than children (1%) with "idiopathic" CP, it remains unclear whether this finding is related to differences in obtaining genetic testing or the number of variants available in testing panels chosen for evaluating adults with CP.

We found that before proceeding to TPIAT, adults were much more likely than children to have undergone celiac or splanchnic nerve blocks, cholecystectomy, and pancreatic operations for CP. While we do not have more granular data in POST about the group that underwent celiac and splanchnic nerve blocks, we speculate that its infrequent use in children (6%) compared to adults (39%) may relate to several factors, including limited expertise in endoscopic ultrasound (EUS) which is a safer and potentially more effective approach to celiac plexus blockade than radiologic

**Table 2**  
Surgical approaches to TPIAT in POST participants.

Variables	Adults ( $\geq 18$ years)	Children (<18y)	P-value
N	195	84	
Surgical Approach, n (%)			<b>0.029</b>
Open	142 (73%)	65 (77%)	
Entirely laparoscopic	1 (1%)	0 (0%)	
Laparoscopic-assisted	38 (19%)	19 (23%)	
Robotic	14 (7%)	0 (0%)	
Completion and total pancreatectomy, n (%)			<b>0.036</b>
Completion	26 (13%)	4 (5%)	
Total	169 (87%)	80 (95%)	
For Total pancreatectomy, n (%)			<b>0.0007</b>
Performed in continuity	96 (57%)	27 (34%)	
Split	73 (43%)	53 (66%)	
Splenectomy performed, n (%)			<b>0.002</b>
Yes	177 (91%)	84 (100%)	
No	18 (9%)	0 (0%)	
Pylorus preserved, n (%)			<b>&lt;0.0001</b>
Yes	130 (67%)	78 (93%)	
No	65 (33%)	6 (7%)	
GI reconstruction, n (%)			<b>&lt;0.0001</b>
Roux-en-Y duodenojejunostomy	68 (35%)	77 (92%)	
Roux-en-Y gastrojejunostomy	58 (30%)	5 (6%)	
Duodenojejunostomy	0 (0%)	0 (0%)	
Duodenojejunostomy	39 (20%)	1 (1%)	
Gastrojejunostomy	30 (15%)	1 (1%)	
Biliary reconstruction, n (%)			<b>0.04</b>
Choledochoduodenostomy	9 (5%)	1 (1%)	
Choledochojejunostomy	144 (74%)	54 (64%)	
Hepaticojejunostomy	42 (22%)	29 (35%)	
Enteral feeding tube placement, n (%)			<b>&lt;0.0001</b>
No feeding tube	73 (37%)	6 (7%)	
Any feeding tube	122 (63%)	78 (93%)	
Type of enteral feeding tube, n (%)			<b>&lt;0.0001</b>
Gastrojejunostomy Tube	68 (56%)	77 (99%)	
Direct Jejunostomy Tube Only	23 (19%)	0 (0%)	
Gastrostomy Tube Only	10 (8%)	0 (0%)	
Both Gastrojejunostomy and Jejunostomy	1 (1%)	1 (1%)	
Nasojejunal Tube	20 (16%)	0 (0%)	

**Table 3**  
Characteristics of the islet graft and islet infusion in children and adults in POST.

Variables	Adults ( $\geq 18$ years)	Children (<18y)	P-value
N	195	84	
COBE purification performed, n (%)			<b>0.0068</b>
Yes	29 (15%)	3 (4%)	
No	166 (85%)	81 (96%)	
Final tissue volume (mL)/kg	0.12 (0.07–0.23)	0.13 (0.06–0.20)	0.89
Total Transplanted, All Sites, median (IQR)			
Total IEQ	215000 (130263–345771)	216875 (132850–272475)	0.37
Total IN	213000 (113200–356650)	276000 (187800–425625)	<b>0.0094</b>
Total IEQ/kg	2909 (1555–4479)	4577 (2816–6517)	<b>&lt;0.0001</b>
Total IN/kg	2670 (1514–4784)	6355 (3757–9520)	<b>&lt;0.0001</b>
All Islets Infused Intraportally, n (%)			0.85
Yes	167 (86%)	71 (85%)	
No, extrahepatic site used	28 (14%)	13 (15%)	
Islet Mass and Number Transplanted Intraportally, median (IQR)			
Intraportal IEQ	203796 (111412–325149)	185795 (127375–253687)	0.31
Intraportal IN	190842 (100900–321700)	258500 (171000–365175)	<b>0.0087</b>
Intraportal IEQ/kg	2740 (1439–4360)	4050 (2594–6152)	<b>&lt;0.0001</b>
Intraportal IN/kg	2524 (1315–4304)	5466 (3504–9293)	<b>&lt;0.0001</b>
Other site(s) where islets were infused, n (%)			
Peritoneal cavity	13 (7%)	13 (15%)	<b>0.025</b>
Omental	8 (4%)	2 (2%)	0.73
Other (pre-peritoneal = 6, mesentery = 1)	7 (4%)	0 (0%)	0.11

Abbreviations: IQR = interquartile range (Q1- Q3), IEQ = islet equivalents, IN = islet number, IEQ/kg = islet equivalents per kilogram body weight, IN/kg = islet number per kilogram body weight.

guidance (i.e., computed tomography) [25], and the limited efficacy and varying duration of effect of celiac nerve blocks for managing pain in CP [26–28].

A prior pancreatic operation for CP was also significantly more common in adults in our study, and this likely relates to differences in the anatomy and morphology of disease in adults versus

**Table 4**  
Hospital length of stay and pre-specified complications within 30 days after TPIAT.

Variables	Adults ( $\geq 18$ years)	Children ( $< 18$ y)	P-value
N	195	83	
Length of stay after TPIAT, median (IQR)	11 (8–14)	15 (14–22)	<b>&lt;0.0001</b>
Readmission within 30 days of TPIAT, n (%)			<b>0.018</b>
Yes	51 (26%)	11 (13%)	
No	144 (74%)	72 (87%)	
Required reoperation within 30 days of TPIAT, n (%)			0.39
Yes	22 (11%)	6 (7%)	
No	170 (89%)	77 (93%)	
Number of reoperations, mean $\pm$ sd	1.2 $\pm$ 0.5	1.2 $\pm$ 0.4	0.94
Primary reason for reoperations, n (%)			0.30
Bleeding	6 (27%)	2 (33%)	
Infection	6 (27%)	0 (0%)	
Small bowel obstruction	3 (14%)	1 (17%)	
Bile leak	0 (0%)	1 (17%)	
Anastomotic leak	3 (14%)	0 (0%)	
Other	4 (18%)	2 (33%)	
Predefined complications of interest, within 30 days of TPIAT, n (%)			
Abdominal infection requiring operative drainage	7 (4%)	0 (0%)	0.11
Abdominal infection requiring IR drainage	9 (5%)	3 (4%)	1.00
Bleeding requiring second surgery	6 (3%)	2 (2%)	1.00
Bile duct obstruction	2 (1%)	1 (1%)	1.00
Bile duct leak	2 (1%)	1 (1%)	1.00
Portal vein thrombosis	20 (10%)	2 (2%)	<b>0.028</b>
Severe hypoglycemia	0 (0%)	0 (0%)	1.00
Wound infection requiring drainage	6 (3%)	2 (2%)	1.00
Mechanical ventilation required $\geq 24$ h post-TPIAT	5 (3%)	1 (1%)	0.67
Vasopressor support required $\geq 24$ h post-TPIAT	5 (3%)	5 (6%)	0.17
Pulmonary embolism	1 (1%)	0 (0%)	1.00
Deep venous thrombosis	5 (3%)	0 (0%)	0.33

Abbreviations: TPIAT = total pancreatectomy islet autotransplantation; IQR = interquartile range (Q1–Q3); IR = interventional radiology. 30 day complications data not yet available for 1 participant at time of report.

children. Adults more commonly present with either a diffusely uniformly dilated main pancreatic duct (i.e., large duct disease), which may be amenable to surgical drainage (e.g., modified Puestow longitudinal pancreaticojejunostomy, Frey procedure), or an inflammatory mass in the head of the pancreas, which may be amenable to a pancreatic head resection (e.g., Whipple pancreatoduodenectomy, Beger procedure, Berne procedure) [29]. Prior Whipple was only reported in adult participants in our cohort. Other surgical procedures may be avoided in children because the response to surgical drainage procedures or partial pancreatic resection is unpredictable and suboptimal in pediatric patients harboring a genetic risk factor for CP [30].

The predominant technical approaches to the TPIAT operation have not been previously reported and variations likely exist depending on the individual surgeon, institutional practice, and patient anatomy (i.e., previous operations). While most TPIATs in both adults and children in POST have been performed using open laparotomy, minimally invasive techniques were used in about 25% of patients. A few small studies have reported the safety and feasibility of minimally invasive approaches to TPIAT including full laparoscopy [31], laparoscopic-assistance [32], and robotic-assistance [33]. The nuances of the TPIAT operation are highly complex, including the critical importance of preserving arterial and venous flow to reduce warm ischemia to the islets during the pancreatic dissection phase and the hazardous retroperitoneum that often exists after many years of recurrent inflammatory attacks, leading to significant scarring, and after prior pancreatic operations. Thus, several questions remain unanswered regarding minimally invasive approaches to TPIAT, including patient selection, overall risk-benefit ratio, and cost. Two studies used a larger incision for dissection or for extraction of the specimen from the abdomen [32,33], and one study reported higher rates of mechanical complications in a laparoscopic-assisted group compared to a matched open TPIAT group [32]. These factors require more

rigorous study to determine the overall benefit of minimally invasive approaches for TPIAT.

We have reported several technical differences between adults and children in specific components of the TPIAT operation. In 9% of adult patients, the spleen was preserved during operation, while splenectomy was performed in all pediatric patients. From a technical perspective, because the body and tail of the pancreas share blood supply with the spleen, preservation of the spleen with sacrifice of the splenic artery and vein may cause areas of splenic infarction and resultant significant left upper quadrant pain and even splenic abscess. Thus, while not universal [16,17], splenectomy is performed during TPIAT in most patients at most centers. The lower rate of splenectomy in adults may reflect differences in standard protocols of the treating centers, rather than considerations related to patient age.

The approach to alimentary tract reconstruction also differs between children and adults with pyloric preservation and Roux-en-Y duodenojejunoscopy more commonly performed in children. Gastrointestinal reconstruction in TPIAT has evolved, as early TPIATs were commonly performed with a duodenoduodenostomy anastomosis and a choledochoduodenostomy anastomosis in the proximal duodenum [34]. A high rate of bile reflux gastritis and ascending cholangitis in patients undergoing this reconstruction led to changes in approach to mitigate these complications. Recently, single center studies have begun reporting gastrointestinal symptoms in patients who have undergone TPIAT. While one retrospective study [35] reported pylorus preservation had no negative impact on delayed gastric emptying or nutritional outcomes of TPIAT, other studies found a 36% prevalence of delayed gastric emptying with associated increased length of hospital stay [36] and overall high rates of chronic gastrointestinal dysmotility [37] following TPIAT. However, this may not be due to the procedure alone, as opioids, other medications, or previous operations may also be associated with delayed gastric emptying. As these

studies have been descriptive and retrospective with small sample sizes, the POST study offers the opportunity to evaluate the clinical implications of different approaches to alimentary tract reconstruction in adults and children undergoing TPIAT. Finally, we found that children undergoing TPIAT in POST were much more likely than adults to have an enteral feeding tube placed at the time of operation. Whether this is related to greater concern for underlying nutritional compromise, higher risk of postoperative delayed gastric emptying, or surgeon/center preference requires further elucidation.

While the primary goal of TPIAT is relief from debilitating pain and improvement in quality of life, the secondary goal is glycemic control and islet function. Islet mass, defined as islet equivalents per kilogram body weight (IEQ/kg), is a strong predictor of insulin independence following TPIAT [3,7]. Specific protocols have been published to optimize isolation of islets from the pancreas of a young patient (as islets from children are more heavily embedded in surrounding exocrine tissue) [21], and use of COBE purification has generally been indicated in clinical scenarios in which the pellet tissue volume is substantial enough ( $>0.25$  ml/kg body weight) to increase the risk of portal vein thrombosis [38]. We have reported that COBE purification was more commonly performed in adults than in pediatric patients. However, it is unclear whether this is due to a higher incidence of elevated ( $>0.25$  ml/kg body weight) pre-purification tissue pellet volumes in adults, or to center-specific preferences, as some centers do not perform COBE purification under any circumstance due to concern about loss of islets during purification and about higher costs. The interquartile range for pellet volume in children suggests that most had tissue volumes below the portal vein thrombosis risk threshold, despite infrequent COBE use. Our finding of higher median IEQ/kg transplanted in children compared to adults is consistent with a previous large single center study reporting higher islet yields in pediatric patients [3]. Numerous factors have been associated with lower islet yield in TPIAT, including longer disease duration [39], greater degree of parenchymal fibrosis [40], and prior pancreatic operation [41,42]. However, such analyses are beyond the scope of this interim report of POST. Future studies from POST will report on insulin independence and overall glycemic control.

TPIAT is a highly complex operation with significant morbidity risk, and it requires a multidisciplinary care team to assure safe preoperative preparation and optimal outcomes. We found that pediatric patients had longer hospital stays for the index surgical admission but a lower rate (13%) of readmission within 30 days compared to adults (26%). Although not evaluated in this study, multiple factors can contribute to a longer hospital stay in children undergoing TPIAT (e.g., complexities of care, predetermined protocolized intensive care unit stay, extended discharge teaching, availability of local facilities for discharge), but longer stay is not clearly related to overall complications of interest or need for reoperation, neither of which differed between adults and children. While reasons for readmission are likewise not available in this study, a recent retrospective study of adult TPIAT patients reported a similar 30-day readmission rate of 25% [43]. That study found that the most common reasons for early readmission included gastrointestinal complaints (e.g., delayed gastric emptying) and surgical site infections.

We found that the portal vein thrombosis rate was higher in adults (10%) compared to children (2%). This low rate of portal vein thrombosis in children is consistent with several reports [7,9] documenting the rarity of this complication in children undergoing TPIAT despite an inherent concern about the small caliber of vessels. Several factors may contribute to risk of thrombotic complications following TPIAT, including the chronic inflammatory state related to the underlying pancreatitis, the operation's extended

length, and the instant blood-mediated inflammatory reaction induced by islet autotransplantation [44]. Whether differences between adults and children in these prothrombotic factors account for the higher rate of portal vein thrombosis in adults is unclear. The POST study will provide a unique opportunity to evaluate the impact of complications on quality of life after TPIAT and on islet function.

Despite the significant findings of this multicenter prospective report on TPIAT, it has several limitations. As it is a multicenter study, institutional practices vary regarding patient selection and postoperative care algorithms and protocols, but the goal of the prospective registry is to capture and critically evaluate the landscape of current clinical practices to determine which should be adopted or abandoned. Because children are seen more commonly at several centers in POST, we cannot entirely separate the impact of age from the impact of surgical centers; none-the-less, these data still reflect current practice differences in pediatric versus adult TPIAT in the United States. Some data elements are not collected (e.g., items that may impact intraoperative decision-making such as portal pressures), which may affect analysis and interpretation of results. The list of complications of interest was generated before POST began and other complications that may be of interest are not currently being captured (e.g., delayed gastric emptying, intestinal anastomotic leak not requiring surgical intervention). This is an interim analysis and patients are still enrolling in POST, so the present study's findings may change with the study's full enrollment. Variation between centers in numbers of patients enrolled (i.e., high versus low volume) may result in bias due to center effects. Finally, due to the low number of complications in this cohort, the study may be underpowered to detect significant differences.

In conclusion, this is the first prospective multicenter report to describe surgical techniques and approaches to TPIAT in patients with debilitating RAP and CP and to compare adults and children undergoing the operation. In patients undergoing TPIAT enrolled in POST, children more commonly underwent splenectomy, pylorus preservation, Roux-en-Y duodenojejunostomy reconstruction, and enteral feeding tube placement, and they received a greater median number of IEQ/kg. Median length of hospital stay was higher in children, but the early readmission rate was higher in adults. Portal vein thrombosis was more frequent in adults than in children, but other complications were similar. The long-term implications of these differences between adults and children undergoing TPIAT will be elucidated in future reports from POST.

#### Data availability statement

Data are available from the corresponding author upon reasonable request.

#### Declaration of competing interest

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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.2021.09.011>.

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