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ABOUT COVER

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MINIREVIEWS

COVID-19 in liver transplant patients: Impact and considerations

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Abstract

The coronavirus disease 2019 pandemic has significantly impacted liver transplantation worldwide, leading to major effects on the transplant process, including the pretransplant, perioperative, and post-transplant periods. It is believed that patients with chronic liver disease, especially those with cirrhosis, have a higher risk of complications from coronavirus disease 2019 infection compared to the general population. However, evaluation of coronavirus disease 2019 effects on liver transplant patients has not uniformly demonstrated worse outcomes. Nonetheless, the pandemic created significant challenges and restrictions on transplant policies and organ allocation.

Key Words: COVID-19; Liver transplantation; Immunosuppression; Living donor; Mortality

Core Tip: The coronavirus disease 2019 pandemic exerted significant challenges to the liver transplant structure worldwide, initially resulting in a decline in liver transplants but soon after rebounded. A better understanding of this infection together with robust guidance by the international transplant societies helped offset this decline. A multitude of considerations should be exercised throughout the liver transplant process to maintain acceptable safety and outcomes.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic was declared an emergency by the World Health Organization in March 2020[1]. Since then it has had major impacts on many aspects of healthcare, including liver transplant in the United States. It greatly affected the pretransplant, perioperative, and post-transplant periods of liver transplantation.

It is widely accepted that patients with chronic liver disease, specifically those with cirrhosis, have a higher rate of hospitalization, length of hospital stay, morbidity, and mortality from COVID-19 infection compared to the general population[2]. In a large meta-analysis that included 40 studies primarily from the United States and China with more than 900000 participants, COVID-19 patients with chronic liver disease had higher odds of developing a severe infection [pooled odds ratio (OR) = 2.44; 95% confidence interval (CI): 1.89-3.16] and mortality (pooled OR = 2.35; 95%CI: 1.85-3.00) when compared to COVID-19 patients without chronic liver disease[3].

In contrast, literature evaluating COVID-19 effects on liver transplant recipients did not consistently demonstrate worse outcomes[4,5]. A systematic review of 1522 liver transplantation recipients who were infected with COVID-19 did not find a difference in cumulative incidence in mortality compared to patients who were not liver transplantation recipients. Additionally, the review did not find a difference in mortality between non-liver transplantation recipients *vs* liver transplantation recipients in patients who received a liver transplantation within 1 year *vs* 1-year post-transplant[4]. Still, the COVID-19 pandemic added significant challenges and restrictions to transplant policies and organ allocation. The healthcare structure was overwhelmed by critically ill patients with COVID-19 resulting in diversion of medical resources away from liver transplantation[6]. Furthermore, early concerns of patients contracting severe COVID-19 infection in light of immunosuppression discouraged their use. These uncertainties culminated in initial hardships in the overall management of patients with chronic liver disease thereby negatively affecting liver transplantation.

To revive the liver transplant process and provide organs for those in dire need, significant changes in liver transplant practice have been implemented per major transplant societies' recommendations[7]. After an initial drop in the number of liver transplants performed in the United States in early 2020, a quick recovery in the latter half of 2020 and early 2021 followed[8]. This was likely due to better understanding of COVID-19, improved adherence to infection prevention recommendations, and replenished healthcare resources. Later, COVID-19 vaccination emerged as an efficient and cost-effective preventive strategy for patients with chronic liver disease, further helping to offset COVID-19-related shortcomings[9].

This comprehensive review discussed the major aspects and effects of the pandemic on the liver transplant process as a whole.

COVID-19 INFECTION IN PATIENTS WITH CIRRHOSIS

Pathogenesis

The liver is prone to direct COVID-19 infection because of expressed angiotensin-converting enzyme 2 receptor in the hepatobiliary epithelial cells. Although not fully understood, it is hypothesized that binding of the virus spike protein to angiotensin-converting enzyme 2 receptors allows viral entry and subsequent host cellular damage[10]. Indirect hepatotoxicity may occur due to hemodynamic instability, drug-induced liver damage, COVID-19-induced immune dysfunction, coagulopathy, and intestinal dysbiosis[11]. Moreover, since the angiotensin-converting enzyme 2 receptors are also expressed on cholangiocytes, some suggest that COVID-19 infection may worsen cholestasis in patients with primary biliary cholangitis and primary sclerosing cholangitis[12].

Clinical presentation

Similar to patients without underlying liver disease, patients with cirrhosis typically develop mildly elevated aminotransferase levels (< 5 times the upper limit of normal); nevertheless, severe acute hepatitis and even acute liver failure have also been reported[13]. Commonly, a pattern of aspartate transaminase greater than alanine transaminase is associated with disease severity[14]. Likewise, a low albumin level is linked to worse COVID-19 disease severity. It is unknown if this is just a marker of disease severity or merely a risk factor for severe disease.

In patients with cirrhosis, COVID-19 infection may result in hepatic decompensation, similar to other infections. In a retrospective, multicenter study from 13 Asian countries, 29% of COVID-19 patients with chronic liver disease presented with hepatic decompensation[15].

Histopathological findings

Liver biopsy in patients with COVID-19-induced liver injury is nonspecific. Histopathological changes include microvesicular steatosis, portal and lobular activity, and zone 3 focal necrosis[16,17]. In an autopsy-based series that included 48 cases, liver histologic findings included variable degrees of parenchymal lymphocytic infiltration in almost all patients and hepatic vascular alterations in some cases[18]. In our opinion, performing a liver biopsy does not add diagnostic benefit unless an alternative diagnosis is considered.

Clinical outcomes

A significant body of research suggests increased mortality in COVID-19 patients with chronic liver disease. According to a multicenter, observational study from the United States, the presence of cirrhosis in those with COVID-19 infection was associated with higher mortality when compared to those without cirrhosis (relative risk: 4.6, 95%CI: 2.6-8.3)[19]. In a database study of COVID-19 patients with chronic liver disease, after adjusting for relevant confounders, the presence of cirrhosis was associated with higher 30-d mortality compared to those without cirrhosis (8.9% *vs* 1.7%; 95%CI: 2.91-3.77)[20]. A subsequent cohort study found that COVID-19-related mortality increased with cirrhosis progression; patients with Child-Pugh class B or C cirrhosis were found to have increased mortality (OR = 4.90, 95%CI: 1.16-20.61 and OR = 28.07, 95%CI: 4.42-178.46, respectively). Mortality was mostly attributed to pulmonary complications (79%), whereas liver-related mortality was seen in 12% of patients[21].

A rare but important long-term sequela of severe COVID-19 is cholangiopathy, at times resulting in progressive biliary destruction and liver failure requiring liver transplantation[22]. In a retrospective study by Faruqui *et al*[22] on patients hospitalized for severe COVID-19, 12 patients ultimately developed some degree of cholangiopathy defined by evidence of cholestasis (alkaline phosphatase ≥ 3 upper limit of normal) or radiologic biliary abnormalities. The majority were male (92%) with a mean time of cholangiopathy diagnosis of 118 d from COVID-19. One patient underwent liver transplantation.

Management

COVID-19 management in patients with cirrhosis follows the same supportive routine measures for the general population, including the use of COVID-specific drug therapy. Deranged liver biochemistries are not an absolute contraindication to using therapy such as remdesivir. Remdesivir use alone can cause a further elevation in liver enzymes (up to 10 times the baseline)[23]. However, its use is discouraged if the alanine transaminase level is ≥ 5 upper limit of normal[24]. Although Paxlovid (combination nirmatrelvir and ritonavir) trials did not show any concerns about its use in cirrhotic patients, it is extensively metabolized by liver cytochrome P450 enzymes. Thus, this drug harbors the risk of accumulation and toxicity in patients with decompensated cirrhosis. We think this medication should be used judicially and in collaboration with infectious disease specialists.

The use of COVID-19 monoclonal antibodies is encouraged early in the infection course in cirrhosis. This is particularly important because cirrhotic patients tend to mount suboptimal humoral responses to COVID-19 vaccination and likely infection as well. Other immunomodulatory COVID-19 therapies include JAK inhibitors (baricitinib) and IL-6 receptor antagonists (tocilizumab)[25]. We learned from baricitinib use in rheumatological disorders that it may cause liver biochemistry abnormalities, and caution and regular monitoring should be exercised[26]. Additionally, the risk of hepatitis B virus reactivation has been documented with both baricitinib and tocilizumab; therefore, obtaining hepatitis B serology before treatment initiation is warranted to assess the need for prophylactic nucleoside analogue therapy[27].

Prevention

Adherence to general preventive measures to avoid COVID-19 in patients with cirrhosis is paramount. These include social distancing, hand hygiene, proper use of personal protective equipment, and telemedicine clinic visits[28]. It is strongly recommended for patients with cirrhosis to receive the COVID-19 vaccine[9]. In a prospective, multicenter study aimed at comparing the humoral response to the COVID-19 vaccine between patients with chronic liver disease (437 individuals) and healthy controls (144 individuals), chronic liver disease was associated with lower rates of post-vaccination COVID-19 antibody positivity (77% *vs* 90%, $P = 0.008$). The rate of antibody positivity was similar among patients with chronic liver disease regardless of cirrhosis presence or even decompensation ($P = 0.894$)[9]. These findings suggest additional doses of COVID-19 vaccine might be warranted in this high-risk patient population to achieve adequate immunity[29]. In a propensity score-matched cohort study of United States veterans with cirrhosis, receiving only one dose of the COVID-19 vaccine (either Pfizer BNT162b2 mRNA or a Moderna mRNA-1273) resulted in a 64.8% reduction in COVID-19 infection and 100% prevention of hospitalization or mortality due to COVID-19 infection after 28 d[30].

PRETRANSPLANT IMPACT AND CONSIDERATIONS

Effect on liver transplant volume

The United States performs the most liver transplants worldwide per year. The second-leading country in the number of liver transplants performed is China, followed closely by Brazil[31]. Currently, over 9000 liver transplants are performed every year in the United States. For the past 9 years, the number of annual liver transplants has increased steadily, setting annual records[32]. Despite the challenges of the COVID-19 pandemic, the year 2020 was no different, as we witnessed an increase of 10.1% in deceased donor liver transplantation. The major impact the pandemic had was on living donor liver transplants, which suffered a significant decline of 22% between February and April 2020. The liver transplants performed in the United States between 2018-2021 is depicted in Figure 1[33].

During the height of the pandemic, non-urgent liver transplantation was deferred to conserve hospital resources. Since the Centers for Medicare and Medicaid services have classified organ transplantation as a tier 3b activity, liver transplant centers were urged to continue the process similar to before the pandemic[34]. However, patients had to wait longer to receive a liver transplant during the pandemic, especially for living donor liver transplants. There is data suggesting that patients who were wait-listed for other solid organ transplantation, such as kidney transplant patients, had worse outcomes with a higher risk of hospitalization and death compared to patients who got the transplant sooner[35]. Data on liver transplant patients is lacking in this regard. The COVID-19 effects on liver transplant-listed patients are highlighted in a special online report by the United Network for Organ Sharing[36] (Figure 2).

On the other hand, the recent changes in the organ allocation system helped offset some of the COVID-19 challenges. As a replacement for geographic areas, nautical miles are now utilized. Priority for receiving organs is triaged by medical urgency within a concentric circle radius of 150, 250, and then 500 nautical miles. While this new policy is imperfect as it better serves well-occupied areas in the center of the United States when compared to other coastal areas, it indeed improved access to solid organs across the country[37].

COVID-19-positive liver transplant donors and candidates

The American Society of Transplantation guidelines and Organ Procurement and Transplantation Network formulated guidelines on using COVID-19-positive donors. The consensus early in the pandemic was to avoid liver transplants in active donor-positive situations due to the risk of developing acute respiratory distress syndrome or COVID-19-related thrombosis. However, given the high prevalence of the virus in the community, some transplant centers started transplanting patients with donor positivity in emergent situations.

In one Italian study, 17 liver transplant patients were studied for more than 1 year from their transplant with a COVID-19-positive donation. One patient tested positive 21 d after transplantation. However, no patients experienced severe complications from COVID-19[38]. Of note, post-transplant immunosuppression was not adjusted, and there was no use of anti-COVID-19 therapy after the transplant. It is important to mention that this study was limited by the small sample size but provided hope for patients receiving a liver transplant from COVID-19-positive donors.

Concern regarding the blood-borne transmission of COVID-19 during liver transplantation discouraged living donor liver transplants during the initial period of the pandemic. However, studies showed that, unlike lung transplant recipients, the risk of transmitting donor-derived COVID-19 infection was not likely in liver transplant patients[39]. Blood-borne transmission does not pose much risk as the degree of COVID-19 viremia is low[40].

Current literature also suggests a higher risk of contracting COVID-19 infection among healthcare providers compared to the general population[41]. Organ donation from a COVID-19-positive patient also has the risk of exposing all transplant team health professionals who typically work closely with other high-risk cirrhotic patients. On the occasion of transmitted COVID-19 infection to medical staff, self-isolation will exert further strain on healthcare staffing and resources. It is therefore imperative to assess the risks and benefits of using organs from a potential COVID-19-infected donor.

Liver transplant centers across the nation have developed their protocols and policies to manage listed patients having COVID-19 infection[42]. This is to ensure maximum benefits for their patients and to cause no harm. In our center, for example, listed patients who are infected with COVID-19 are temporarily inactivated until they are symptom-free and 3 wk have elapsed since their diagnosis. Moreover, we often perform a contrast-enhanced computed tomography of the chest and pulmonary function tests if the patient had respiratory symptoms prior to reactivation. On the contrary, if the patient did not develop any respiratory symptoms, they are reactivated without any further testing.

Ethical considerations

Fair allocation of liver grafts, possibly the scarcest organ of all, remains an ethical question in those with active COVID-19 infection[43]. The main principle of allocation is to achieve the greatest good for both the patient and the community. While benefiting those needing livers is likely to result in improved survival and health of patients and grafts, real risks of increased mortality or significant surgical

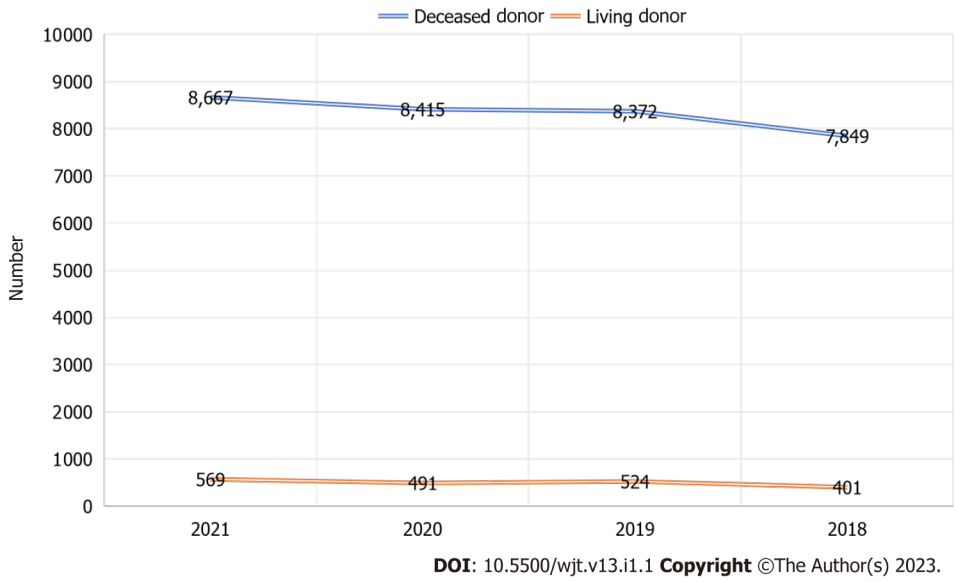

Figure 1 The Organ Procurement and Transplantation Network report of liver transplants by donor type between 2018-2021.

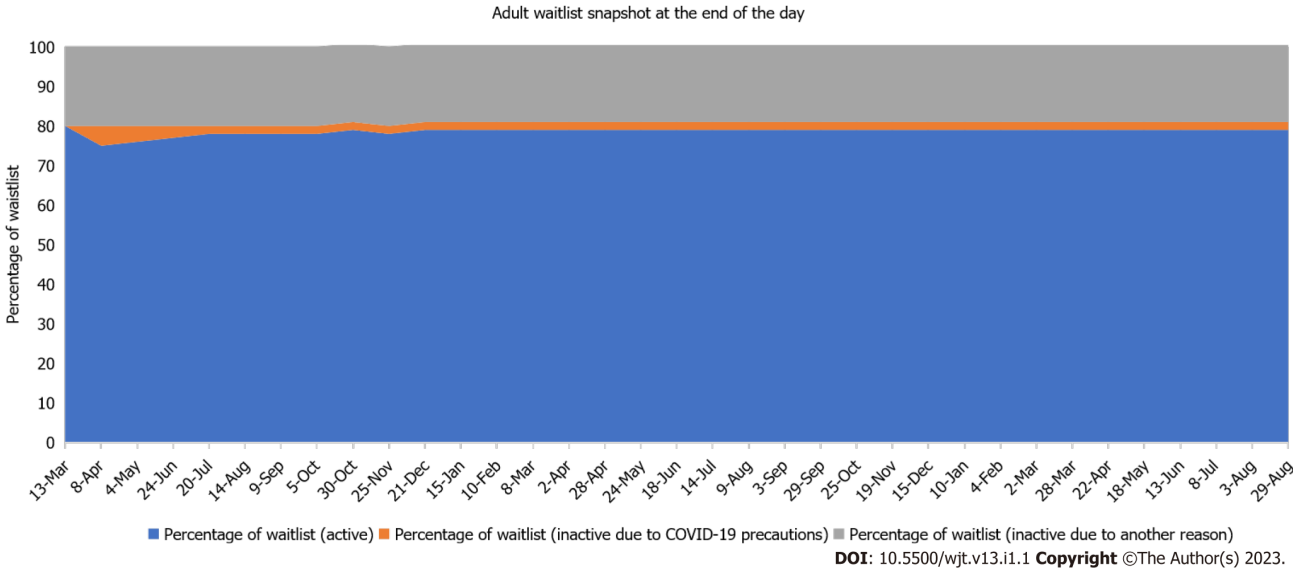

Figure 2 United Network for Organ Sharing special report of adult liver transplant waitlist showing coronavirus disease 2019 effects between March 2020 to August 2022. COVID-19: Coronavirus disease 2019.

complications exists in those with active COVID-19 infection. Considering the uncertainty regarding outcomes of liver transplant in candidates with active COVID-19 infection, these vital organs are better redirected to more suitable candidates with a higher chance of benefit pending infection resolution[44].

Additionally, it is important to note that exposure of health care providers to infected transplant patients continues to significantly burden hospital structures throughout the country. The ethical principles of justice and utility should dictate the just allocation of organs to those who would get the greatest benefit[45].

POST-TRANSPLANT IMPACT CONSIDERATIONS

Risk in liver transplant recipients

The post-transplant risk of COVID-19 is the risk of acquiring severe infection as a solid organ recipient on chronic immunosuppression with an inherent risk of prolonged viral shedding. The Spanish Society of Liver Transplantation found that liver transplant recipients may have double the risk of acquiring COVID-19 within an epidemic scenario (standardized incidence ratio: 191.2; 95%CI: 190.3-192.2) as

compared to an age and sex-matched cohort[46]. A 2022 prospective double-center study from southern Italy followed 30 liver transplant recipients who were infected with COVID-19 and found that liver transplant recipients were more often symptomatic but did not have an increased risk for hospitalization or mortality[47].

Clinical presentation and outcomes

The clinical presentation reported in observational studies included fever (61.4%), cough (58.6%), and dyspnea (36.2%)[48]. Webb *et al*[49] reported that gastrointestinal symptoms were common (27.9%). Interestingly, the liver transplant recipients had more gastrointestinal symptoms compared to the control group (30% *vs* 12%, $P < 0.0001$), whereas no significant difference was observed in respiratory symptoms. The same study compared outcomes of COVID-19 infection between those who underwent liver transplant (124 patients) and matched cohorts (474 patients). No difference in hospitalization (82% *vs* 76%, $P = 0.106$) or need for intensive care unit (31% *vs* 30%, $P = 0.837$) were observed. Overall, 28 (19%) patients in the liver transplant cohort died compared to 167 (27%) patients in the matched cohort ($P = 0.046$).

In a meta-analysis and systematic review by Kulkarni *et al*[4], which included 18 studies with a total of 1522 COVID-19-infected liver transplant recipients, there was no difference in mortality between liver transplant and non-liver transplant COVID-19 patients up to 1 year post-transplant. Approximately 23% of liver transplant patients had severe COVID-19 infection. Regarding immunosuppression, 71% and 49% of patients were on tacrolimus and mycophenolate mofetil, respectively. More than half of these patients required some adjustment of their immunosuppression medication. This analysis suggested that COVID-19-infected liver transplant recipients are not at an increased risk of poor outcomes.

Management

The severity of COVID-19 infection often dictates the management of immunosuppressive agents. For example, those with a mild disease not requiring oxygen therapy may be managed as an outpatient without adjustment in their immunosuppressive agents. In contrast, liver recipient patients with moderate-to-severe COVID-19 infection are often managed in the hospital. Guidance for managing these patients stems largely from expert opinions. It is generally advised to lower the cumulative degree of immunosuppression, particularly mycophenolate. While steroid dose generally requires no modification during an active infection, calcineurin inhibitor drug monitoring is recommended to avoid acute kidney injury.

Other agents used in treating COVID-19 infection include oral antivirals such as molnupiravir and Paxlovid. The former is likely safe and effective in liver transplant recipient patients and considered a drug of choice by many hepatologists[50]. Paxlovid strongly interacts with calcineurin and mammalian target of rapamycin inhibitors. Therefore, concomitant use is prohibited[51]. In a single-center, retrospective study that included liver and kidney transplant recipients, COVID-19 monoclonal antibody treatment (casirivimab-imdevimab or bamlanivimab) reduced hospitalization from 32% to 15% ($P = 0.045$) with no mortality (13% *vs* 0%, $P = 0.04$)[52].

The Food and Drug Administration issued an Emergency Use Authorization in January of 2022 for Evusheld (tixagevimab and cilgavimab), a long-acting monoclonal antibody for pre-exposure prophylaxis of COVID-19, in patients with moderate-to-severe immune suppression including those who received a solid organ transplant[53]. This is an appealing preventive option for high-risk liver transplant recipients.

It is important to note that the quality of the literature presented in this review was affected by the evolving understanding of the COVID-19 virus and the ensuing rapid changes in liver society guidelines in response. Moreover, most of the discussed studies were limited by small sample size and retrospective, single center designs affecting the generalizability of their outcomes. In addition, the changes in liver allocation policies that occurred midway through the pandemic may have confounded the overall number of liver transplants performed in the United States.

CONCLUSION

While COVID-19 infection appears to be poorly tolerated in patients with chronic liver disease, liver transplant recipients, despite immunosuppression, have a similar rate of complications and mortality when compared to the general population. It is imperative to recognize important drug-drug interactions in liver transplant patients, notably Paxlovid interaction with calcineurin inhibitors to avoid drug toxicity. We also advocate for wider utilization of monoclonal antibody pre-exposure prophylaxis of COVID-19 infection in liver transplant patients.

FOOTNOTES

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META-ANALYSIS

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_{1C}) 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

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.

MATERIALS AND METHODS

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_{1C} 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^2 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.

RESULTS

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[1]	Q2[2]	Q3[3]	Q4[4]	Q5[5]	Q6[6]	Q7[7]	Q8[8]	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)

[1]Representativeness of the exposed cohort.
[2]Selection of the non-exposed cohort.
[3]Ascertainment of exposure.
[4]Demonstration that outcome of interest was not present at the beginning of the study.
[5]Cohort comparability based on design.
[6]Assessment of outcome.
[7]Was follow-up long enough for outcomes to occur.
[8]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_{1C}) 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[1]	Q2[2]	Q3[3]	Q4[4]	Q5[5]	Q6[6]	Q7[7]	Q8[8]	Overall quality
Fan *et al*[34]	2017	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good
Toledo-Pereyra *et al*[40]	1983	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good
Rossi *et al*[38]	1986	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good

[1]Does the patient(s) represent the whole experience of the investigator?
[2]Was the exposure (diagnosis) adequately ascertained?
[3]Was the outcome adequately ascertained?
[4]Were other alternative causes that may explain the observation ruled out?
[5]Was there a challenge/re-challenge phenomenon?
[6]Was there a dose-response effect?
[7]Was follow-up long enough for outcomes to occur?
[8]Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners maker inferences related to their own practice?
Q: question, Y: Yes, N: No, NA: Not available.

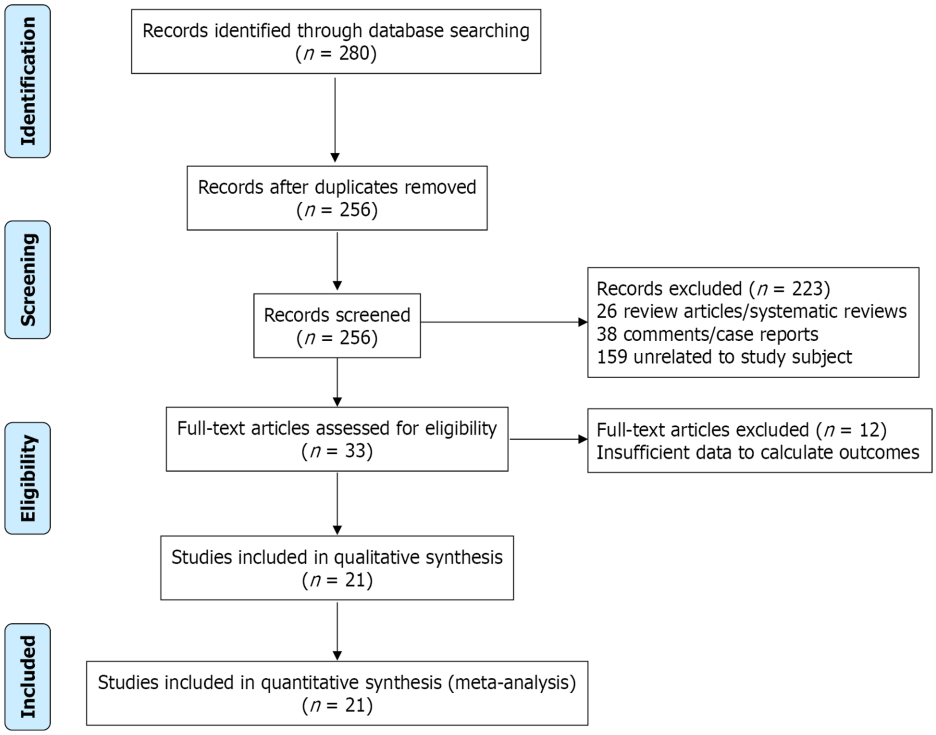

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Figure 1 Flow diagram illustrating the selection process.

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

[1]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_{1c} 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 *et al*[39]	Unknown	9 (35)	1 (4)	8 (31)	0	6 (23)	0	3 (60)	0 (0)	
Najarian *et al*[30]	0 (0)	6 (60)	1 (10)	3 (30)	1 (10)[1]	0 (0)	0 (0)	7 (78)	4 (40) at range 1-38 mo	
White *et al*[31]	0 (0)	8 (18)	2 (5)	13 (30)[2]	0 (0)	1 (2)	0 (0)	16 (77)	8 (33) transient/3 (13) at writing	
Mokadem *et al*[32]	0 (0)	4 (7)	2 (4)	19 (63)	0 (0)	5 (17)	0 (0)	9 (16)	4 (15)	
Garcae *et al*[24]	Unknown	19 (32)	5 (8)	31 (52)	0 (0)	0 (0)	0 (0)	27 (45)	11 (19)	
Gruessner *et al*[33]	Unknown	7 (11)	0 (0)	45 (73)	10 (16)	0 (0)	0 (0)	43 (71)	12 (19) at range 1-24 mo	
Fan *et al*[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 *et al*[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 *et al*[16]	32 (8)	27 (7)	36 (9)	169 (41)	58 (14)	71 (17)	0 (0)	241 (59) at 2 yr[3]	123 (30) at 3 yr[4]	
Colling *et al*[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 *et al*[40]	0 (0)	3 (50)	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)		2 (50) at 20 and 25 mo	
Ahmad *et al*[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 *et al*[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 *et al*[36]	11 (14)	Unknown	Unknown	Unknown	Unknown	Unknown	0 (0)	NA	31 (41) at 6 mo	
Bellin *et al*[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 *et al*[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 *et al*[41]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	14 (64) at mean 5 yr	

Rossi *et al*[38]	Unknown	2 (20)	0 (0)	8 (80)	0 (0)	1 (10)	0 (0)	9 (90)	7 (70) at 2 yr	
Wahoff *et al* [50]	2 (4)	9 (19)	8 (16)	27 (56)	0 (0)	2 (4)	0 (0)	31 (81)	13 (34)	
Garcea *et al*[51]	0 (0)	18 (36)	5 (10)	24 (48)	0 (0)	0 (0)	0 (0)	30 (59.8) at 1 yr		
Pediatrics										
Sutton *et al*[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 *et al*[17]	Unknown	0 (0)	0 (0)	21 (28)	41 (55)	0 (0)	0 (0)	13(17)	31 (41)	
Bellin *et al*[18]	0 (0)	0 (0)	0 (0)	2 (12)	14 (82)	1 (6)	0 (0)	17 (100)	14 (82)	
Bellin *et al*[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

[1]Unconfirmed.
[2]Two identified as idiopathic/trauma.
[3]61% in pediatric patients.
[4]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

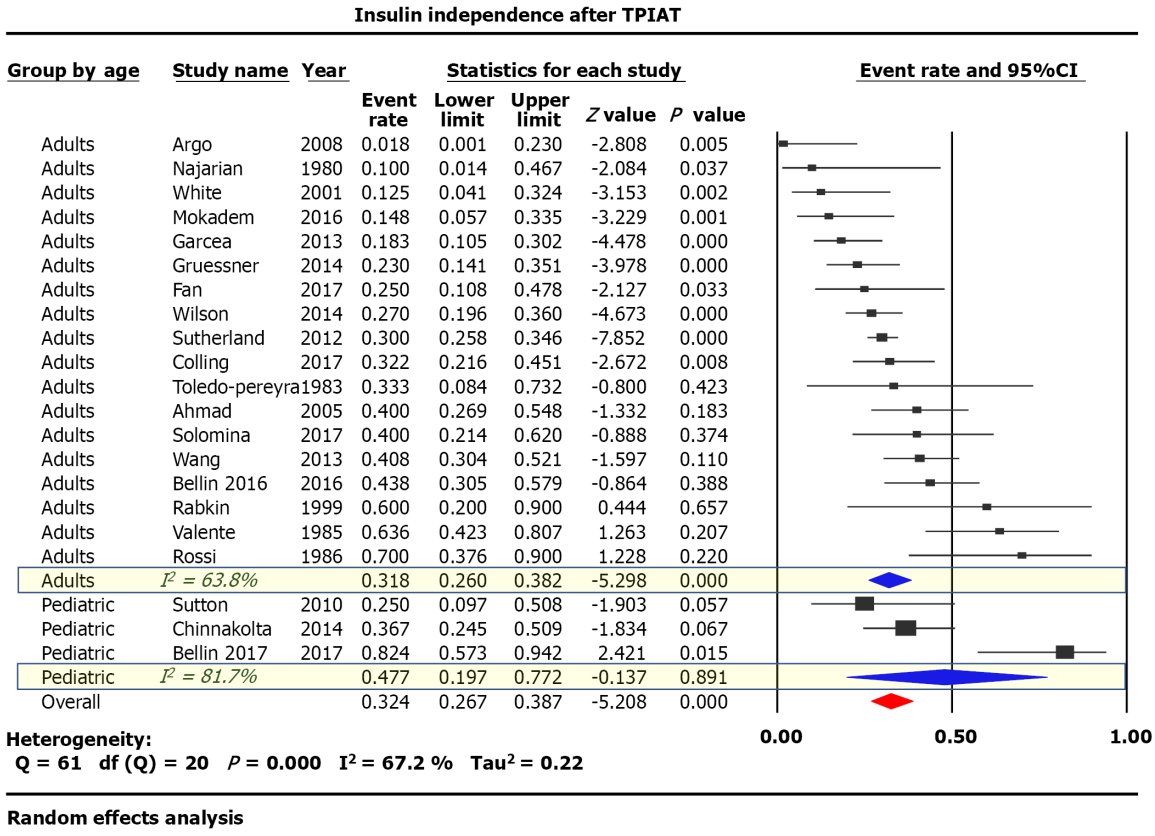

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Figure 2 Summary of event rates assessing insulin independence after total pancreatectomy with islet autotransplantation.

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

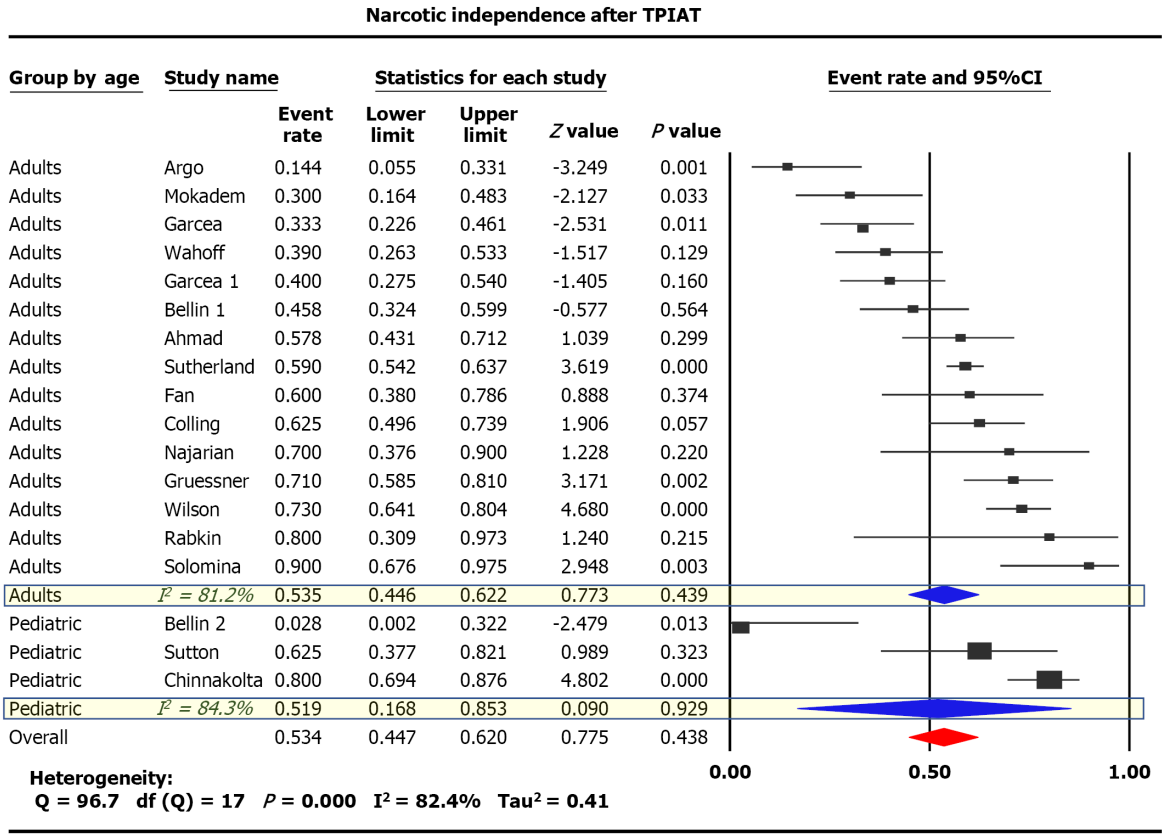

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Figure 3 Summary of event rates assessing narcotic independence after total pancreatectomy with islet autotransplantation.

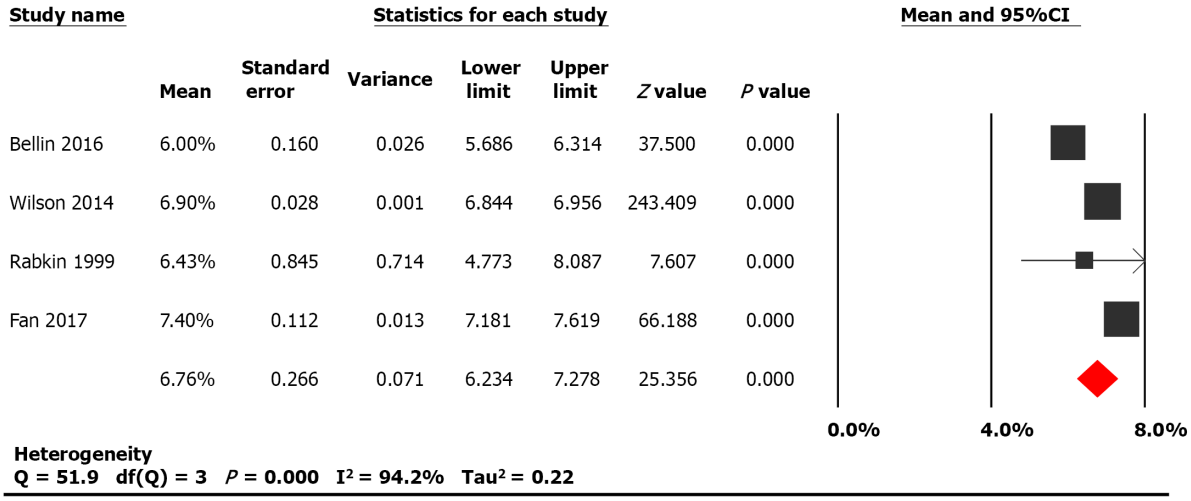

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Figure 4 Pooled HgA_{1c} means after total pancreatectomy with islet autotransplantation.

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 TI-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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