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ORIGINAL ARTICLE

Efficacy and safety of islet autotransplantation after total pancreatectomy in chronic pancreatitis: A systematic review and meta-analysis including 17 studies

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KEYWORDS
Islet;
Autotransplantation;
Pancreatectomy;
Pancreatitis

Summary
Aims: Islet autotransplantation (IAT), in conjunction with total pancreatectomy (TP), is used to relieve pain in patients with chronic pancreatitis (CP), while reducing the incidence of brittle diabetes. We aimed to evaluate the efficacy and safety of IAT after TP (TPIAT) in this setting.
Methods: We searched PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials since 1977. Data were extracted from published papers. Random-effects meta-analysis and meta-regression models were built to assess the outcomes and effect of different factors. Subgroup and sensitivity analyses were conducted to examine the between-study heterogeneity, which was assessed using Cochrane's Q and I^2 statistic.
Results: A total of 17 studies, including 1024 patients, met the eligibility criteria. The median cohort size was 21 patients (range: 5–409). The pooled incidence rates of insulin independence, narcotic independence and mortality at last follow-up were 11.47 per 100 patient-years (95% CI: 6.79–21.60, $I^2 = 91.0\%$), 18.11 per 100 patient-years (95% CI: 5.29–62.04, $I^2 = 98.8\%$) and 2.88 per 100 patient-years (95% CI: 1.75–4.74, $I^2 = 46.8\%$), respectively. However, the heterogeneity level of our results was high, which was due to differences in research methods and definitions of outcomes between studies. Therefore, our results should be interpreted with caution.

Abbreviations: TP, total pancreatectomy; IAT, islet autotransplantation; TPIAT, islet autotransplantation after total pancreatectomy; CP, chronic pancreatitis; NOS, Newcastle–Ottawa Scale; 95% Cis, 95% confidence intervals; HbA1c, glycosylated hemoglobin; NI, narcotic independence; II, nsulin independence; IEQ, islet equivalents; DM, diabetes mellitus; NR, not reported; PY, person-year.

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Conclusions: TPIAT can effectively relieve pain and reduce the risk of surgical diabetes with no increase in mortality or morbidity. Prospective, randomized, clinical trials are required to further evaluate selection of patients and the timing of TPIAT.

Introduction

Chronic pancreatitis (CP) is a persistent inflammatory disease that progressively destroys pancreatic exocrine tissue and is characterized by changes in the normal structure and function of the pancreas [1]. The main clinical manifestations of patients with chronic pancreatitis are intractable pain, pancreatic endocrine and exocrine insufficiency, and a variety of complications. The pain is often difficult to control with drugs, and excessive use of narcotic drug analgesia, often resulting in drug abuse. Most of the patients with CP are treated with alcohol, drugs for pain relief, nutritional support, and oral digestive aids. Some patients are treated with drainage and partial pancreatectomy at the later stage. Total pancreatectomy (TP) is an effective method to relieve intractable pain in patients whose symptoms cannot be alleviated after medical treatment and standard surgical treatment. However, TP alone will inevitably lead to irreversible dysfunction of endocrine and exocrine functions, and eventually develop into ''brittle diabetes'' [2].

Islet autotransplantation (IAT) provides a theoretical possibility to prevent this type of diabetes. IAT, in conjunction with TP, can not only relieve the intractable pain caused by CP, but also retain endocrine function of the pancreas and reduce the risk of diabetes mellitus [3]. In 1977, the University of Minnesota performed the world's first clinical IAT and achieved satisfactory results [4]. Since then, an increasing amount of clinical centers have begun to attempt TPIAT to treat CP. However, because of limitations of islet isolation technology and other factors, the amount of surgery carried out in a single-center is limited, and the published results are different. The efficacy and safety of TPIAT are still unclear.

Meta-analysis is a powerful statistical tool for overcoming the limitation of different sample sizes from individual studies and to generate the best estimation. In this study, we performed a systematic review and meta-analysis to estimate the rate of insulin independence, narcotic independence, mortality, and major complications of TPIAT.

Materials and methods

Study design

We performed the study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines and MOOSE guidelines [5,6]. This systematic review and meta-analysis was registered at International Prospective Register of Systematic Reviews (number CRD42019129102).

Search strategy

We searched PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials since 1977. The main search concepts were CP, pancreatectomy, TP, pancreatic resection and IAT. Additionally, we further manually searched the references of the relevant articles.

Inclusion criteria and exclusion criteria

Studies were eligible for inclusion if they fulfilled the following criteria:

- patients of any age who were diagnosed with CP before surgery;
- patients with CP who were treated with total, subtotal, or completion (> 95%) pancreatectomy followed by IAT;
- studies that contained at least one major outcome indicator.

The latest and most complete study was selected if multiple articles were published using the same cohort.

The exclusion criteria were as follows:

- patients with other diseases (malignant tumors, etc.) that affect survival;
- case reports or clinical studies of less than 5 people, or the mean or median follow-up time was less than 6 months;
- studies with insufficient data for estimating the incidence rate;
- repeated publications.

A study that met any of the four exclusion criteria was excluded.

Data extraction and quality assessment

Two independent reviewers used standardized data collection forms to extract the following information from each study: first author, year of operation, clinical research center, description of study participants, and the outcomes that we were interested in (e.g. rates of insulin independence, narcotic independence, mortality, and major complications). Any data discrepancy was resolved by referring back to the original studies.

Two investigators independently determined study eligibility and assessed the quality with a modified version of the Newcastle—Ottawa Scale (NOS) [7]. The NOS consists of three main areas:

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- selection process of cohorts;
- comparability of cohorts on the basis of the design or analysis;
- assessment of outcome of interest.

NOS scores of 6 or more were assigned as high-quality studies [7].

Statistical analysis

The measures used to present the outcomes of TPIAT were event rates (risk) for mortality, insulin independence, narcotic independence, and major complications. When we described the rates of mortality, insulin independence, and narcotic independence at last follow-up, the number of positive patients per 100 person-years was used to rule out follow-up length heterogeneity in different studies. In order to calculate the total person-times, either the sample size and mean (or median) follow-up per patient, or the sample size and cumulative incidence rate should be extracted. For each study, the natural logarithm of the incidence rate (number of positive cases/100 person-years) was estimated, along with the standard error $\left(1/\sqrt{positive\ \ cases}\right)$ [8]. When the number of positive patients was zero, we used a correction factor of 0.5 for both the number of positive cases and total person-years at last follow-up [8]. These measures were pooled across studies using a random-effects model and estimated from the reported 95% confidence intervals (95% CIs) [9]. Between-study heterogeneity was examined by Cochrane's Q and I^2 tests [10]. I^2 values of < 25%, 25%—50%, and > 50% represent minimal, moderate, and substantial heterogeneity, respectively. We conducted subgroup analyses on the basis of country and the NOS score (NOS < 6 and NOS ≥ 6). Sensitivity analysis and meta-regression were also applied to examine the origin of heterogeneity. Publication bias was assessed with Begg's and Egger's tests. Two-sided $P \leq 0.05$ was considered statistically significant. Stata/SE version 15.1 (Stata Corporation, USA) was used to conduct the meta-analysis.

Results

Study selection and patients' characteristics

We retrieved 1059 studies from the electronic database and the reference lists of the included studies. Seventeen studies were ultimately included, which involved a total of 1024 patients [11—27]. Detailed search results are summarized in

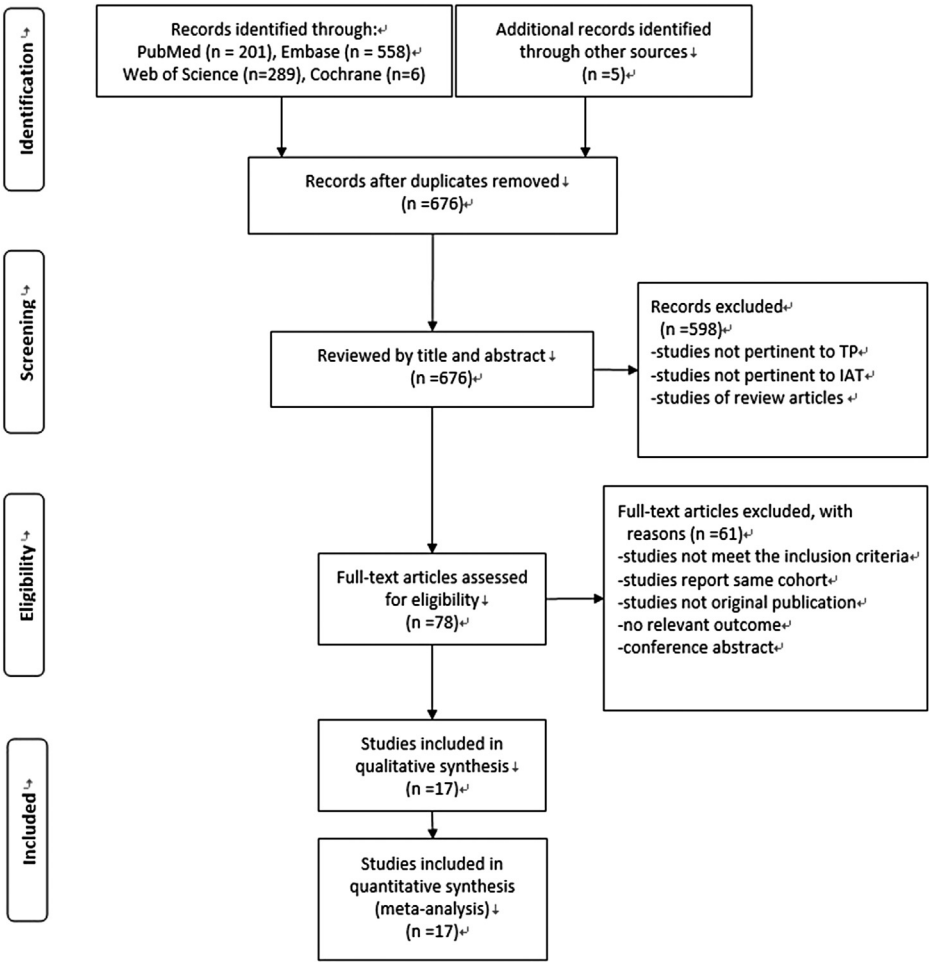

Figure 1 Flow diagram for study selection.

Table 1 Characteristics of patients with TPIAT in the included studies.

Studies	Year	Year of period	Country	Group	No. of patients	Age (years)	Female (%)	BMI (kg/m^2)	Duration of CP (years)	Baseline-DM (%)	Alcoholic (%)	Islet yield (IEQ/kg)
Cameron et al. [11]	1981	1978—1980	USA	Johns Hopkins	8	43.1 ± 10.9	13	NR	6.7	0	75	NR
Hinshaw et al. [12]	1981	1979—1980	USA	California	5	42.4 ± 5.7	20	NR	5.6 ± 3.8	20	80	NR
Rastellini et al. [13]	1997	1990—1996	USA	Pittsburgh Center	5	NR	NR	NR	NR	0	NR	NR
Oberholzer et al. [14]	2000	1992—1999	Europe	Geneva	6	NR	NR	NR	NR	NR	NR	2785 (386—3223)
Argo et al. [15]	2008	2005—2007	Europe	UAB	21	43.5 ± 2.4	40	22.0 ± 0.99	NR	100	30	1551 ± 363
Dixon et al. [16]	2008	1998—2008	USA	South Carolina	7	35	57	NR	NR	0	NR	NR
Sutherland et al. [17]	2012	1977—2011	USA	Minnesota	409	35.3	74	24.5	6.6	8	7	NR
Walsh et al. [18]	2012	2007—2010	USA	Cleveland Clinic	20	43 ± 13.3	40	NR	NR	0	25	3846 (3063—5430)
Garcea et al. [19]	2013	1990—2013	Europe	Leicester	60	43 (21—65)	NR	NR	5	NR	32	NR
Gruessner et al. [20]	2014	2009—2013	USA	Tucson	61	42.2 ± 1.6	64	26.6 ± 0.91	NR	NR	12	3048 ± 461
Tai et al. [21]	2015	2007—2013	USA	California	6	26.7	67	21.7	NR	NR	0	6359
Wilson et al. [22]	2015	2000—2014	USA	Cincinnati	64	38	72	23.5 ± 0.7	NR	14	8	4732 ± 492
Mokadem et al. [23]	2016	1998—2008	USA	Indiana	30	39.9 ± 14	80	NR	7	0	13	NR
Quartuccio et al. [24]	2017	2011—2016	USA	Johns Hopkins	34	39.3	62	24	NR	0	15	NR
Shahbazov et al. [25]	2017	2006—2014	USA	Baylor	73	41	68	26.2	6.2	NR	NR	5182
Solomina et al. [26]	2017	NR	USA	Chicago	20	41	65	26.4	8.5	10	NR	2980
Morgan et al. [27]	2018	2009—2017	USA	South Carolina	195	40.3	72	26.5	8.1	19	6	3253

TP: total pancreatectomy; IAT: islet autotransplantation; IEQ: islet equivalents; DM: diabetes mellitus; NR: not reported.

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Fig. 1. Most of the reasons for exclusion were the lack of effective information.

Patients' characteristics are shown in Table 1. Of the 17 studies, fourteen were performed in the United States [11—13,16—18,20—27] and three in Europe [14,15,19]. The mean age of the patients was 53 years, and 69.5% of participants were female. The follow-up ranged from 1—210 months. Preoperative diabetes mellitus status was found in 146 patients. The quality of the included studies was suboptimal (Supplementary table* 1) because most were single-center, small-sample case series. Only one study included a control group [19].

There was no evidence of publication bias (*P*-values for Begg's and Egger's tests for all outcomes were > 0.05, Supplementary table* 2). However, because the number of studies was less than 20, the publication bias tests were unreliable.

Outcomes of TPIAT in chronic pancreatitis

The outcomes reported by included studies are shown in Table 2 and the results of random-effects meta-analysis are shown in Table 3. Figs. 2—4 shows a meta-analysis of the incidence density of insulin independence, narcotic independence, and mortality at last follow-up, respectively. The results of the meta-regressions and the number of studies included in each analysis are shown in Table 4. Unfortunately, we could not include all of the studies because of missing data.

Insulin independence rate

The rate of insulin independence at 1 year was 33.29% (95% CI: 27.77—39.05%, I^2 = 32.3%) in 603 patients in eight studies [11,12,14,17,24—27]. The rate of insulin independence at last follow-up was reported in 15 studies that included 595 patients [11—16,18—25,27]. The rate of insulin incidence in individual studies ranged from 0—41.10 per 100 person-years. The incidence density of insulin independence was 11.47 per 100 person-years with high between-study heterogeneity (95% CI: 6.79—21.60, I^2 = 91.0%, Fig. 2). Subgroup analysis showed that the rate of insulin independence in the United States was significantly higher than that in Europe (Table 5). Notably, heterogeneity was present in American studies [11—13,16,18,20—25,27], but not in European studies [14,15,19]. Otherwise, the pooled insulin independence rate in low-quality studies was higher than that in high-quality studies.

Narcotic independence rate

Eleven studies reported preoperative use of narcotic drugs, and almost all patients were preoperatively dependent on narcotic drugs [11,12,15—19,21—23,26]. The incidence rate of narcotic independence postoperatively was 18.11 per 100 person-years (95% CI: 5.29—62.04, I^2 = 98.8%, Fig. 3) in 535 patients in 10 studies [11,12,16—20,22,23,25]. Subgroup analyses based on country and the NOS score were not statistically significant (Table 5).

Mortality

The 30-day mortality was 1.32% (95% CI: 0.68—2.16, I^2 = 0.0%) and the 1-year mortality was 2.54% (95% CI: 1.32—4.16, I^2 = 17.6%). The rate of mortality at last follow-up was reported in 13 studies that included 805 patients [11—18,21,23,25—27]. The incidence density of cumulative mortality was 2.88 per 100 person-years (95% CI: 1.75—4.74, I^2 = 46.8%) (Fig. 4). Subgroup analyses showed superior survival in American studies [11—13,16—18,21,23,25—27] compared with European studies [14,15], and showed that the region and quality score of studies may be a source of heterogeneity (Table 5).

Major complication rate

The incidence rate of major complications postoperatively was 28.5% (95% CI: 19.3—38.71, I^2 = 84.6%) in 838 patients in 11 studies [11,12,15,17—19,21—23,26,27]. This rate varied from 0%—62% in the different included studies.

Metabolic outcomes

The levels of glycosylated hemoglobin (HbA1c) at last follow-up were described in four studies with a mean or median of 7.72% [18], 6.8% [21], 7.8% [22], and 7.35% [23]. HbA1c levels at 6 months were reported by two studies, with mean values of 5.88% [14] and 7.5% [15]. Additionally, Solomina et al. reported that the median HbA1c level was 6.0%, 5.8%, and 6.0% at 1, 2, and 3 years, respectively [26]. Fasting C-peptide levels at 6 months were reported by two studies with mean values of 1.7 [15] and 0.91 ng/mL [22]. Sutherland et al. also reported that 90% of patients had C-peptide levels > 0.6 ng/mL at 3 years postoperatively [17]. Only two studies reported that the median fasting C-peptide level at last follow-up were 0.4 ng/mL [18] and 1.0 ng/mL [21]. The data of HbA1c and C-peptide levels were insufficient for a meta-analysis.

Sensitivity analysis

We conducted sensitivity analyses for the three primary outcomes by repeating the analyses with exclusion of studies one by one. Sensitivity analyses showed no significant source of heterogeneity (Supplementary Figs. 1—3).

Discussion

TP is an effective method for treating severe CP, but it inevitably causes brittle diabetes. Unlike other forms of diabetes mellitus, patients with pancreatic diabetes not only lack insulin, glucagon and other regulatory hormones are also significantly deficient. Therefore, metabolic-related complications easily occur [15]. Development of IAT can help to avoid severe hypoglycemic episodes that result in brittle diabetes, even when patients are not insulin independent [16]. However, the procedure of IAT is not without risk and it may cause bleeding and portal vein thrombosis. In recent years, many physicians have realized that insulin independence should not be the primary goal of patients with TPIAT,

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Table 2 Outcomes of interest.

Studies	No. of patients	Months	NI rate at last follow-up (%)	Mortality (%)			II rate (%)		Major complications postoperative	C-peptide at last follow-up (ng/mL)	HbA1c at last follow-up (%)
				30-day	1-year	Last	1-year	Last			
Cameron et al. [11]	8	NR	37.50%	13	NR	13	25	38	25	NR	NR
Hinshaw et al. [12]	5	13 ± 5.2	100%	0	NR	0c	67	40	20	NR	NR
Rastellini et al. [13]	5	3–64	NR	0	NR	0	NR	80	NR	NR	NR
Oberholzer et al. [14]	6	45.7 ± 17.5	NR	0	NR	50	50	0	NR	NR	NR (5.88 ± 0.84 at 6 months)
Argo et al. [15]	21	6.7 ± 1.7	NR	0	NR	0	NR	0	62	NR (1.7 ± 0.57, at 6 months)	NR (7.5 ± 0.47 at 6 months)
Dixon et al. [16]	7	NR	14%	0	NR	14	NR	20	NR	NR	NR
Sutherland et al. [17]	409	NR	49%	1.2	3	38	28	NR	15.9	NR (90% > 0.6 at 3 years)	NR
Walsh et al. [18]	20	12 (6.75–24)	30%	0	0	0	NR	20	45	0.4 (0.27–1.0)	7.72 ± 2.05
Garcea et al. [19]	60	138 (6–210)	45%	1.7	NR	NR	NR	18.6	53.3	NR	NR
Gruessner et al. [20]	61	1–24	71%	0	NR	NR	NR	19	NR	NR	NR
Tai et al. [21]	6	NR	NR	0	NR	0	NR	33.3	0	1.0	6.8
Wilson et al. [22]	64	23.4 (8.2–34.6)	51.6%	NR	NR	NR	NR	20	18.8	0.91, at 6 months	7.8
Mokadem et al. [23]	30	36 (6–120)	30%	NR	NR	10	NR	15	13.3	NR	7.35
Quartuccio et al. [24]	34	11.8 ± 2.1	NR	NR	NR	NR	29.4	29.4	NR	NR	NR
Shahbazov et al. [25]	73	12	50.7%	0	0	0	41.1	41.1	NR	NR	NR
Solomina et al. [26]	20	28 (2–38)	NR	0	0	0	53	NR	40	NR	6 (5.5–6.8), 1 year; 5.8 (5.5–6.2), 2 years; 6 (5.4–6.6), 3 years
Morgan et al. [27]	195	6–60	NR	1	3.6	6.7	29.2	23.1	19	NR	NR

NI: narcotic independence; II: insulin independence; NR: not reported.

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Table 3 Results of random-effects meta-analysis.

Outcomes of interest	Studies	Events	Total	Rate	95%CI	I^2%
II rate at the 1-year follow-up (%)	8	189	603	33.29	27.77—39.05	32.3
II rate at the last follow-up (100-PY)	15	141	595	11.47	6.79—21.60	91.0
30-day mortality (%)	14	9	896	1.32	0.68—2.16	0.0
1-year mortality (%)	5	19	717	2.54	1.32—4.16	17.6
Cumulative mortality at last follow-up (100-PY)	13	176	805	2.88	1.75—4.74	46.8
NI rate at the last follow-up (100-PY)	10	260	737	18.11	5.29—62.04	98.8
Major complications postoperative (%)	11	183	838	28.53	19.31—38.71	84.6

NI: narcotic independence; II: insulin independence; PY: person-year.

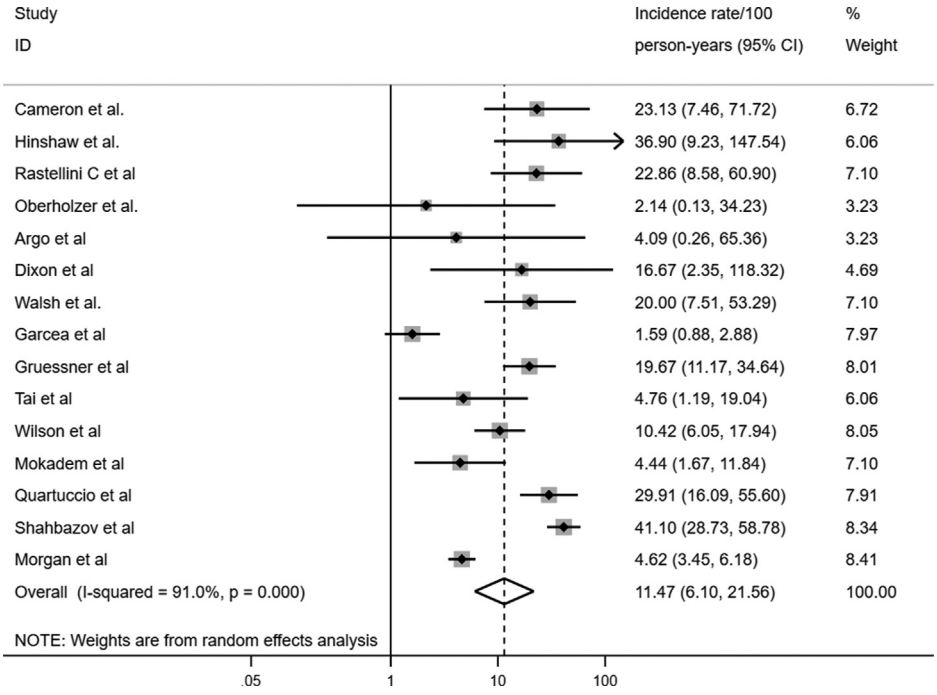

Figure 2 Pooled rate of insulin independence at last follow-up by random-effects meta-analysis. The incidence density of insulin independence at last follow-up was 11.47 per 100 patient-years (95% CI: 6.79—21.60, $I^2 = 91.0\%$).

Table 4 Results of meta-regression models.

Outcomes	Characteristics	No. of studies	No. of patients	*P*-value
II rate at last follow-up	IEQ/kg	8	446	0.565
	Baseline-DM	10	389	0.496
	Female (%)	12	524	0.101
	Alcoholic (%)	11	504	0.74
	Duration	6	371	0.963
NI rate at last follow-up	IEQ/kg	4	114	0.552
	Alcoholic (%)	8	222	0.891
	Female (%)	9	233	0.118
	Duration	6	182	0.859
Mortality at last follow-up	IEQ/kg	7	341	0.317
	Female (%)	11	794	0.127
	Duration	7	740	0.299

NI: narcotic independence; II: insulin independence; IEQ: islet equivalents; DM: diabetes mellitus.

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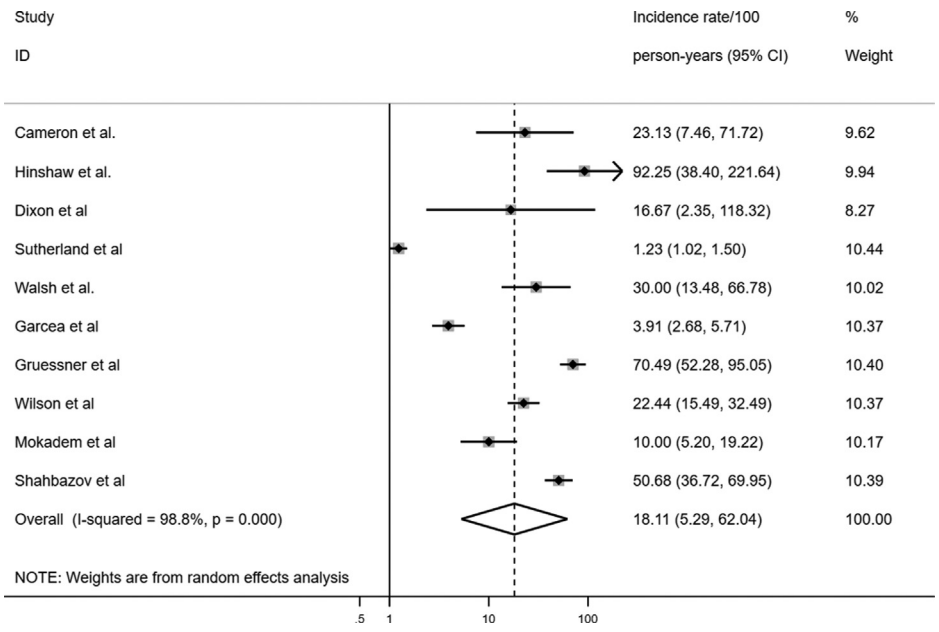

Figure 3 Pooled rate of narcotic independence at last follow-up by random-effects meta-analysis. The incidence density of narcotic independence at last follow-up was 18.11 per 100 patient-years (95% CI: 5.29—62.04, $I^2 = 98.8\%$).

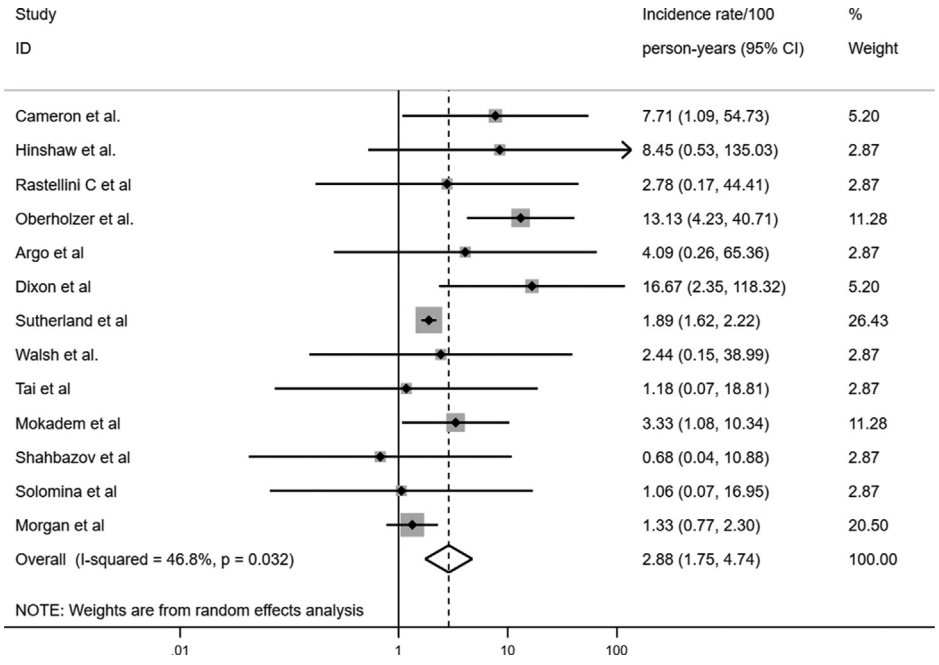

Figure 4 Pooled rate of mortality at last follow-up by random-effects meta-analysis. The incidence density of mortality at last follow-up was 2.88 per 100 patient-years (95% CI: 1.75—4.74, $I^2 = 46.8\%$).

but should be aimed at improving the quality of life [26]. By alleviating pain while preventing or minimizing surgical diabetes, the quality of life for patients with CP who undergo TPIAT can be improved [28]. A large number of studies have investigated the value of TPIAT in CP, but the efficacy and safety of this procedure are still inconclusive. Therefore, we conducted a meta-analysis of 1024 patients from 17 studies to derive a more precise estimation of TPIAT.

In this systematic review and meta-analysis, we found that the rate of insulin independence at last follow-up varied from 0%—80%. The rate of insulin independence in our analysis (11.47/100 person-years) is higher than that in previous studies [29,30]. Garcea et al. found a significant reduction in the daily insulin dosage at 8 years after an operation in patients with TPIAT compared with those who underwent TP alone [19]. The factors that may affect insulin independence are still unclear. Cincinnati and Minnesota's studies suggest that insulin independence correlates with islet yield [31,32]. Chinnakotla et al. also showed that low islet yield (< 2000 IEQ/kg) is the most significant risk factor for islet

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Table 5 Results of subgroup analyses.

Outcomes	Subgroup		No. of Studies	No. of patients	Subtotal		Overall	
					I^2%	*P*-value	I^2%	*P*-value
II rate at last follow-up	Country	USA	12	508	90.0	< 0.05	91.0	< 0.05
		Europe	3	87	0.0	0.796		
	The NOS score	NOS < 6	9	217	73.9	< 0.05		
		NOS ≥ 6	6	378	92.3	< 0.05		
NI rate at last follow-up	Country	USA	9	677	98.9	< 0.05	98.8	< 0.05
		Europe	1	60	—	—		
	The NOS score	NOS < 6	6	184	85.0	< 0.05		
		NOS ≥ 6	4	553	98.7	< 0.05		
Mortality at last follow-up	Country	USA	11	778	11.4	0.336	46.8	< 0.05
		Europe	2	27	0.0	0.445		
	The NOS score	NOS < 6	8	156	10.4	0.350		
		NOS ≥ 6	5	649	0.0	0.780		

NI: narcotic independence; II: insulin independence.

failure [33]. Additionally, Quartuccio et al. showed that preoperative β-cell function was the most robust predictor of insulin independence, which was measured by HOMA-beta (calculated by fasting glucose and insulin values) [24]. These authors concluded that a preoperative low-level oral glucose tolerance test was of great significance in predicting insulin independence. The degree of histopathological changes, preoperative C-peptide levels, and early surgical history are considered to be related to islet yield [34,35]. Patients who undergo a previous Frey or Puestow procedure have difficult in achieving high islet yields because it may make islet isolation more difficult [22]. Morgan and colleagues demonstrated that patients with prior pancreatic surgery were more likely to require insulin postoperatively because of lower islet yield [27]. However, our meta-regression showed no significant correlation between insulin independence and any of these factors. Differences in isolation and purification techniques of islets from different centers also have an important effect on islet yield. Therefore, a uniform standard is required to eliminate the heterogeneity of technological sources.

Disappearance of pain is important for improving the quality of life of patients with CP [36]. The rate of narcotic independence in our analysis ranged from 14% to 100%. With a lack of pain, patients can return to school, pursue a successful career, establish a happy family, and enjoy life. Intrathecal narcotic pump infusion is a relatively mild new technique that can produce similar analgesic effects compared with TPIAT (77% vs. 80%), but it has better glycemic control at the same time [23,37]. However, more cases and longer follow-up are required to verify this conclusion. For patients with CP, pre-TPIAT use of narcotics for chronic pain may lead to increased sensitivity to pain. Therefore, achieving complete narcotic independence after an operation is difficult. This indicates that the narcotic independent rate may not be the most accurate reflection of postoperative pain relief [38]. The difference in pain sensitivity between different patients can also partly explain the high heterogeneity of the pooled narcotic independent rate.

In our analysis, the 30-day mortality rate varied from 0%—13%. The incidence density of last follow-up mortality was 2.88 per 100 person-years. Compared with TP alone, TP with IAT not only reduced insulin requirements, but also conferred a survival advantage. Garcea et al. found that the difference in survival between TP without IAT and TP with IAT was statistically significant (12.9 vs. 16.5 ears, $P = 0.011$) [19]. Previous studies have shown that the incidence of major complications after TPIAT is similar to that of other pancreatic operations [39]. In our meta-analysis, the overall pooled incidence of major complications in patients with TPIAT was 28.53%. Common postoperative complications included bleeding, anastomotic leakage, abdominal abscess, and wound infection [15,19]. In islet transplantation, bleeding is the most common complication, which is associated with high portal pressure during injection [17]. Because of the different criteria for grading the severity of complications in different research groups, there is likely to be bias in outcome reporting.

Our systematic review and meta-analysis has the following advantages. Our study included 1024 patients from 17 studies, and the results of this sample size are somewhat more likely to be credible. Compared with previous studies [29,30], our insulin independence rate at last follow-up was more than twice that of the previous insulin independence rate, which could possibly be explained by the fact that we added several recent studies into our study. Additionally, the present review pooled the rates of narcotic independence and major postoperative complications, which were more comprehensive in assessing the safety and effectiveness of TPIAT. Previous studies ignored these indicators. Furthermore, we only included patients with CP who were treated with total, subtotal, or completion (95%) pancreatectomy followed by IAT. This maximized the effect of residual pancreatic tissue on insulin independence and metabolic-related complications after surgery.

Our study also has several limitations. Firstly, the main limitation of our research is high heterogeneity, which greatly affected our pooled results. Although we

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conducted subgroup analyses, sensitivity analyses, and meta-regression, we failed to determine the causes of heterogeneity. The incidence rates are sensitive to selection of participants and the duration of follow-up. Therefore, potential heterogeneity for descriptive epidemiological studies is much greater than that for other studies. Secondly, the studies that we included were all non-randomized controlled studies, and the level of evidence in such studies was relatively low. Most studies lacked a comparative cohort and had relatively small-sample sizes. Because of significant and unexplained heterogeneity ($I^2 > 50\%$) and methodological differences between studies, our results pose a great risk of random and systematic errors. Thirdly, the differences in surgical indications and timing in different periods have a great influence on the results of the article. Early surgery may not be considered until the late stages of the disease, resulting in differences in surgical outcomes at different periods. There is no doubt that insulin independence is affected by islet isolation techniques in different centers, and mortality is closely related to the severity of the patient's condition before surgery, which may also lead to differences in the outcomes of different studies. Inconsistent reporting also limited our ability to estimate the effect of preoperative indicators on surgical outcomes. Further individual patients' data in a meta-analysis might be able to address these issues.

Conclusion

TPIAT can effectively relieve pain and reduce the risk of surgical diabetes with no increase in mortality or morbidity. Even if patients cannot achieve insulin independence, they can significantly improve the quality of life. However, the outcomes of TPIAT differ in patients with CP. Therefore, a multidisciplinary team approach is necessary to evaluate the risk and benefit before the operation. Prospective, randomized, clinical trials are required to further evaluate selection of patients and the timing of TPIAT.

Authors' contributions

Conception and design of the study: Ya-Jun Zhang.

Generation, collection, assembly, analysis, and/or interpretation of data: Dan-Dan Duan, Hang Yuan, Ya-Jun Zhang.

Drafting of the manuscript: Ya-Jun Zhang.

Revision of the manuscript: Dan-Dan Duan, Hang Yuan.

Approval of the final version of the manuscript: Ya-Jun Zhang, Dan-Dan Duan, Hang Yuan.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2019.08.004.

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