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## Outcomes of total pancreatectomy with islet autotransplantation: A systematic review and meta-analysis

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### Abstract

#### BACKGROUND

Despite the increased use of total pancreatectomy with islet autotransplantation (TPIAT), systematic evidence of its outcomes remains limited.

#### AIM

To evaluate the outcomes of TPIAT.

#### METHODS

We searched PubMed, EMBASE, and Cochrane databases from inception through March 2019 for studies on TPIAT outcomes. Data were extracted and analyzed using comprehensive meta-analysis software. The random-effects model was used for all variables. Heterogeneity was assessed using the  $I^2$  measure and Cochrane Q-statistic. Publication bias was assessed using Egger's test.

#### RESULTS

Twenty-one studies published between 1980 and 2017 examining 1011 patients

were included. Eighteen studies were of adults, while three studied pediatric populations. Narcotic independence was achieved in 53.5% [95% Confidence Interval (CI): 45-62,  $P < 0.05$ ,  $I^2 = 81\%$ ] of adults compared to 51.9% (95%CI: 17-85,  $P < 0.05$ ,  $I^2 = 84\%$ ) of children. Insulin-independence post-procedure was achieved in 31.8% (95%CI: 26-38,  $P < 0.05$ ,  $I^2 = 64\%$ ) of adults with considerable heterogeneity compared to 47.7% (95%CI: 20-77,  $P < 0.05$ ,  $I^2 = 82\%$ ) in children. Glycated hemoglobin (HbA<sub>1c</sub>) 12 mo post-surgery was reported in four studies with a pooled value of 6.76% ( $P = 0.27$ ). Neither stratification by age of the studied population nor meta-regression analysis considering both the study publication date and the islet-cell-equivalent/kg weight explained the marked heterogeneity between studies.

### CONCLUSION

These results indicate acceptable success for TPIAT. Future studies should evaluate the discussed measures before and after surgery for comparison.

**Key Words:** Islet autotransplantation; Pancreatectomy; Pancreatitis; Narcotics

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**Core Tip:** Surgical intervention is required for the management of debilitating and refractory abdominal pain in chronic pancreatitis (CP) patients failing medical therapy. Since first introduced in 1978, total pancreatectomy with islet autotransplantation (TPIAT) has shown promising results in CP patients, but the literature remains limited. This systematic review and meta-analysis found that TPIAT provided acceptable levels of pain relief and insulin independence.

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## INTRODUCTION

Chronic pancreatitis (CP) is characterized by progressive inflammation of the pancreas with eventual fibrosis, ductal alteration, and permanent structural damage. CP has a reported mortality of nearly 50% within the first 20-25 years of diagnosis[1,2]. It significantly impairs the quality of life (QoL) of the affected patients, often requiring frequent Emergency Department (ED) visits and hospitalizations due to pain, infections, malnutrition, and recurrent acute on chronic pancreatitis[3]. The clinical manifestations include varying degrees of abdominal pain, malabsorption from exocrine insufficiency, and the development of diabetes mellitus (DM). Although the compromised exocrine function and DM can be treated with oral pancreatic enzyme supplementation and insulin, the hallmark symptom of CP is pain, which often is intractable and debilitating[4].

The commonly used first-line therapies for CP primarily focus on mitigating the unrelenting and recurring abdominal pain. These include dietary modifications with a low-fat diet, pancreatic enzyme supplementation, strict smoking cessation, and alcohol abstinence[5]. Despite these initial measures, many patients often end up requiring frequent escalating doses of narcotics with consequent opioid dependence[6]. Patients who require chronic opioids are often candidates for invasive procedures in an attempt to eliminate or modify the underlying source of pain[7]. Frequently, endoscopic treatments such as sphincterotomy and/or stent placement are employed to treat fibrotic strictures of the pancreatic duct or stone extraction if present[8,9]. When the usual medical and endoscopic therapies fail to address the severe pain and subsequent life disruption, surgical treatments, including functional operative diversion (*i.e.*, pancreatojejunostomy) or operative gland extirpation (*i.e.*, pancreatectomy), are advocated depending on the pancreatic ductal and parenchymal anatomy.

A recent randomized control trial (RCT) demonstrated that surgical approaches are more effective at eliminating pain and have more extended durability, thus reducing the need for repeated interventions when compared to endoscopic therapies. The creation of a longitudinal pancreatojejunostomy in functional diversion alleviates some of the exocrine insufficiency in CP; however, the retained native gland often leads to the recurrence of chronic pain and subsequent treatment failure. This pitfall also applies to the other types of partial pancreatectomies, such as the isolated resection of the pancreatic head (with or without duodenal preservation) or resection of the body/tail of the pancreas.

Total pancreatectomy (TP), which involves the excision of the entire gland, is often successful in eradicating the underlying cause of pain in CP. TP has historically been avoided due to the heightened risk of exocrine dysfunction and the difficulty in managing the brittle endocrine dysfunction associated with this procedure[10]. Subsequently, TP with islet autotransplantation (TPIAT) was introduced for the management of CP[11]. This procedure involves complete resection of the pancreas with trans portal islet cell transplantation (IAT)[12]. This comprehensive procedure has been postulated to eliminate the visceral source of pain along with a reduced risk of post-surgical DM. The use of concomitant IAT has been demonstrated to reduce or eliminate the need for exogenous insulin administration after a TP in many modern studies[13-16]. TPIAT has been reported to be more cost-effective than the medical management of CP in a recent single-center cost analysis. While it was initially recommended for adult patients with long-standing pancreatitis, TPIAT is now also being utilized in pediatric patients with CP and even in adults with intractable acute recurrent pancreatitis[17,18]. Although the open approach remains the standard, this surgical procedure has evolved over time, with some centers offering minimally invasive laparoscopic operative options.

Despite the emerging popularity of TPIAT for CP, the available data on the appropriate indications, procedural technique, and short and long-term outcomes-such as narcotic dependence and development of DM-is variable. Thus, we conducted a systematic review and meta-analysis of the available clinical trials to determine the overall outcomes of CP patients treated with TPIAT.

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## MATERIALS AND METHODS

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### **Search strategy and selection criteria**

We performed a comprehensive literature search in PubMed, EMBASE, and Cochrane databases from inception through March 2019, to identify all studies that evaluated post-procedural insulin or narcotic independence rates after TPIAT. We used the following keywords in different combinations for our search: Pancreatectomy, pancreatic resection, islet, autotransplantation, chronic, pancreatitis, insulin independence, narcotic independence, pain, outcome, and diabetes. The search was limited to human studies with no restrictions placed on region, publication type, or language. References of all included studies were manually searched for additional eligible papers.

### **Data extraction and quality assessment**

Two authors independently performed the literature review (SB and BE). The data from the included studies were entered into a standardized table for analysis. To be included, studies were required to meet the following criteria: (1) Implemented a well-defined RCT, case-control, cohort, or case-series design; and (2) either presented an odds ratio (OR) for our main outcomes with a 95% confidence interval (CI) or presented the data sufficient to calculate the OR with a 95%CI. Studies were excluded if they provided insufficient information to calculate the OR for narcotic independence, insulin-independence, or HbA<sub>1c</sub> levels 12 mo post-surgery. Studies were excluded if they were letters to editors, case reports, or review articles.

The quality of included studies was assessed independently by two of the authors (ZI and BE) using the Newcastle-Ottawa scale for cohort studies (Table 1) and the Murad tool for case series (Table 2), respectively[19,20]. Case series were considered of good methodological quality if they reported adequately on the domains of selection, exposure, outcome, and follow-up. Two authors (ZI and BE) addressed the discrepancies by joint evaluation of the original article.

### **Statistical analysis**

Statistical analysis was performed using the Comprehensive Meta-Analysis (CMA), Version 3 software (BioStat, Inc., Englewood, NJ, United States). Effect estimates from the individual studies were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird[21]. A random effect model was used as a high probability of between-study variance was suspected due to variation in the study population and methodology. A pooled OR was calculated. A Cochran's Q-test and an I<sup>2</sup> statistic were used to evaluate heterogeneity and quantify variation across the selected studies [22]. A funnel plot was then created to evaluate for publication and other reporting biases and then the plot was examined visually for asymmetry. Then, an Egger test for the asymmetry of a funnel plot was conducted. All authors had access to the study data and reviewed and approved the final manuscript.

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## RESULTS

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### **Search results**

Our initial comprehensive search yielded 280 citations. All citations underwent a title and abstract review, with the majority being excluded as duplicates, letters to editors, case reports, review articles, or unrelated to the study subject. Of our initial yield, 33 citations underwent a full-length article review. Of

**Table 1 Risk of Bias assessment for cohort studies using the Newcastle Ottawa Scale**

Ref.	Publish year	Study design	Q1 <sup>1</sup>	Q2 <sup>2</sup>	Q3 <sup>3</sup>	Q4 <sup>4</sup>	Q5 <sup>5</sup>	Q6 <sup>6</sup>	Q7 <sup>7</sup>	Q8 <sup>8</sup>	Total
Adult cohorts											
Argo et al[39]	2008	Cohort, R	*		*	*		*	*	*	***** (6)
Najarian et al[30]	1980	Cohort, R	*	*	*	*			*	*	***** (6)
White et al[31]	2001	Cohort, P	*	*	*	*	*	*	*	*	***** (8)
Mokadem et al[32]	2016	Cohort, R	*	*	*	*		*	*		***** (6)
Garcae et al[24]	2013	Cohort, P	*	*	*	*		*	*	*	***** (7)
Gruessner et al[33]	2014	Cohort, P	*		*	*		*	*	*	***** (6)
Wilson et al[15]	2014	Cohort, R	*		*	*		*	*	*	***** (6)
Sutherland et al[16]	2012	Cohort, R	*		*	*		*	*	*	***** (6)
Colling et al[35]	2017	Cohort, R	*	*	*	*	**	*	*	*	***** (9)
Ahmad et al[29]	2005	Cohort, R	*		*	*		*	*	*	***** (6)
Solomina et al[25]	2017	Cohort, R	*		*	*		*	*	*	***** (6)
Wang et al[36]	2013	Cohort, R	*		*	*		*	*	*	***** (7)
Bellin et al[18]	2016	Cohort, P	*		*	*		*	*	*	***** (6)
Rabkin et al[37]	1999	Cohort, R	*		*	*		*	*	*	***** (6)
Valente et al[41]	1985	Cohort, R	*		*	*		*	*	*	***** (6)
Wahoff et al[50]	1995	Cohort, R	*		*	*		*	*	*	***** (6)
Garcea et al[51]	2009	Cohort, P	*	*	*	*		*	*	*	***** (7)
Pediatric cohorts											
Sutton et al[44]	2010	Cohort, R	*		*	*		*	*	*	***** (6)
Chinnakotla et al[17]	2014	Cohort, R	*		*	*		*	*	*	***** (6)
Bellin et al[18]	2016	Cohort, R	*	*	*	*		*	*	*	***** (7)
Bellin et al[52]	2010	Cohort, R	*		*	*		*	*		***** (5)

<sup>1</sup>Representativeness of the exposed cohort.

<sup>2</sup>Selection of the non-exposed cohort.

<sup>3</sup>Ascertainment of exposure.

<sup>4</sup>Demonstration that outcome of interest was not present at the beginning of the study.

<sup>5</sup>Cohort comparability based on design.

<sup>6</sup>Assessment of outcome.

<sup>7</sup>Was follow-up long enough for outcomes to occur.

<sup>8</sup>Follow-up adequacy in terms of completeness.

R: Retrospective; P: Prospective; Q: Question.

these, 12 were excluded as review articles or did not provide sufficient information to calculate post-procedural insulin or narcotic independence rates in the studied populations. A flow diagram illustrates the selection process, in **Figure 1**. Consequently, a total of 21 studies met our inclusion criteria and were included in the meta-analysis. Published between 1980 and 2017, these papers included 1011 patients. Eighteen papers reviewed adult populations, while three studied pediatric populations (SM2). The baseline characteristics of the included studies and involved cohorts are summarized in **Tables 3 and 4**.

**Post-procedural insulin and narcotic independence rates**

Twenty-one studies examining 1011 patients were included in this study. Insulin-independence post-procedure was achieved in 31.8% (95%CI: 26-38,  $P < 0.05$ ,  $I^2 = 64\%$ ) of adults compared to 47.7% (95%CI: 20-77,  $P < 0.05$ ,  $I^2 = 82\%$ ) of children, **Figure 2**. Narcotic independence was achieved in 53.5% (95%CI: 45-62,  $P < 0.05$ ,  $I^2 = 81\%$ ) of adults compared to 51.9% (95%CI: 17-85,  $P < 0.05$ ,  $I^2 = 84\%$ ) of children (**Figure 3**). Glycated hemoglobin (HbA<sub>1c</sub>) 12 mo post-surgery was reported in four studies evaluating adult populations with a pooled value of 6.76% ( $P = 0.27$ ) (**Figure 4**).

**Table 2 Methodological quality of case series using the Murad tool**

Ref.	Year	Design	Q1 <sup>1</sup>	Q2 <sup>2</sup>	Q3 <sup>3</sup>	Q4 <sup>4</sup>	Q5 <sup>5</sup>	Q6 <sup>6</sup>	Q7 <sup>7</sup>	Q8 <sup>8</sup>	Overall quality
Fan <i>et al</i> [34]	2017	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good
Toledo-Pereyra <i>et al</i> [40]	1983	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good
Rossi <i>et al</i> [38]	1986	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good

<sup>1</sup>Does the patient(s) represent the whole experience of the investigator?

<sup>2</sup>Was the exposure (diagnosis) adequately ascertained?

<sup>3</sup>Was the outcome adequately ascertained?

<sup>4</sup>Were other alternative causes that may explain the observation ruled out?

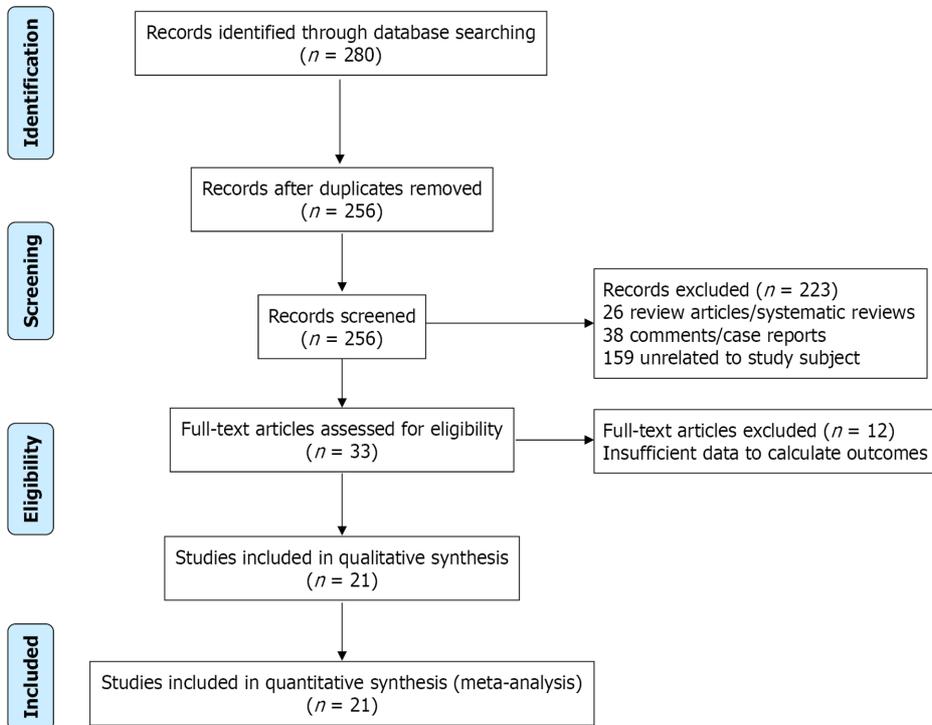
<sup>5</sup>Was there a challenge/re-challenge phenomenon?

<sup>6</sup>Was there a dose-response effect?

<sup>7</sup>Was follow-up long enough for outcomes to occur?

<sup>8</sup>Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

Q: question, Y: Yes, N: No, NA: Not available.



**Figure 1** Flow diagram illustrating the selection process.

**Evaluation for publication bias**

Funnel plots were generated to evaluate post-procedural insulin and narcotic independence. The plots are symmetric and do not suggest the presence of publication bias. Egger’s regression asymmetry testing was also done to demonstrate no evidence of publication bias ( $P > 0.05$ ).

**Sensitivity analysis**

Neither stratification by age of the studied population nor meta-regression analysis considering both the study publication date and the islet-cell-equivalent/kg weight were able to explain the marked heterogeneity between studies.

Table 3 Data summary of the included studies

Ref.	Study design	Data collected	Year published	Participants enrolled, <i>n</i>	Patients underwent TPIAT, <i>n</i>	Age, mean (SD)/range, yr	Female sex, <i>n</i> (%)
Adults							
Argo <i>et al</i> [39]	Retrospective cohort	2005-2007	2008	26	26	43.8 (2.1)	12 (46)
Najarian <i>et al</i> [30]	Retrospective cohort	1977-1980	1980	18	10	24-57	4 (40)
White <i>et al</i> [31]	Prospective cohort study	1994-1999	2001	37	24	44 (NA)	14 (58)
Mokadem <i>et al</i> [32]	Retrospective cohort	1998-2008	2016	70	57	39.9 (14)	32 (56)
Garcae <i>et al</i> [24]	Prospective cohort study	1990-2012	2013	97	60	43 (NA) 21-65	Unknown
Gruessner <i>et al</i> [33]	Prospective cohort study	2009-2013	2014	61	61	42.2 (1.6)	39 (64)
Fan <i>et al</i> [34]	Case series	2013-2015	2017	32	20	39 (13) 21-58	12 (60)
Wilson <i>et al</i> [15]	Retrospective cohort	2000-2013	2014	166	166	37.3 (1.1) 14-62	75 (67)
Sutherland <i>et al</i> [16]	Retrospective cohort	1977-2011	2012	409	409 <sup>1</sup>	35.3 (0.7) 5-69	301 (74)
Colling <i>et al</i> [35]	Retrospective cohort	2002- 2014	2017	59	59	Unknown	30 (51)
Toledo-Pereyra <i>et al</i> [40]	Case series	1979-1981	1983	6	6	35.5 (6.0) 28-41	1 (17)
Ahmad <i>et al</i> [29]	Retrospective cohort	2000-2004	2005	45	45	39 (NA) 16-62	30 (67)
Solomina <i>et al</i> [25]	Retrospective cohort	unknown	2017	20	20	41 (NA) 15-60	13 (65)
Wang <i>et al</i> [36]	Retrospective cohort	2009-2011	2013	76	76	42.1 (11.4)	Unknown
Bellin <i>et al</i> [18]	Retrospective cohort	2007-2013	2016	49	49	32.8 (7.8)	42 (86)
Rabkin <i>et al</i> [37]	Retrospective cohort	1994-1997	1999	5	5	42 ( NA)	4 (80)
Valente <i>et al</i> [41]	Retrospective cohort	unknown	1985	25	22	Unknown	Unknown
Rossi <i>et al</i> [38]	Case series	1981-1985	1986	10	10	34 (NA) 23-65	6 (60)
Wahoff <i>et al</i> [50]	Retrospective cohort	1977-1995	1995	48	48	35 (NA) 12-60	36 (75)
Garcea <i>et al</i> [51]	Prospective cohort study	1996-2006	2009	85	50	43 (NA) 21-65	26 (52)
Pediatrics							
Sutton <i>et al</i> [44]	Retrospective cohort	2000-2009	2010	188	118	31.4 (NA) 15-59	8 (50)
Chinnakotla <i>et al</i> [17]	Retrospective cohort	1989-2012	2014	75	75	13.8 (0.4)	42 (56)
Bellin <i>et al</i> [18]	Retrospective cohort	2000-2014	2016	17	17	6.8 (NA)	9 (53)
Bellin <i>et al</i> [52]	Retrospective cohort	1989-2006	2010	18	18	12.8 (4.08) 5.8-18.9	10 (55.6)

<sup>1</sup>Includes 53 children.

NA: Not available.

## DISCUSSION

When persistent abdominal pain in patients with CP becomes debilitating and the best medical management cannot stop the intractable pain, surgical intervention is indicated. Since first described by Sutherland *et al*[23] in 1978, TPIAT has shown promising results for patients with CP. Sutherland *et al* [23] hypothesized that by combining TP with IAT, TPIAT removes the primary pain source while maintaining endocrine function. TPIAT preserves insulin-secreting capacity and avoids post-surgical DM through the conservation of beta cell mass and C-peptide positivity[23]. In the years following the first-performed TPIATs, the procedure is being increasingly used for patients with CP and intractable pain[24]. QoL metrics show TPIAT as equal or superior to traditional TPs[24-27]. Morbidity and mortality metrics also support TPIAT as a safe and feasible procedure[28]. However, over this same time, minimal systematic evidence has been collected on metabolic function and pain control following TPIAT. In this paper, we present the most current meta-analysis to date and a systemic review of literature on insulin and narcotic independence after TPIAT.

Our study examined 1011 patients across 21 studies and found that 31.8% of adults were insulin independent after TPIAT[15,16,18,24,25,29-41]. Additionally, many patients who were not insulin-independent following TPIAT required only minimal amounts of exogenous insulin to achieve blood sugar control. HbA<sub>1c</sub> is 6.76% 12 mo post-surgery in four studies of 240 adult patients[15,18,34,37]. In total, these studies describe populations that vary by age, sex, and disease etiology. Data were collected on patients from two countries and nearly four decades to present the largest known meta-analysis to date on this topic.

Our analysis also reviewed insulin and narcotic independence after TPIAT in pediatric patients. The first TPIAT performed on a pediatric patient occurred in 1996[42]. Since, several authors have reviewed QoL, morbidity, and mortality metrics in this particular patient population. We identified studies that have reviewed insulin dependence after TPIAT in pediatric populations, totaling 181 patients[16,17,43,44]. Our research found 47.7% of children were insulin-independent post-TPIAT.

The majority of TPIATs were performed on patients with idiopathic CP (49.10%). Other common etiologies were genetically linked pancreatitis (21.10%), pancreatic divisum (11.60%), alcohol-induced CP (11.00%), and biliary tract disease (6.90%). Six percent of patients were insulin-dependent before TPIAT. Among pediatric patients, the majority of TPIATs were performed on patients with genetically linked CP (74.40%). Twenty-four percent of pediatric patients had idiopathic CP, and one pediatric patient had pancreatic divisum (0.44%).

Insulin independence and insulin requirements after TPIAT generally appear to correlate with higher islet yield, defined as the number of islet equivalents (IEs) transplanted per kilogram (kg) of recipient body weight[16,35,36,42,45,46]. However, overall TPIAT outcomes are likely multifactorial[31]. Several studies, including White *et al*[31], suggest additional factors may influence whether a patient achieves insulin independence after TPIAT: Prior pancreatic operations; poor islet yield due to pathogenic severity, calcification, and/or fibrosis; pathologic damage preventing islet purification of pancreatic tissue; toxic damage from reagents with high levels of endotoxins used in islet purification; the intraportal site being a suboptimal place for islet transplantation as it does not regulate insulin or glucose secretion; and chronic rejection of islet allotransplants[31,35].

Wang *et al*[36] showed that prior surgery is strongly correlated with pancreatic fibrosis and islet yield. Fewer islets are obtained from more fibrotic pancreases, because of both the disease process itself and increased difficulty in islet processing for transplant[36]. Prior history of pancreatic surgery may be used to predict postoperative islet function and determine the optimal timing for TPIAT surgery[36]. Sutton *et al*[44] make a similar observation regarding TPIAT in pediatric patients with genetically linked CP. Sixty-three percent of patients in Sutton *et al*[44] have the CFTR mutation. The authors advocate against trial resections or decompression surgeries before TP, as this treatment often compromises future endocrine function by limiting islet yield. None of the patients who had undergone previous pancreatic operations were insulin independent after TPIAT, and patients with previous pancreatic operations had approximately half the islet yield compared to patients without previous surgery.

The probability of TPIAT success is predicted by the morphologic features of the pancreas[42]. With plain films, ultrasonography, computed tomography (CT), or Endoscopic retrograde cholangiopancreatography (ERCP), Wahoff *et al*[42] suggest that the pre-operative prediction of the severity of the fibrosis helps estimate the number of islets available for autotransplantation. The severity of pain is notably an unreliable predictor of pancreas morphology and islets available for transplantation[42]. ERCP with transduodenal biopsy allows for assessing pancreas morphology directly and is likely the most useful means of evaluating islets pre-operatively[42].

Multiple papers suggest that women have better C-peptide positivity and glycemic control postoperatively because they often receive more IEs/kg. Univariate analyses by Ahmad *et al*[29] demonstrate that female gender, lower body weight, lower mean insulin requirements for the first 24 h postoperatively, and lower mean insulin requirements at the time of discharge are also associated with insulin

**Table 4** Data summary of the included studies (continued)

Ref.	Pre-operative diabetes, n (%)	Alcohol induced pancreatitis, n (%)	Biliary tract disease, n (%)	Idiopathic pancreatitis, n (%)	Genetic mutation, n (%)	Pancreatic divism, n (%)	Autoimmune pancreatitis, n (%)	Post-operative narcotic independence, n (%)	Post-operative insulin independence, n (%)	Mean percent glycosylated hga1c, %, (SD), range
Adults										
Argo <i>et al</i> [39]	Unknown	9 (35)	1 (4)	8 (31)	0	6 (23)	0	3 (60)	0 (0)	
Najarian <i>et al</i> [30]	0 (0)	6 (60)	1 (10)	3 (30)	1 (10) <sup>1</sup>	0 (0)	0 (0)	7 (78)	4 (40) at range 1-38 mo	
White <i>et al</i> [31]	0 (0)	8 (18)	2 (5)	13 (30) <sup>2</sup>	0 (0)	1 (2)	0 (0)	16 (77)	8 (33) transient/3 (13) at writing	
Mokadem <i>et al</i> [32]	0 (0)	4 (7)	2 (4)	19 (63)	0 (0)	5 (17)	0 (0)	9 (16)	4 (15)	
Garcae <i>et al</i> [24]	Unknown	19 (32)	5 (8)	31 (52)	0 (0)	0 (0)	0 (0)	27 (45)	11 (19)	
Gruessner <i>et al</i> [33]	Unknown	7 (11)	0 (0)	45 (73)	10 (16)	0 (0)	0 (0)	43 (71)	12 (19) at range 1-24 mo	
Fan <i>et al</i> [34]	Unknown	2 (10)	0 (0)	6 (30)	9 (45)	3 (15)	0 (0)	12 (60) at 6 mo	5 (25) at 12.5 mo	7.4 (0.5)
Wilson <i>et al</i> [15]	14 (13)	3 (3)	0 (0)	84 (75)	15 (13)	10 (9)	0 (0)	91 (55) at 1 yr /121 (73) at 5 yr	62 (38) at 1 yr/45 (27) at 5 yr	6.9 (0.3) 5.85-8.3
Sutherland <i>et al</i> [16]	32 (8)	27 (7)	36 (9)	169 (41)	58 (14)	71 (17)	0 (0)	241 (59) at 2 yr <sup>3</sup>	123 (30) at 3 yr <sup>4</sup>	
Colling <i>et al</i> [35]	3 (5)	0 (0)	2 (3)	6 (10)	49 (83)	4 (7)	0 (0)	35 (66) at 1 yr	19 (32) at 1 yr	
Toledo-Pereyra <i>et al</i> [40]	0 (0)	3 (50)	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)		2 (50) at 20 and 25 mo	
Ahmad <i>et al</i> [29]	1 (2)	2 (4)	0 (0)	39 (87)	1 (2)	8 (18)	0 (0)	23 (72) at 5 mo	18 (40) at mean 18 mo	
Solomina <i>et al</i> [25]	Unknown	0 (0)	0 (0)	3 (15)	13 (65)	3 (15)	1 (5)	18 (87) at 1 yr	8 (53) at 1 yr	
Wang <i>et al</i> [36]	11 (14)	Unknown	Unknown	Unknown	Unknown	Unknown	0 (0)	NA	31 (41) at 6 mo	
Bellin <i>et al</i> [18]	2 (4)	0 (0)	13 (27)	18 (37)	4 (8)	11 (22)	0 (0)	22 (46) at 1 yr	21 (45) at 1 yr	6.0 (0.9) at 1 yr
Rabkin <i>et al</i> [37]	0 (0)	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	3 (60)	4 (80)	3 (60) at median 23 mo	6.43 (1.50) 5.1-8.0
Valente <i>et al</i> [41]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	14 (64) at mean 5 yr	

Rossi <i>et al</i> [38]	Unknown	2 (20)	0 (0)	8 (80)	0 (0)	1 (10)	0 (0)	9 (90)	7 (70) at 2 yr	
Wahoff <i>et al</i> [50]	2 (4)	9 (19)	8 (16)	27 (56)	0 (0)	2 (4)	0 (0)	31 (81)	13 (34)	
Garcea <i>et al</i> [51]	0 (0)	18 (36)	5 (10)	24 (48)	0 (0)	0 (0)	0 (0)	30 (59.8) at 1 yr		
Pediatrics										
Sutton <i>et al</i> [44]	0 (0)	0 (0)	0 (0)	0 (0)	16 (100)	0 (0)	0 (0)	10 (63) at mean 22 mo	4 (25) at mean 22 mo	
Chinnakotla <i>et al</i> [17]	Unknown	0 (0)	0 (0)	21 (28)	41 (55)	0 (0)	0 (0)	13(17)	31 (41)	
Bellin <i>et al</i> [18]	0 (0)	0 (0)	0 (0)	2 (12)	14 (82)	1 (6)	0 (0)	17 (100)	14 (82)	
Bellin <i>et al</i> [52]	0 (0)	0(0)	1 (6)	7 (39)	7 (39)	3 (17)	0 (0)	11 (61) at median 2.5 (0.2-17.1)	11 (61) at 1 year or longer	6.40 (2.34) 5.0-12.5 at 4.5 (5.2); n = 8

<sup>1</sup>Unconfirmed.

<sup>2</sup>Two identified as idiopathic/trauma.

<sup>3</sup>61% in pediatric patients.

<sup>4</sup>25% in adults, 55% in pediatric patients.

RC: Retrospective cohort; PCS: Prospective control study; CS: Case series; TPIAT: Total pancreatectomy with islet autotransplantation; NA: Not available.

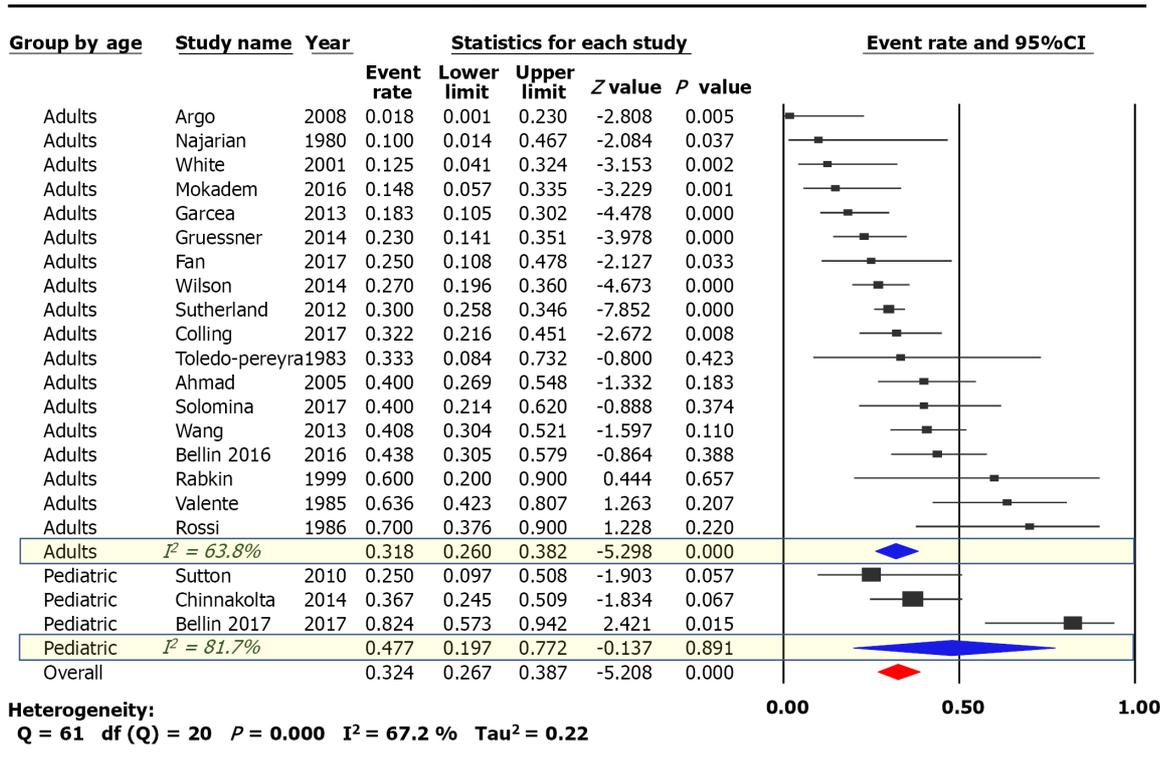
independence. Seventeen of 18 insulin-free patients were female in Ahmad *et al*[29]. Multiple logistic regressions including gender, body mass index (BMI), and IEs/kg found gender to be an important independent variable. In their series, men were heavier than women on average by 10 kg, and they explained these findings as the result of weight differences among the sexes, saying patients with increased BMI are less likely to benefit from TPIAT and ought to be counseled on losing weight before surgery as their likelihood of glycemic control afterward is associated with their BMI[29].

Insulin independence and insulin requirements after TPIAT appear to correlate with higher islet yield in pediatric patients as well[17,44]. Multivariate analysis by Chinnakotla *et al*[17], demonstrated male gender, lower body surface area, and higher total IEs/kg were associated with insulin independence after TPIAT in pediatric populations. Total IEs greater than 2500 IE/kg was the most strongly associated with insulin independence.

In addition to gender, BMI, and previous pancreatic operations, the amount of time between CP diagnosis and TPIAT procedure has been demonstrated to have a direct impact on islet yield[33]. Gruessner *et al*[33] discovered that outcomes improved when patients were referred at earlier disease stages, before surgical procedures, and after inadequate endoscopies. Gruessner *et al*[33] was the first paper to document fully robotically assisted TPIAT. They found that approximately 80% of their patients had undergone previous surgical procedures and that 91% had abnormal results on preoperative continuous glucose monitoring tests[33].

The auto-transplanted islet function appears to be durable[15,47]. Wilson *et al*[15] conducted one of the largest series reviewing long-term outcomes after TPIAT. The study found that insulin independence rates decline over time but that most patients maintain stable glycemic control past 13

Insulin independence after TPIAT



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Figure 2 Summary of event rates assessing insulin independence after total pancreatectomy with islet autotransplantation.

years post-operation and have minimal long-term complications associated with DM. Wilson *et al*[15] hypothesize that the toxic environment created by the liver is what ultimately contributes to declines in islet function over time.

While preservation of beta cell function is an important consideration, the success of TPIAT is ultimately determined by its ability to relieve pain and restore QoL in patients with CP[16]. Constant pain is the strongest predictor of poor QoL in patients with CP[48]. Relieving pain and reducing narcotic use is the primary objective of TPIAT[49]. In our meta-analysis, narcotic independence was achieved in 53.5% of adults post-TPIAT and 51.9% of children post-TPIAT[15-17,25,29,30,32-35,37,39,43,44,50-52].

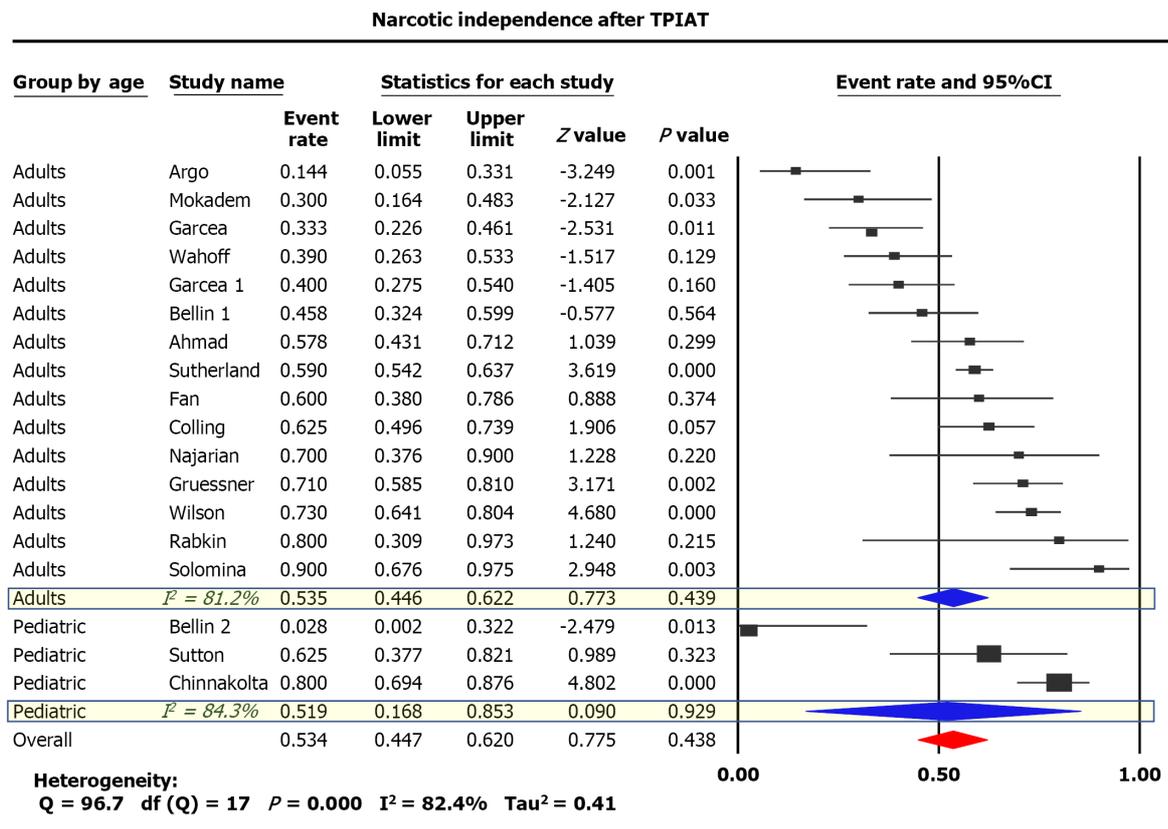
Some authors suggest that CP patients often have multiple comorbidities that cause pain after TP[53]. Patients with these additional comorbidities often require opioid analgesia beyond patients undergoing TP without comorbidities[53]. Additionally, long-term use of opioids can lead to dependence and addiction, causing long-term analgesic requirements[33,53].

Surgical intervention earlier in the course of the disease is associated with improved pain control and less narcotic use[26,54,55]. Interestingly, Bellin *et al*[18] demonstrated that TPIAT benefits even those without evident CP by improving QoL and reducing narcotic use. Patients with recurrent acute pancreatitis and limited surgical treatment options after medical and endoscopic therapy failed to remit their pain had outcomes similar to those patients with CP[18].

Several studies, including Colling *et al*[35], demonstrated that TPIAT can be an effective and safe treatment option for patients with cystic fibrosis (CF) and debilitating CP. Of note, these patients are likely at increased risk for pulmonary and luminal GI tract complications. Colling *et al*[35] had a cohort of 20 patients with CF and 19 CFTR carriers with TPIAT outcomes similar to other patient populations. Sutton *et al*[44] also demonstrated TPIAT was a successful treatment option in patients with genetically linked pancreatitis, finding narcotic independence rates of 63% and drastic decreases in narcotic requirements.

Fan *et al*[34] demonstrated that laparoscopic TPIAT (L-TPIAT) can be beneficial to CP patients as it reduced total operative and islet isolation time, shortened length of stay, and minimized the surgical pain spike compared to open and robot-assisted TPIATs. Fan *et al*[34] suggest reducing these metrics by performing L-TPIATs allows for opioid independence to be achieved more quickly. To Fan *et al*[34]'s point, Wilson *et al*[15] argue that minimizing warm ischemia time to the islets is one of the most important considerations during the operation.

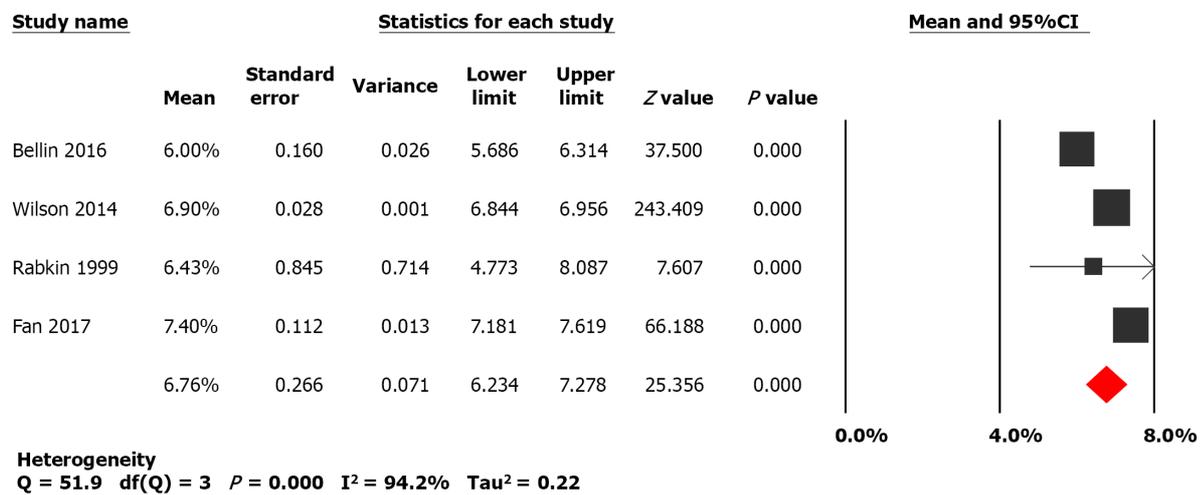
While our meta-analysis spanned 37 years, data on TPIAT outcomes remains sparse. Various researchers have used a variety of evaluative tools to evaluate pain after TPIAT, including visual analog



Random effects analysis

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Figure 3 Summary of event rates assessing narcotic independence after total pancreatectomy with islet autotransplantation.



Random effects analysis

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Figure 4 Pooled HgA<sub>1c</sub> means after total pancreatectomy with islet autotransplantation.

pain scores and inference scores. Treatment centers have followed patients for various lengths of time post-operatively, tracking their insulin independence at a variety of different post-operative times. Our meta-analysis draws on a large cohort of patients with CP undergoing TPIAT. The current study incorporates multiple treatment centers in two countries and a diversity of disease etiology, duration, and severity. We chose to evaluate the most objective data regarding post-operative pain and endocrine function: insulin and narcotic independence. As such, our meta-analysis uses the strengths of the available literature to maximize the reliability of our results.

## CONCLUSION

TPIAT produces acceptable levels of pain relief in patients with CP. Over half of patients were narcotic-independent post-operatively. Regaining endocrine function after TPIAT appears to be multifactorial as a majority of patients continue to remain insulin-dependent following surgery, albeit there is a substantial improvement in glycemic control as reflected by lower HBA1C levels in the postoperative period. Future studies should evaluate the discussed measures before and after surgery for comparison. Clear definitions of patient populations, surgical procedures as well as post-surgical care are needed to limit heterogeneity in outcomes. Long-term prospective studies will be needed to further examine the longevity of insulin and opioid independence.

## ARTICLE HIGHLIGHTS

### **Research background**

Debilitating abdominal pain and diabetes mellitus are hallmark clinical manifestations of chronic pancreatitis (CP). Current management strategies revolve around pain mitigation and treatment of endocrine failure. One available treatment option is total pancreatectomy with islet cell auto transplantation (TP-IAT). Although several studies have suggested a promising role of TP-IAT in CP patients; minimal systematic evidence has been collected on the effect of this procedure on endocrine failure and pain relief in patients with CP.

### **Research motivation**

Emerging data from multiple studies highlight that TP-IAT results in considerable pain relief and insulin independence; however, systemic evidence from high-quality studies is limited.

### **Research objectives**

We performed a systemic review and meta-analysis to evaluate clinical outcomes such as pain control and glucose intolerance following TP-IAT.

### **Research methods**

A comprehensive literature search spanning Pubmed, EMBASE, and Cochrane databases was performed from inception to March 2019. Studies conducted on outcomes of TP-IAT in patients with CP were identified. Comprehensive meta-analysis software was used to extract and analyze data. The random-effects model was used for all variables. Heterogeneity was assessed using the  $I^2$  measure and Cochrane Q-statistic. Publication bias was assessed using Egger's test.

### **Research results**

Our meta-analysis evaluated a total of 1100 patients across 21 studies. We found that TP-IAT results in narcotic independence in over 50% of adult and pediatric patients with CP. IAT results in meaningful islet cell function with insulin independence noted in almost one-third of adults and nearly half of pediatric patients following surgery.

### **Research conclusions**

TP-IAT results in acceptable narcotic independence and preservation of beta cell function.

### **Research perspectives**

Long-term prospective studies with clear definitions of patient populations, surgical procedures, and post-surgical care are needed to definitively evaluate insulin and narcotic independence before and after surgery.

## FOOTNOTES

**Author contributions:** Khazaaleh S and Babar S contributed to study design, data interpretation, manuscript writing, and administrative support; Alomari M contributed to literature review and data collection; Imam Z and Chadalavada AJ contributed to data assembly, and data analysis including statistical analysis and creating tables and graphs; Kurdi BE contributed to supervisory role, data interpretation and primary investigator; all authors contributed to the paper writing, and manuscript revision and approved the submitted version of this manuscript.

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