A Study on the Effect of Patient Characteristics, Geographical Utilization, and Patient Outcomes for Total Pancreatectomy Alone and Total Pancreatectomy With Islet Autotransplantation in Patients With Pancreatitis in the United States

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Objectives: A selective therapy for pancreatitis is total pancreatectomy and islet autotransplantation. Outcomes and geographical variability of patients who had total pancreatectomy (TP) alone or total pancreatectomy with islet autotransplantation (TPIAT) were assessed.

Methods: Data were obtained from the Healthcare Cost and Utilization Project National Inpatient Sample database. Weighed univariate and multivariate analyses were performed to determine the effect of measured variables on outcomes.

Results: Between 2002 and 2013, there were 1006 TP and 825 TPIAT in patients with a diagnosis of chronic pancreatitis,` and 1705 TP and 830 TPIAT for any diagnosis of pancreatitis. The majority of the TP and TPIAT were performed in larger urban hospitals. Costs were similar for TP and TPIAT for chronic pancreatitis but were lower for TPIAT compared with TP for any type of pancreatitis. The trend for TP and TPIAT was significant in all geographical areas during the study period.

Conclusions: There is an increasing trend of both TP and TPIAT. Certain groups are more likely to be offered TPIAT compared with TP alone. More data are needed to understand disparities and barriers to TPIAT, and long-term outcomes of TPIAT such as pain control and glucose intolerance need further study.

Key Words: total pancreatectomy,
total pancreatectomy with islet autotransplantation, chronic pancreatitis, pancreatitis, health care utilization

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Chronic pancreatitis is a progressive fibroinflammatory disease, which can lead to endocrine and exocrine gland failure. There are genetic, toxic, environmental, idiopathic etiologies, and other risk factors, including previous acute pancreatitis, which predispose to the disease.[1–3] It can lead to substantial loss of quality of life, decreased productivity and unemployment, and narcotic dependence.[4] The pain, which is frequently relapsing and incapacitating, is the most significant complaint of all quality of life measures and thus remains the most significant target for treatment. The incidence of chronic pancreatitis varies from 4 to 14 per 100,000 per year with a prevalence of 13 to 52 per 100,000 persons.[5–7]

Treatment strategies involve pain control, behavioral modification (quitting alcohol and tobacco smoking), endoscopic interventions, and surgical pancreas duct drainage or resection procedures.[8–10] Total pancreatectomy is considered in highly selected patients with pain refractory to standard therapy.[10] Concomitant pancreas islet autologous transplantation should be considered to prevent or lessen the severity of postoperative diabetes and hypoglycemic unawareness.[11–19]

Total pancreatectomy and islet autotransplantation (TPIAT) is a low-volume procedure performed in centers scattered throughout the United States and the world (see www.citregistry.org).[20] Other

indications include recurrent acute pancreatitis, anticipated large loss of islet mass due to surgery to treat benign disease (trauma, disconnected pancreas duct), potentially malignant lesions such as intrapapillary mucinous neoplasm, or pancreas malignancy of different etiologies.[21–24]

Disease duration affects islet yield, but other criteria to improve patient selection and estimate outcomes are needed.[25] Escalating costs of health care and a shift toward value based care make it important to assess the current state of TPIAT. Major collaborative efforts to better understand and characterize phenotypes to short- and long-term outcomes are underway including the National Institutes of Diabetes and Digestive and Kidney Diseases supported Prospective Observational Study of TPIAT consortium (NIDDK, R01-DK109124, PI M. Bellin).[26]

The study aim was to assess the national use of total pancreatectomy with or without islet autotransplantation in a cohort with a diagnosis of chronic pancreatitis and any diagnosis of pancreatitis, determine geographical variability, and compare health care utilization and outcomes in patients undergoing a total pancreatectomy with or without islet autotransplantation using a large validated database.

MATERIALS AND METHODS

Data Source

Data were extracted from the Healthcare Cost and Utilization Project (HCUP; www.hcup-us.ahrq.gov) National Inpatient Sample (NIS) database, which was previously named Nationwide Inpatient Sample until the methodology to capture data was revised in 2012. The HCUP is sponsored by the Agency for Healthcare Quality and Research through a federal-state-industry partnership. The NIS database is an administrative, deidentified, and publically accessible database, which produces national estimates of hospital inpatient stays by compiling a 20% stratified sample of discharges, which is extracted from the State Inpatient Databases. This represents more than 97% of the population of the United States. The sample size of diagnoses and outcomes obtained by the NIS are representative of national outcomes.[27,28] Data are captured from the hospitals from 48 States and the District of Columbia, which contribute data regardless of payer, so it also includes uninsured patients. The information is used in research and by policy makers to estimate health care utilization, access to care, quality of care, financial charges, and outcomes and for health care decision-making at the national, state, and local levels.

Study Population

The study population consisted of patients who had a total pancreatectomy with a diagnosis of chronic pancreatitis and who had islet autotransplantation or not. A secondary analysis for any diagnosis of pancreatitis was also performed. *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis and procedure codes were used to perform a query on the NIS-HCUP database for adults (≥18 years old) who had a TP or TPIAT between 2002 and 2013 for a diagnosis of pancreatitis and for chronic pancreatitis specifically. The *ICD-9-CM* codes 577.0 for acute and 577.1 for chronic pancreatitis were used, respectively. Patients with a concomitant diagnosis of any pancreas neoplasia, under age of 18 years, or pregnant were excluded. The full list of codes and selection hierarchy is in Supplemental Table 1, http://links.lww.com/MPA/A741.

The Ohio State University Data and Specimen Policy and Human Subjects Research Policy does not require institutional review board approval for analyses conducted on a population-based public data set.

Patient Characteristics and Outcomes

Demographics (age, sex, and race), income status, type of insurance, comorbidities, and hospital characteristics were analyzed. Income was stratified according to quartiles based on zip codes. Type of insurance was classified into private, Medicare, Medicaid, and uninsured. Elixhauser comorbidity index of less than 3 and greater than or equal to 3 was used to stratify comorbidities. Differences in length of stay, mortality, and cost of hospitalization over the study period were also studied.

Hospitals were classified into rural, urban nonacademic, and urban academic. The geographical variability of TPIAT was studied using census information, which divides the country into 4 regions (Northeast, Midwest, South, and West, see https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf). A trend analysis was performed for TP and for TPIAT over the study period and for each region to determine geographical variability.

Statistical Analysis

Patient and hospital characteristics were summarized with means and standard errors, for continuous variables, or frequencies and percentages, for categorical variables. Because of the large sample size, Student t test and χ^2 were adequate to determine differences between the 2 study groups. All analyses were weighed to reflect national estimates. Multivariate linear regression models were used to determine the effect of length of stay and cost, which were adjusted for hospital type and size. Multivariate logistic regression was used to determine independent predictors of receiving islet autotransplantation. Confidence intervals (CIs) that were presented were appropriate. The Cochran-Armitage test was used to test for trends of associations during the study period from 2003 to 2013. All models were adjusted for age, sex, race, income, type of insurance, Elixhauser comorbidity score, and geographical region using weighted data and survey procedures to produce national estimates. Significance was determined with a $P < 0.05$. All analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Total Pancreatectomy Compared With TPIAT in Chronic Pancreatitis

Patient Characteristics

There were 1006 TP and 825 TPIAT between the years 2002 to 2013 in patients with a diagnosis of chronic pancreatitis. Univariate analysis showed that the TPIAT cohort was significantly younger (41 vs 55 years, $P < 0.001$) and predominantly female (69 vs 55%, $P < 0.001$), and TPIAT was more likely to be performed in the Midwest region of the country. There was no clear racial disparity because most patients were described as "white" or "other." Income was not different, but the TPIAT cohort was more likely to have private insurance (70% vs 46%, $P < 0.001$). Total pancreatectomy with islet autotransplantation was not performed in rural nonteaching urban hospitals, or small and medium hospitals. The majority (94%) of the surgeries were performed in urban, tertiary academic medical centers. Comorbidities were similar in both groups (Table 1).

Outcomes

Mortality was higher for TP compared with TPIAT (3.4 vs 0%, $P < 0.01$). Crude length of stay was similar, 17 days for TP and 15 days for TPIAT ($P = 0.55$), but became statistically longer by 4.86 days ($P = 0.013$) for TP alone after adjusting for demographics and hospital characteristics. Cost for both interventions

TABLE 1. Chronic Pancreatitis Patient Characteristics, Hospital Settings, Outcomes, and Cost

	Overall (n = 1831)	TP (n = 1006)	TPIAT (n = 825)	*P*
Age, mean ± SE	46.35 ± 1.17	50.86 ± 1.16	40.86 ± 0.91	<0.001
Sex, n (%)				<0.001
Male	707 (38.63)	450 (44.75)	257 (31.17)	
Female	1124 (61.37)	556 (55.25)	568 (68.83)	
Race, n (%)				<0.001
White	948 (51.78)	584 (58.08)	364 (44.11)	
Black	96 (5.22)	71 (7.03)	25 (3.03)	
Hispanic	46 (2.5)	36 (3.54)	10 (1.22)	
Other	741 (40.49)	315 (31.35)	426 (51.64)	
Income quartile, US $,* n (%)				0.160
First (1–37,999)	365 (20.32)	229 (23.3)	136 (16.74)	
Second (36,000–47,999)	466 (25.92)	226 (23.05)	239 (29.36)	
Third (46,000–63,999)	450 (25.04)	258 (26.31)	192 (23.52)	
Fourth (62,000–64,000+)	516 (28.72)	268 (27.34)	248 (30.39)	
Insurance, n (%)				<0.001
Medicare	372 (21.01)	319 (32.47)	54 (6.79)	
Medicaid	154 (8.71)	126 (12.8)	29 (3.62)	
Private	998 (56.32)	447 (45.55)	551 (69.69)	
Other	247 (13.96)	90 (9.18)	157 (19.9)	
Hospital type, n (%)				
Rural	20 (1.09)	20 (1.99)	0	
Urban nonteaching	94 (5.16)	94 (9.4)	0	
Urban teaching	1713 (93.75)	888 (88.6)	825 (100)	
Hospital bed size, n (%)				
Small	13 (0.71)	13 (1.29)	0	
Medium	124 (6.78)	124 (12.36)	0	
Large	1690 (92.51)	865 (86.35)	825 (100)	
Hospital region, n (%)				0.002
Northeast	142 (7.76)	100 (9.9)	42 (5.15)	
Midwest	827 (45.2)	351 (34.87)	477 (57.79)	
South	599 (32.71)	382 (37.95)	217 (26.33)	
West	262 (14.33)	174 (17.28)	89 (10.73)	
Elixhauser comorbidity, n (%)				0.784
<3	996 (54.55)	553 (55.31)	443 (53.64)	
≥3	830 (45.45)	447 (44.69)	382 (46.36)	
Mortality, n (%)	34 (1.85)	34 (3.36)	0	
LOS, mean ± SE, d	16.24 ± 0.76	17.42 ± 1.23	14.79 ± 0.69	0.055
Cost, mean ± SE, d	59,613 ± 4243	57,609 ± 5859	61,998 ± 3282	0.389

*Quartile ranges vary from 2002 to 2013.

SE indicates standard error; LOS, length of stay.

was similar; TP was US $4782, and TPIAT was the reference (95% CI, −8691 to 18,255, $P = 0.483$) (Table 2).

Trend Analysis

A significant trend of total pancreatectomy alone in patients with chronic pancreatitis was noted during the study period (Supplemental Table 2, http://links.lww.com/MPA/A741). This trend was numerically higher in the Midwest. The trend of undergoing autotransplantation after total pancreatectomy for chronic pancreatitis also increased significantly during the study period, and this trend was numerically also higher in the Midwest (Figs. 1–3; Supplemental Figure 1 and Supplemental Table 2, http://links.lww.com/MPA/A741).

Subset Analyses of Total Pancreatectomy Compared With TPIAT for Any Type of Pancreatitis

Patient Characteristics

There were 1705 TP and 830 TPIAT between the years 2002 and 2013. Forty-eight percent of the cohort who had a total pancreatectomy alone had a diagnosis of acute pancreatitis, whereas 12% of the TPIAT cohort had a diagnosis of acute pancreatitis. Univariate analysis showed that the TPIAT cohort was significantly younger (41 vs 50 years, $P < 0.001$) and predominantly female (69 vs 50%, $P < 0.001$). High/very high–income individuals were more likely to have TPIAT instead of TP alone. No differences were observed based on type of medical insurance. The majority (90%) of the surgeries were performed in tertiary

TABLE 2. Adjusted Length of Stay and Cost for Patients With Chronic Pancreatitis Who Had TP Alone Compared With TPIAT

	Adjusted Coefficient (95% CI)	*P*
Length of stay, d	4.86 (1.03–8.70)	0.013
Costs, US $	4782 (−8691 to 18,255)	0.483

TPIAT was cost reference.

academic medical centers. Comorbidities were similar in both groups (Table 3).

Outcomes

After adjustment, TP had a statistically longer length of stay (24 vs 15 days, $P < 0.001$) and a higher mortality (7.5% vs 0%, $P < 0.001$) compared with TPIAT. The cost of TP was also significantly higher compared with TPIAT, with a cost difference of US $19,050 (95% CI, 2408–35,691; $P = 0.025$) (Supplemental Table 3, http://links.lww.com/MPA/A741).

Trend Analysis

A significant trend for TP and for TPIAT for patients with any type of pancreatitis was noted for the study period (Supplemental Figure 2, http://links.lww.com/MPA/A741). As mentioned previously for the cohort with chronic pancreatitis, the Midwest was numerically more represented for both procedures compared with the other regions.

DISCUSSION

The study showed an increasing trend for total pancreatectomy and total pancreatectomy with islet autotransplantation for patients with chronic pancreatitis and with any type of pancreatitis for the study period. Unlike a previous study on TPIAT only, this study also included subjects who had a total pancreatectomy without islet autotransplantation.[29] The number of national TPIAT became similar to, or surpassed TP alone starting in 2008, but increased trend for both was noted in all geographical zones. The South region showed a substantial increase in TPIAT in 2013, but all regions performed more TPIAT over time probably indicating more active programs. The higher activity for TPIAT in the Midwest may indicate higher-volume programs in the United States and could also be owing to referral bias. Not surprisingly, all TPIATs were performed in large and urban teaching hospitals. Most of the TPs alone were also performed in similar settings, but about 10% of the cases were carried out in small to medium, and rural or urban nonteaching hospitals. The large number of TP alone still being performed for patients with chronic pancreatitis is intriguing and could indicate a lack of patient or physician access to referral centers, a cohort with exclusion criteria for TPIAT, a need to educate patients and health care workers of the indications for TPIAT, or a need to establish more centers performing TPIAT. Most of the TPIATs were performed in subjects with a diagnosis of chronic pancreatitis, as only 12% were coded as acute pancreatitis or other (and probably most patients had recurrent acute pancreatitis). Interestingly, 47% of the TPs alone were performed in patients with acute pancreatitis. The database cannot establish an etiology of the acute pancreatitis, and there are limitations with the current *ICD* classifications, so this code may have included subjects with severe acute pancreatitis, pancreas necrosis, iatrogenic or trauma-induced acute pancreatitis, pancreas leaks or abscesses, and others, which could have led to a total pancreatectomy. It is also possible that patients who had extensive pancreatic debridements or resections were coded as TP. The data on TP compared with TPIAT for all types of pancreatitis have to be interpreted with caution.

In this study, patients with chronic pancreatitis and TPIAT were associated with a shorter length of stay and no mortality compared with those undergoing TP alone. Subjects with any type of pancreatitis undergoing TPIAT also had a shorter hospitalization, no mortality, and lower cost compared with those who had a total pancreatectomy alone. These results are different to a study using the National Surgical Quality Improvement Program data, which described that TPIAT was associated with increased postoperative morbidity and longer length of stay without any difference in mortality. Differences may be explained by methodologies between National Surgical Quality Improvement Program and NIS and not identifying subjects with chronic pancreatitis alone in comparison with this study.[30,31] The improved outcomes of a shorter length of stay and no mortality in this TPIAT cohort could

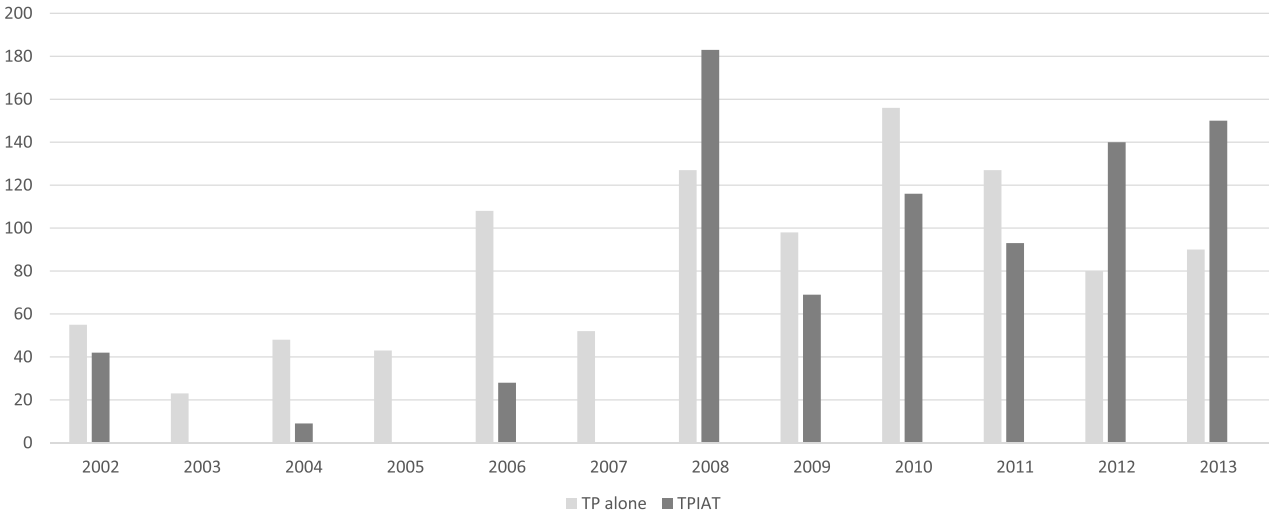

FIGURE 1. The bar graph depicts the trend of TP alone and TPIAT in patients with chronic pancreatitis during the study period. Cell sizes less than 10 were not reported because they might not reflect a difference between groups. Cochran-Armitage test indicates a significant trend for TPIAT, $P < 0.01$.

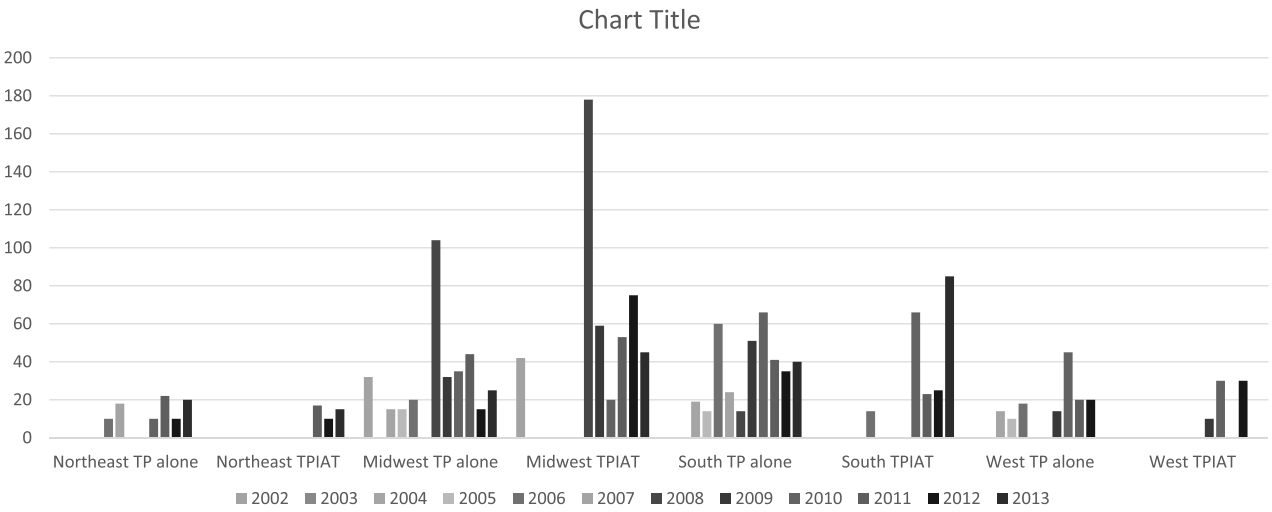

FIGURE 2. The bar graph shows the trend of TP and TPIAT in patients with chronic pancreatitis during the study period 2002 to 2013 according to census derived geographical areas of the United States. Cell sizes less than 10 were not reported because they might not reflect a difference between groups. Cochran-Armitage test indicates a significant trend for TPIAT in all regions, $P < 0.001$.

be a result of selection bias of healthier patients because TPIAT is usually an elective procedure, whereas TP may have been performed acutely, and for other indications already discussed. The Elixhauser comorbidity score was similar in both groups, so other differences not measured in the database may have existed. The lower cost for TPIAT found in the any pancreatitis group could be owing to the shorter duration of hospitalization. No cost difference was found in the chronic pancreatitis cohorts, but at least 1 previous study indicated that for minimal change chronic pancreatitis TPIAT was cost-effective and increased quality adjusted survival compared with medical management.[32] More studies to understand the costs associated with TPIAT are needed.

A few factors favored TPIAT for patients with chronic pancreatitis, and this included younger age, female sex, and having private insurance. These results are not unexpected. Case series of TPIAT show a higher prevalence of females in this age group. Total pancreatectomy with islet autotransplantation is not covered by Medicare or Medicaid, but it is covered by most private insurers, which limits the procedure availability (see https://www.cms.gov/medicare-coverage-database) and may bias toward a younger and presumably healthier group.[18,33,34] For all types of pancreatitis, TPIAT was associated with younger age, female sex, and higher-income bracket. Although insurance coverage did not predict TPIAT in this group, the higher-income bracket could be associated with an increased likelihood of having private insurance and thus access to TPIAT. The younger age may indicate a selection bias that may affect suitability for TPIAT. For example, the presence of diabetes mellitus is usually a latter occurrence in chronic pancreatitis, so patients are usually older, and may disqualify patients for TPIAT. Also noteworthy, 45% of the patients who had TP alone in the any type of pancreatitis cohort were covered by Medicare or Medicaid. It would be concerning if these patients had a TP alone owing to lack of insurance coverage. More than half of the patients were coded as *other race*, followed by whites, so it is not possible to

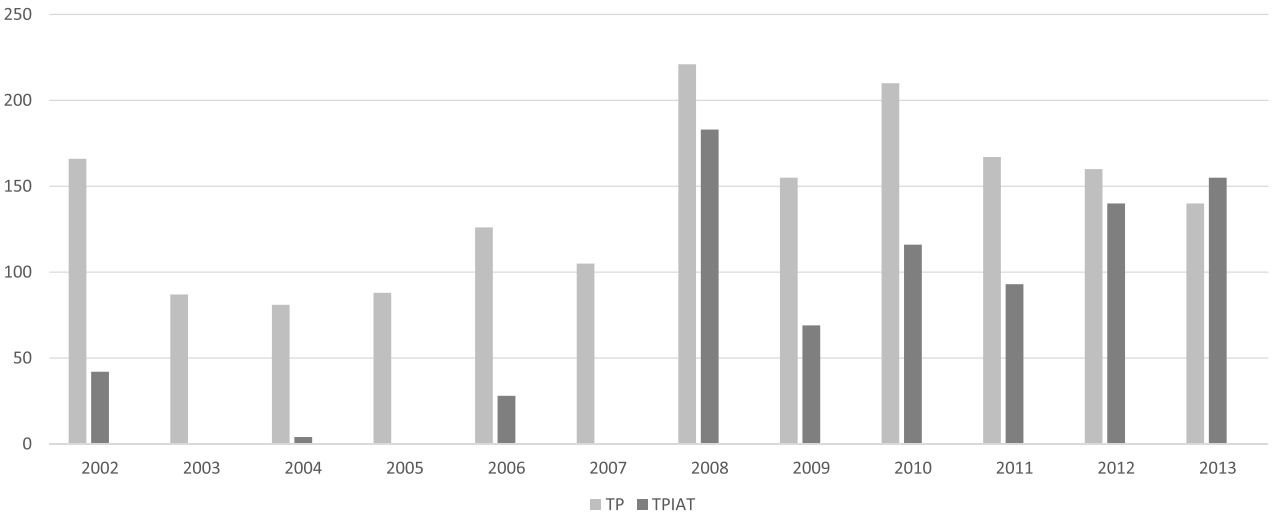

FIGURE 3. The bar graph shows the trend of TP alone and TPIAT in patients with any type of pancreatitis during the study period. Cell sizes less than 10 were not reported because they might not reflect a difference between groups. Cochran-Armitage test indicates a significant trend for TPIAT in all regions, $P < 0.001$.

TABLE 3. All Pancreatitis Patient Characteristics, Hospital Settings, Outcomes, and Cost

	Overall (n = 2535)	TP (n = 1705)	TPIAT (n = 830)	*P*
Age, mean ± SE, y	47.28 ± 1.03	50.42 ± 0.84	40.81 ± 0.90	<0.001
Sex, n (%)				<0.001
Male	1104 (43.5)	847 (49.67)	257 (30.98)	
Female	1431 (56.45)	858 (50.33)	573 (69.02)	
Race, n (%)				<0.001
White	1373 (54.15)	1004 (58.87)	369 (44.44)	
Black	153 (6.05)	129 (7.54)	25 (3.01)	
Hispanic	75 (2.94)	65 (3.78)	10 (1.22)	
Other	934 (36.85)	508 (29.81)	426 (51.33)	
Insurance, n (%)				0.147
Medicare	504 (20.36)	367 (22.04)	136 (16.63)	
Medicaid	657 (26.41)	412 (24.74)	244 (29.79)	
Private	642 (25.81)	450 (27.01)	192 (23.37)	
Other	684 (27.53)	437 (26.21)	248 (30.2)	
Income bracket, n (%)				<0.001
Low	639 (25.81)	585 (34.83)	54 (6.75)	
Moderate	203 (8.22)	170 (10.11)	34 (4.23)	
High	1334 (53.89)	784 (46.62)	551 (69.25)	
Very high	299 (12.09)	142 (8.45)	157 (19.77)	
Hospital type, n (%)				
Rural	34 (1.35)	34 (2)	0	
Urban nonteaching	209 (8.26)	209 (12.3)	0	
Urban teaching	2288 (90.39)	1458 (85.7)	830 (100)	
Hospital bed size, n (%)				
Small	51 (2)	51 (2.97)	0	
Medium	197 (7.79)	197 (11.58)	0	
Large	2284 (90.22)	1454 (85.45)	830 (100)	
Hospital region, n (%)				0.002
Northeast	244 (9.62)	201 (11.81)	42 (5.12)	
Midwest	1071 (42.26)	590 (34.58)	482 (58.05)	
South	833 (32.84)	615 (36.09)	217 (26.17)	
West	387 (15.28)	299 (17.53)	89 (10.67)	
Elixhauser Comorbidity, n (%)				0.941
<3	1347 (53.6)	904 (53.74)	443 (53.32)	
≥3	1166 (46.4)	778 (46.26)	387 (46.68)	
Acute Pancreatitis, n (%)	916 (36.15)	814 (47.74)	102 (12.33)	<0.001
Chronic Pancreatitis, n (%)	1831 (72.21)	1006 (58.98)	825 (99.4)	<0.001
Mortality, n (%)	129 (5.09)	129 (7.58)	0	
LOS, mean ± SE, d	20.67 ± 1.08	23.53 ± 1.22	14.80 ± 0.69	<0.001
Cost, mean ± SE, $US dollars	68,462 ± 3495	71,808 ± 4839	62,001 ± 3262	0.066

determine racial disparity with certainty, a known limitation of the database.[35] The role of factors associated with TPIAT needs to be studied further to determine the disparities that affect patient selection, which may prevent other groups from receiving TPIAT, possibly including insurance coverage.

It was interesting to note the regional variability of TPIAT. Improving referral opportunities, patient and caregiver education, and possibly having more centers performing TPIAT could improve access. Although the number of smaller and rural hospitals performing TP alone was small, it would be interesting to know possible factors that deterred referral to a higher level of care.

There are several limitations worth reviewing. As large as the NIS database is, it is retrospective and weighted to represent national estimates using a 20% sample, so lack of data may only indicate that patients who may have actually had TP alone or TPIAT were not in the sample and not that the procedures were not performed. Samples with less than 10 patients were excluded from statistical analysis.[36] Still, the trend of both procedures showed that both are being performed more frequently and that TPIAT is becoming more commonplace. As an administrative database, the results are dependent on the accuracy of the billing codes, which are subject to error.[35] For this study, subjects were found by selecting total pancreatectomy, then islet autotransplantation, and then chronic (or any) pancreatitis, so it is likely that patients with this diagnosis actually had the disease. The number of evaluable variables in the NIS is large, but more specific data to understand etiologies, patient characteristics, and comorbidities, which may have affected suitability for TPIAT and outcomes, are not available.[37]

In conclusion, this study shows an increasing trend of both TP and TPIAT and suggests that some geographical variance exists.

Barriers to access TPIAT need to be explored because it appears that certain groups are more likely to be offered the procedure. Total pancreatectomy without islet autotransplantation is still being performed regularly, so more data to understand if this is related to disease activity, access, or knowledge about TPIAT would be helpful. Expanding TPIAT insurance coverage to Medicare and Medicaid patients should also be explored. Further studies to understand when to pursue TP alone and how to select patients for TPIAT, barriers to TPIAT access, potential racial disparities, and long-term outcomes such as improvement in pain, quality of life, productivity, and euglycemia, are necessary.[33,34,38–41]

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