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Clinical outcomes following endoscopic retrograde cholangiopancreatography-based therapy compared with surgery in chronic pancreatitis: evidence from a multicentric cohort

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Abstract

Background Real-world comparative outcomes of endoscopic retrograde cholangiopancreatography-based endoscopic therapy vs. pancreatic surgery in chronic pancreatitis (CP) remain incompletely defined.

Methods We performed a retrospective comparative effectiveness study using the TriNetX US Collaborative Network. Adults with CP undergoing endoscopic therapy or pancreatic surgery were identified, and propensity score matching generated 1451 patients in each cohort. Outcomes were assessed from 1-1095 days after the index event, using risk-based analyses as the primary comparative summaries and Kaplan-Meier analyses as secondary time-to-event summaries. Outcomes included chronic opioid prescriptions, opioid use disorder (OUD), celiac plexus block/neurolysis, pain codes, acute pancreatitis, exocrine and endocrine pancreatic insufficiency, emergency visits, and all-cause mortality.

Results Mean follow up was 771.494 days for endoscopy and 827.285 days for surgery. New chronic opioid prescriptions occurred in 146/1092 (13.4%) endoscopic vs. 79/1032 (7.7%) surgical patients (odds ratio [OR] 1.862, 95% confidence interval [CI] 1.396-2.484; P<0.001; hazard ratio [HR] 1.861, 95%CI 1.415-2.448). Acute pancreatitis occurred in 167/530 (31.5%) vs. 65/565 (11.5%) patients (OR 3.539, 95%CI 2.578-4.858; P<0.001; HR 3.341, 95%CI 2.506-4.453). Exocrine pancreatic insufficiency occurred in 200/1213 (16.5%) vs. 132/1206 (10.9%) patients (OR 1.606, 95%CI 1.269-2.034; P<0.001; HR 1.585, 95%CI 1.272-1.975). Endocrine pancreatic insufficiency, mortality, emergency visits, and OUD did not differ significantly between cohorts.

Conclusions Endoscopic therapy was associated with higher chronic opioid prescribing, acute pancreatitis, celiac plexus block/neurolysis, and exocrine pancreatic insufficiency. These findings are associative and should be interpreted in the context of residual confounding and coding-based outcome ascertainment.

Keywords Chronic pancreatitis, endoscopic retrograde cholangiopancreatography, surgery, safety, outcome

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Conflict of Interest: None

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Introduction

Chronic pancreatitis (CP) is a progressive fibroinflammatory disorder characterized by irreversible pancreatic injury, recurrent or persistent abdominal pain, and progressive exocrine and endocrine dysfunction [1]. It imposes a substantial clinical burden, with reported prevalence ranging from 13.5-52.4 per 100,000 persons and an incidence of approximately 8.6 per 100,000 person-years [2-4]. Disease expression is heterogeneous, reflecting variable contributions from environmental, genetic, obstructive and recurrent inflammatory factors [5].

Pain is the dominant driver of morbidity in CP and contributes substantially to impaired quality of life, recurrent healthcare utilization and opioid exposure [1,2,5]. Progressive pancreatic injury may also result in exocrine pancreatic insufficiency (EPI) and diabetes during the disease course [5-7]. Management, therefore, requires treatment of pain and ductal obstruction, nutritional support, screening for pancreatic functional decline, and attention to opioid stewardship throughout follow up.

For symptomatic obstructive CP, endoscopic therapy is commonly used as a less invasive strategy, particularly when pancreatic duct drainage, stent therapy, stone management or sphincter intervention is considered appropriate [1,2]. Surgical options, including drainage and resection-based approaches, are generally considered for refractory pain, complications, or disease anatomy less likely to respond durably to endoscopic therapy [5,8]. Randomized evidence in selected patients with painful obstructive CP and a dilated pancreatic duct has suggested better pain outcomes with early surgery than with an endoscopy-first strategy [9].

However, randomized trials include selected populations and may not fully represent routine clinical practice, where treatment decisions are influenced by comorbidity, disease phenotype, local expertise, surgical candidacy and patient preference. Real-world comparative analyses can complement trial data by describing outcomes across broader populations, while remaining limited by residual confounding and coding-based outcome ascertainment [10]. Such data are useful for hypothesis generation, service planning, and identifying outcomes requiring prospective evaluation. This study was conducted in accordance with the Revised STROCSS 2025 guideline for reporting cohort, cross-sectional, and case-control studies in surgery [11].

The present study aimed to compare electronic health record (EHR)-based clinical outcomes after endoscopic retrograde cholangiopancreatography (ERCP)-based endoscopic therapy vs. pancreatic surgery in adults with CP, using propensity score-matched data from the TriNetX US Collaborative Network. Outcomes of interest included chronic opioid prescriptions, opioid use disorder, celiac plexus block/neurolysis, pain codes, acute pancreatitis, exocrine and endocrine pancreatic insufficiency, emergency visits, all-cause mortality, and repeat intervention.

Materials and methods

Study design and data source

This study was conducted using the TriNetX federated health research network, which provides access to electronic medical records, including diagnoses, procedures, medications, laboratory values and genomic information. The analysis was performed in May 2026 and evaluated comparative outcomes between 2 treatment strategies for CP using the US Collaborative Network.

Study population and cohort selection

Patients were included if they met the following criteria: (1) age ≥18 years; (2) diagnosis of CP (ICD-10-CM codes K86.0 [alcohol-induced] or K86.1 [other chronic]); and (3) an endoscopic or surgical intervention defined below, where any instance of the intervention occurred within 6 months during or after any instance of CP. This 6-month window was used to temporally relate the CP diagnosis and intervention. Patients were excluded if they had a diagnosis of pancreatic malignancy (C25), cystic fibrosis (E84), or secondary malignancy (C77, C78, C79).

Cohort A (endoscopic intervention)

Included 11,203 patients who underwent ERCP-based endoscopic intervention. A total of 56 providers from 67 responding healthcare organizations contributed patients to this cohort (Fig. 1).

Cohort B (surgical intervention)

Included 2252 patients who underwent surgical interventions, including distal subtotal pancreatectomy,

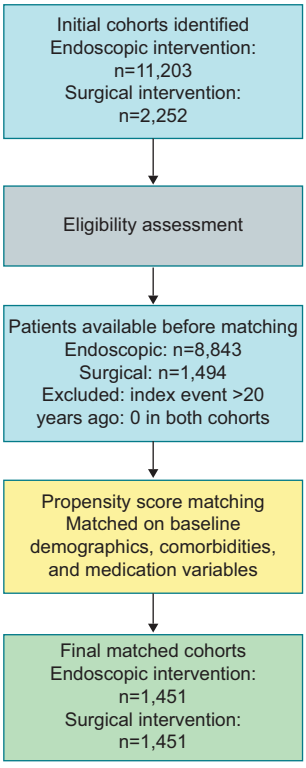

Figure 1 Study flow diagram showing cohort selection and propensity score matching

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proximal subtotal pancreatectomy (Whipple or pylorus-sparing Whipple-type procedures), or ampulla of Vater excision. A few procedures (e.g., Whipple's/excision of ampulla) are not specific to CP-directed surgery; however, they were retained in the surgical code list because they can be used in specific cases of CP, and we could not confirm the indications for these procedures. A total of 47 providers from 70 responding healthcare organizations contributed patients to this cohort.

Procedures and interventions

Endoscopic interventions were restricted to ERCP-based pancreaticobiliary procedures: ERCP with removal and exchange of biliary or pancreatic duct stent(s) (CPT 43276), ERCP with placement of an endoscopic stent into the biliary or pancreatic duct (CPT 43274), and ERCP with trans-endoscopic balloon dilation of biliary/pancreatic duct(s) or of the ampulla/sphincteroplasty (CPT 43277).

Surgical interventions included distal subtotal pancreatectomy with or without pancreaticojejunostomy (CPT 48140, 48145), proximal subtotal pancreatectomy with total duodenectomy and choledochoenterostomy/gastrojejunostomy (CPT 48150, 48152), proximal subtotal pancreatectomy with pylorus-sparing technique (CPT 48153, 48154), and excision of ampulla of Vater (CPT 48148).

Propensity score matching

Propensity score matching was performed to balance baseline characteristics between cohorts before the outcome analysis. Matching was performed on demographics (age, sex, race/ethnicity), body mass index (BMI) categories, comorbid diagnoses, and baseline medication variables (including opioid medications). Available proxies for smoking status and alcohol-related CP included tobacco use and alcohol-related disorders. Pancreatic duct diameter, ductal stricture, intraductal stone burden, inflammatory mass, disease duration and detailed disease anatomy were not available as matching variables in this output and, therefore, could not be included in the propensity model.

After propensity score matching, the following patient numbers were available for analysis:

Cohort A (endoscopic intervention): 1451 patients (matched from 8843 pre-matching)

Cohort B (surgical intervention): 1451 patients (matched from 1494 pre-matching)

Follow-up time after matching

Cohort A mean 771.494 days (standard deviation [SD] 401.864), median 1095 days (interquartile range [IQR] 725); Cohort B mean 827.285 days (SD 391.715), median 1095 days (IQR 569) (Table 1). The median exceeded the mean because at least half of each matched cohort was followed to the 1095-day end of the analysis window, while patients with shorter available observation reduced the mean follow up; Kaplan-Meier methods were used to account for variable follow up and censoring.

Outcome definitions and analyses

The analysis evaluated the following primary and secondary outcomes:

Chronic opioid prescriptions: Receipt of any of the following opioid medications: morphine, oxycodone, methadone, buprenorphine, oxymorphone, fentanyl, tapentadol, hydromorphone or hydrocodone. This outcome captured post-index prescription records, but did not measure duration, dose, morphine milligram equivalents or persistence of use.

Opioid use disorder (OUD): Diagnosis of opioid abuse (F11.1), opioid dependence (F11.2) or opioid use unspecified (F11.9).

Celiac plexus block/neurolysis: Procedures for pain management including celiac plexus injection with anesthetic agent (CPT 64530) or destruction by neurolytic agent (CPT 64680).

All-cause mortality: Recorded demographic status of deceased.

Emergency room (ER) visits: Visit type recorded as emergency (HL7 visit type: EMER).

Acute pancreatitis: Diagnosis of acute pancreatitis (ICD-10-CM K85).

EPI: Diagnosis of exocrine pancreatic insufficiency (ICD-10-CM K86.81).

Endocrine pancreatic insufficiency: Diagnosis of diabetes mellitus due to underlying condition (E08), Type 2 diabetes mellitus (E11), or other specified diabetes mellitus (E13).

Need for repeat intervention: Occurrence of any of the following procedure codes: 43274, 43276, 43277, 48140, 48145, 48148, 48150, 48153, 48152, 48154.

Pain codes: Documentation of abdominal and pelvic pain (R10), pain not elsewhere classified (G89), or pain unspecified (R52).

Statistical analysis

Measure of association analyses calculated the incidence and comparative risk of outcomes between cohorts, reporting risk, risk difference, risk ratio (RR) and odds ratio (OR) with 95% confidence intervals (CI). Risk-based estimates were treated as the primary comparative summaries because they directly described outcome occurrence within the analysis window. Kaplan-Meier survival analyses were used as time-to-event summaries, estimating cumulative event-free probabilities over follow up using daily time intervals, with censoring applied to account for patients exiting the cohort. Log-rank tests and hazard ratios with proportionality testing compared survival curves between cohorts. Analyses excluded patients with outcomes documented prior to the analysis time window. The analysis time window included outcomes that occurred

Table 1 Patient characteristics before and after propensity score matching

Demographics								
Characteristic	Endoscopic (n=8843)	Surgical (n=1494)	P-value	Std. Diff	Endoscopic (n=1451)	Surgical (n=1451)	P-value	Std. Diff
Age at index, mean±SD (years)	54.7±15.3	54.9±14.5	0.739	0.010	54.8±15.1	54.9±14.4	0.832	0.008
Race/Ethnicity								
White, n (%)	6456 (73.0)	1118 (76.8)	0.002	0.087	1116 (76.9)	1113 (76.7)	0.895	0.005
Black or African American, n (%)	1178 (13.3)	179 (12.3)	0.283	0.031	179 (12.3)	179 (12.3)	>0.99	<0.001
Asian, n (%)	251 (2.8)	43 (3.0)	0.807	0.007	42 (2.9)	43 (3.0)	0.912	0.004
American Indian/Alaska Native, n (%)	58 (0.7)	10 (0.7)	0.893	0.004	10 (0.7)	10 (0.7)	>0.99	<0.001
Native Hawaiian/Pacific Islander, n (%)	26 (0.3)	10 (0.7)	0.019	0.056	0 (0)	10 (0.7)	0.002	0.118
Other race, n (%)	314 (3.6)	32 (2.2)	0.008	0.081	27 (1.9)	32 (2.2)	0.511	0.024
Unknown race, n (%)	560 (6.3)	76 (5.2)	0.102	0.048	83 (5.7)	76 (5.2)	0.568	0.021
Sex								
Female, n (%)	3793 (42.9)	698 (47.9)	<0.001	0.101	694 (47.8)	694 (47.8)	>0.99	<0.001
Male, n (%)	5042 (57.0)	758 (52.1)	<0.001	0.100	757 (52.2)	757 (52.2)	>0.99	<0.001
Comorbidities								
Characteristic	Endoscopic (n=8843)	Surgical (n=1494)	P-value	Std. Diff	Endoscopic (n=1451)	Surgical (n=1451)	P-value	Std. Diff
Essential (primary) hypertension, n (%)	4673 (52.8)	761 (52.3)	0.682	0.012	791 (54.5)	758 (52.2)	0.219	0.046
Chronic kidney disease, n (%)	1006 (11.4)	99 (6.8)	<0.001	0.160	97 (6.7)	99 (6.8)	0.882	0.005
Chronic ischemic heart disease, n (%)	1378 (15.6)	165 (11.3)	<0.001	0.125	188 (13.0)	165 (11.4)	0.191	0.049
Heart failure, n (%)	738 (8.3)	62 (4.3)	<0.001	0.169	70 (4.8)	62 (4.3)	0.476	0.026
Atrial fibrillation and flutter, n (%)	717 (8.1)	91 (6.3)	0.015	0.072	113 (7.8)	91 (6.3)	0.110	0.059
Other chronic obstructive pulmonary disease, n (%)	1062 (12.0)	144 (9.9)	0.020	0.068	161 (11.1)	144 (9.9)	0.303	0.038
Disorders of lipoprotein metabolism, n (%)	3222 (36.4)	552 (37.9)	0.279	0.031	568 (39.1)	548 (37.8)	0.445	0.028
Tobacco use, n (%)	1254 (14.2)	160 (11.0)	0.001	0.096	156 (10.8)	159 (11.0)	0.858	0.007
Alcohol-related disorders, n (%)	2505 (28.3)	289 (19.8)	<0.001	0.199	299 (20.6)	289 (19.9)	0.644	0.017
Type 2 diabetes mellitus, n (%)	2759 (31.2)	470 (32.3)	0.410	0.023	500 (34.5)	468 (32.3)	0.208	0.047
Obesity classification								
Obesity due to excess calories, n (%)	559 (6.3)	84 (5.8)	0.420	0.023	92 (6.3)	81 (5.6)	0.388	0.032
Morbid (severe) obesity, n (%)	26 (0.3)	10 (0.7)	0.019	0.056	10 (0.7)	10 (0.7)	>0.99	<0.001
Overweight, n (%)	177 (2.0)	25 (1.7)	0.468	0.021	24 (1.7)	25 (1.7)	0.885	0.005
Other obesity, n (%)	254 (2.9)	57 (3.9)	0.031	0.058	45 (3.1)	53 (3.7)	0.411	0.031
BMI 30-39, adult, n (%)	1091 (12.3)	157 (10.8)	0.092	0.049	154 (10.6)	154 (10.6)	>0.99	<0.001
BMI ≥40, adult, n (%)	340 (3.8)	45 (3.1)	0.160	0.041	61 (4.2)	45 (3.1)	0.113	0.059
Other comorbidities								
Obstructive sleep apnea, n (%)	737 (8.3)	110 (7.6)	0.316	0.029	125 (8.6)	108 (7.4)	0.246	0.043
Cholelithiasis, n (%)	2404 (27.2)	229 (15.7)	<0.001	0.282	238 (16.4)	229 (15.8)	0.649	0.017
Pancreatic steatorrhea, n (%)	24 (0.3)	10 (0.7)	0.010	0.060	10 (0.7)	10 (0.7)	>0.99	<0.001
Exocrine pancreatic insufficiency, n (%)	932 (10.5)	187 (12.8)	0.009	0.072	199 (13.7)	185 (12.7)	0.443	0.028
Acute pancreatitis, n (%)	6038 (68.3)	829 (56.9)	<0.001	0.236	823 (56.7)	828 (57.1)	0.851	0.007
Medications								
Characteristic	Endoscopic (n=8843)	Surgical (n=1494)	P-value	Std. Diff	Endoscopic (n=1451)	Surgical (n=1451)	P-value	Std. Diff
Tramadol, n (%)	1854 (21.0)	220 (15.1)	<0.001	0.153	227 (15.6)	219 (15.1)	0.681	0.015
Buprenorphine, n (%)	146 (1.7)	18 (1.2)	0.241	0.035	18 (1.2)	18 (1.2)	>0.99	<0.001

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Table 1 (*Continued*)

	Medications							
Characteristic	Endoscopic (n=8843)	Surgical (n=1494)	P-value	Std. Diff	Endoscopic (n=1451)	Surgical (n=1451)	P-value	Std. Diff
Hydromorphone, n (%)	4820 (54.5)	700 (48.1)	<0.001	0.129	745 (51.3)	698 (48.1)	0.081	0.065
Fentanyl, n (%)	4693 (53.1)	722 (49.6)	0.014	0.070	753 (51.9)	717 (49.4)	0.181	0.050
Morphine liposomal, n (%)	910 (10.3)	87 (6.0)	<0.001	0.158	89 (6.1)	87 (6.0)	0.876	0.006
Hydrocodone, n (%)	2407 (27.2)	317 (21.8)	<0.001	0.127	324 (22.3)	317 (21.8)	0.754	0.012
Methadone, n (%)	180 (2.0)	27 (1.9)	0.648	0.013	23 (1.6)	27 (1.9)	0.568	0.021
Morphine, n (%)	4223 (47.8)	501 (34.4)	<0.001	0.274	523 (36.0)	501 (34.5)	0.393	0.032
Oxycodone, n (%)	4595 (52.0)	649 (44.6)	<0.001	0.148	682 (47.0)	646 (44.5)	0.180	0.050
Oxymorphone, n (%)	21 (0.2)	10 (0.7)	0.004	0.066	10 (0.7)	10 (0.7)	>0.99	<0.001

SD, standard deviation; BMI, body mass index

starting 1 day after the first occurrence of the index event and ending 1095 days after the first occurrence of the index event. The index event was derived from the cohort definitions and was defined separately for each cohort based on the first date on which the patient met the selected cohort-specific criteria. The index event was limited to events occurring up to 20 years prior; in this analysis, 0 patients in Cohort 1 and 0 patients in Cohort 2 were excluded for having an index event ≥20 years ago. Analyses were performed on cohorts after propensity score matching to reduce measured baseline imbalance between treatment groups; the design cannot eliminate residual confounding by unmeasured disease-specific variables.

Results

After propensity score matching, 1451 patients were included in each cohort, reduced from 8843 in the endoscopic cohort and 1494 in the surgical cohort before matching. Mean follow up after matching was 771.494 days (SD 401.864; median 1095 days, IQR 725) in the endoscopic cohort and 827.285 days (SD 391.715; median 1095 days, IQR 569) in the surgical cohort. Key comorbidities relevant to surgical selection were balanced after matching, including chronic ischemic heart disease (standardized difference 0.049), type 2 diabetes mellitus (standardized difference 0.047), and obesity/BMI variables (standardized differences ≤0.059).

For pain-related outcomes, new chronic opioid prescriptions occurred in 146/1092 patients in the endoscopic cohort and 79/1032 in the surgical cohort (risk 0.134 vs. 0.077), corresponding to a risk difference of 0.057 (95%CI 0.031-0.083; P<0.001), a RR of 1.747 (95%CI 1.346-2.266), and an OR of 1.862 (95%CI 1.396-2.484). Kaplan-Meier analysis showed survival probabilities at the end of the time window of 83.71% and 91.36%, respectively, with log-rank P<0.001 and a hazard ratio (HR) of 1.861 (95%CI 1.415-2.448). OUD occurred in 75/1362 vs. 52/1278 patients (risk 0.055 vs. 0.041), with a risk difference of 0.014 (95%CI -0.002 to 0.031; P=0.084), a RR of 1.353 (95%CI 0.958-1.912), and an OR of 1.374 (95%CI 0.956-1.974). Kaplan-Meier analysis showed survival probabilities of 92.60% and 95.10%, with a log-rank P-value of 0.058 and an HR of 1.406 (95%CI 0.987-2.003). Celiac plexus block/neurolysis was recorded in 42/1439 and 11/1421 patients (risk 0.029 vs. 0.008), yielding a risk difference of 0.021 (95%CI 0.012-0.031; P<0.001), a RR of 3.770 (95%CI 1.949-7.293), and an OR of 3.854 (95%CI 1.976-7.516). Corresponding Kaplan-Meier survival probabilities were 96.35% and 99.03%, with log-rank P<0.001 and an HR of 3.986 (95%CI 2.052-7.744). Pain codes were documented in 201/452 patients in the endoscopic cohort and 152/325 in the surgical cohort (risk 0.445 vs. 0.468), with a risk difference of -0.023 (95%CI -0.094 to 0.048; P=0.525), a RR of 0.951 (95%CI 0.814-1.110), and an OR of 0.911 (95%CI 0.685-1.213). Kaplan-Meier analysis showed median survival of 824 days in the endoscopic cohort and 872 days in the surgical cohort, with survival probabilities of 46.55% and 49.18%, log-rank P=0.049, and an HR of 0.806 (95%CI 0.652-0.995).

Pancreatic outcomes also differed between groups. Acute pancreatitis occurred in 167/530 patients in the endoscopic cohort and 65/565 in the surgical cohort (risk 0.315 vs. 0.115), corresponding to a risk difference of 0.200 (95%CI 0.153-0.248; P<0.001), a RR of 2.739 (95%CI 2.110-3.555), and an OR of 3.539 (95%CI 2.578-4.858). Kaplan-Meier survival probabilities at the end of follow up were 60.21% and 86.76%, with log-rank P<0.001 and an HR of 3.341 (95%CI 2.506-4.453) (Fig. 2). EPI developed in 200/1213 vs. 132/1206 patients (risk 0.165 vs. 0.109), with a risk difference of 0.055 (95%CI 0.028-0.083; P<0.001), a RR of 1.506 (95%CI 1.227-1.849), and an OR of 1.606 (95%CI 1.269-2.034). Kaplan-Meier survival probabilities were 78.72% in the endoscopic cohort and 87.39% in the surgical cohort, with log-rank P<0.001 and an HR of 1.585 (95%CI 1.272-1.975). Endocrine pancreatic insufficiency occurred in 125/881 patients in the endoscopic cohort and 117/885 in the surgical cohort (risk 0.142 vs. 0.132), with a risk difference of 0.010 (95%CI -0.022 to 0.042; P=0.554), a RR of 1.073 (95%CI 0.849-1.356), and an OR of 1.085 (95%CI 0.827-1.424). Kaplan-Meier survival probabilities were 81.18%

and 83.64%, with a log-rank P-value of 0.372 and an HR of 1.122 (95%CI 0.872-1.443).

For healthcare utilization and survival, all-cause mortality accounted for 100/1447 patients in the endoscopic cohort and 90/1449 in the surgical cohort (risk 0.069 vs. 0.062), yielding a risk difference of 0.007 (95%CI -0.011 to 0.025; P=0.447), a RR of 1.113 (95%CI 0.845-1.465), and an OR of 1.121 (95%CI 0.835-1.505). Kaplan-Meier survival probabilities were 90.97% and 92.81%, with a log-rank P-value of 0.287 and an HR of 1.167 (95%CI 0.878-1.552). Emergency room visits occurred in 181/937 vs. 174/1016 patients (risk 0.193 vs. 0.171), with a risk difference of 0.022 (95%CI -0.012 to 0.056; P=0.210), a RR of 1.128 (95%CI 0.934-1.362), and an OR of 1.159 (95%CI 0.920-1.458). Kaplan-Meier survival probabilities were 74.94% in the endoscopic cohort and 80.13% in the surgical cohort, with a log-rank P-value of 0.082 and an HR of 1.202 (95%CI 0.976-1.481). Survival probabilities at the end of the analysis window for each outcome are summarized in Fig. 3.

Discussion

This comparison of patients with CP undergoing index endoscopic therapy (ERCP-based intervention) vs. pancreatic surgery showed differences across selected outcomes, without

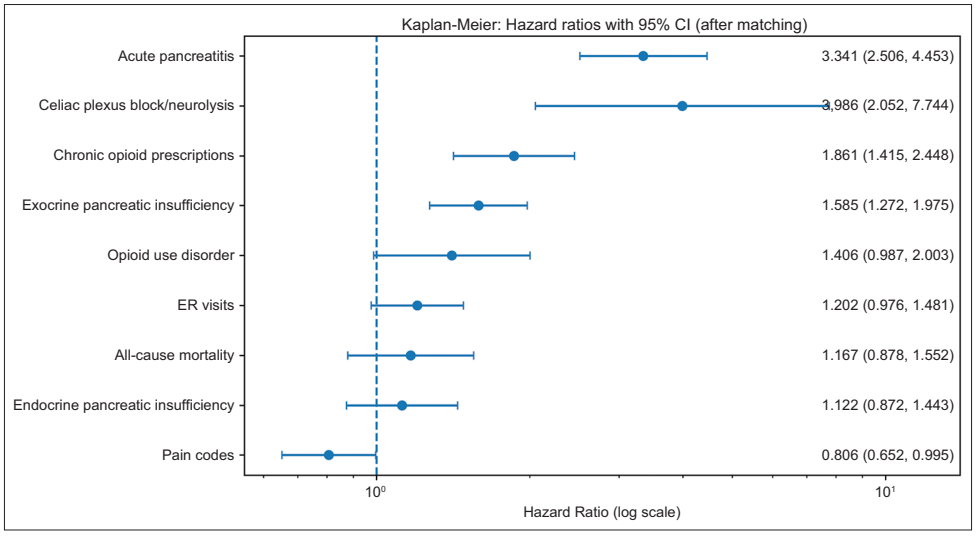

Figure 2 Forest plot of hazard ratios for post-matching time-to-event outcomes
CI, confidence interval; ER, emergency room

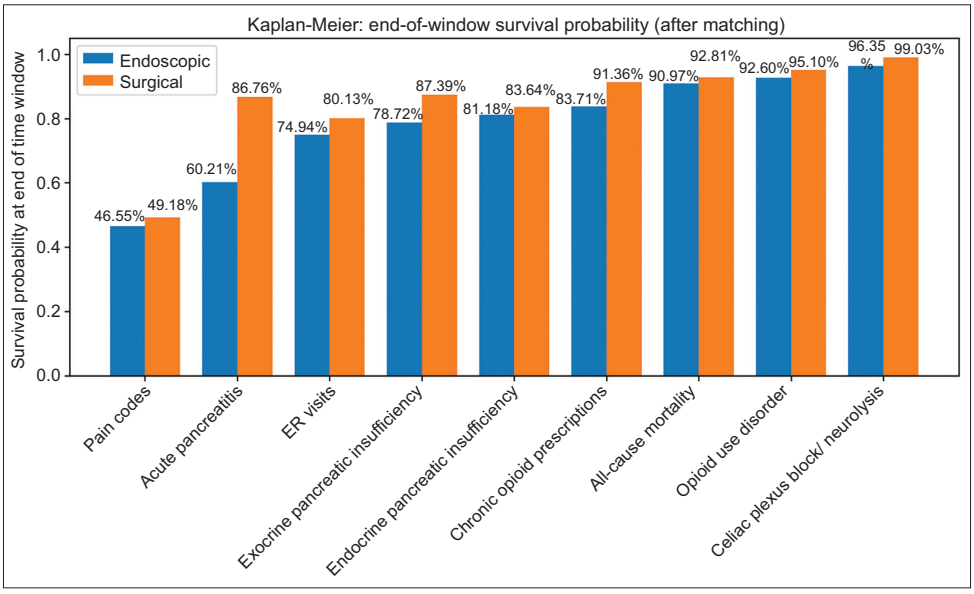

Figure 3 Kaplan-Meier end-of-window survival probabilities for post-matching outcomes in the endoscopic and surgical cohorts
ER, emergency room

a consistent advantage for either approach. In the matched cohorts, endoscopic therapy was associated with higher rates of new chronic opioid prescriptions, celiac plexus block/neurolysis, acute pancreatitis and EPI. In contrast, OUD, endocrine pancreatic insufficiency, emergency department utilization, and all-cause mortality were not significantly different between groups on risk-based or Kaplan-Meier analyses. Pain-code documentation did not differ significantly in the risk analysis, although the Kaplan-Meier output reported a statistically significant log-rank result with an HR below 1; this coded proxy should therefore be interpreted cautiously. The main new information from this study is that a multicenter EHR cohort demonstrated higher endoscopic-associated signals for opioid prescribing, acute pancreatitis, celiac plexus block/neurolysis and EPI, while mortality, emergency department utilization, OUD, endocrine insufficiency, and primary risk-based pain-code outcomes did not differ significantly. These observations are hypothesis-generating and should not be interpreted as proof of treatment superiority.

Pain in CP is multifactorial, and may reflect inflammatory, obstructive and neuropathic mechanisms; accordingly, guideline-based care emphasizes multidimensional assessment and multimodal management rather than reliance on any single surrogate, such as a diagnostic code or prescription pattern [12]. Within that context, the higher incidence of new chronic opioid prescriptions after endoscopic therapy may indicate less durable symptom control in some patients, recurrent inflammatory episodes prompting escalation of analgesia, or differences in disease phenotype not fully captured by EHR-based covariates. However, the opioid endpoint captured prescription occurrence, rather than duration, dose, morphine milligram equivalents, or patient-reported analgesic response. Celiac plexus block/neurolysis was also more frequent after endoscopic therapy, whereas OUD and pain-code documentation on risk analysis were not significantly different.

Randomized data in selected patients with painful obstructive CP have suggested that early surgery can provide better pain control than an endoscopy-first approach [9]. Longer-term follow up from the same comparison also indicates that the 2 strategies may diverge over time in clinically meaningful outcomes [13]. Our findings are directionally consistent with those data with respect to chronic opioid exposure, but they do not demonstrate a clear difference across all pain-related endpoints. These findings should be interpreted in the context of disease phenotype, symptom drivers and timing of intervention.

Despite higher chronic opioid prescribing after endoscopic therapy, OUD was not significantly different between groups. This finding should be interpreted carefully, because OUD may be under-recognized or inconsistently coded in routine practice, and because opioid exposure in CP may reflect both disease burden and prescribing culture. Nonetheless, CP remains a clinical setting in which opioid stewardship, longitudinal monitoring and attention to non-opioid pain strategies are important, irrespective of treatment pathway [14].

Acute pancreatitis occurred more frequently after endoscopic therapy than after surgery. This association is clinically plausible, as ERCP-based pancreatic duct manipulation is associated with procedure-related pancreatitis risk, and repeated instrumentation or incomplete control of ductal obstruction may contribute to recurrent inflammatory events in some patients [15]. However, we cannot reliably distinguish post-ERCP pancreatitis from disease-related flares; this outcome is not directly comparable between cohorts, and should be interpreted as an observed association, rather than a direct mechanistic effect of the procedure itself.

Recent randomized data evaluating endoscopic duct decompression strategies, including extracorporeal shock-wave lithotripsy plus endoscopy, suggest that the benefit may be modest and not universal, again emphasizing the heterogeneity in response [16]. These findings support selective use of endoscopic therapy, with early surgical review when disease characteristics suggest limited endoscopic durability.

EPI was more frequent after endoscopic therapy. In CP, EPI reflects cumulative parenchymal injury and progressive loss of exocrine function, and current guidance emphasizes early recognition and treatment, because maldigestion and malnutrition have important clinical consequences [17]. One possible interpretation is that the higher burden of acute pancreatitis observed in the endoscopic cohort may be accompanied by greater ongoing pancreatic injury in some patients. However, residual confounding, differential clinical surveillance and coding practices may also have contributed to this difference.

Endocrine pancreatic insufficiency did not differ significantly between the endoscopic and surgical cohorts in our study. Although pancreatic surgery, particularly when resection is involved, may reduce endocrine reserve in a gland that is already functionally compromised by CP, the present EHR-based comparison did not demonstrate a statistically significant difference in endocrine insufficiency during the analysis window. The definition included diabetes mellitus due to underlying condition, type 2 diabetes mellitus, and other specified diabetes mellitus; therefore, it does not isolate pancreatogenic diabetes and may misclassify diabetes etiology. Pancreatogenic diabetes remains a recognized complication of both CP and pancreatic surgery, and consensus guidance supports systematic screening and structured management in this setting [18].

Emergency department utilization was not significantly different between groups on either risk-based analysis or Kaplan-Meier analysis. Given the higher rates of acute pancreatitis and chronic opioid prescriptions after endoscopic therapy, a signal toward greater unscheduled care might be clinically plausible, but it was not statistically demonstrated. Healthcare utilization remains influenced by local practice patterns, access to care, and EHR capture.

All-cause mortality also did not differ significantly between groups on risk-based analysis or Kaplan-Meier analysis. Mortality was defined as a recorded demographic status of "deceased" and was not adjudicated as CP-attributable, procedure-related, or due to other causes. This should not be taken as evidence of equivalence, because the cause of death was not adjudicated,

and important factors such as frailty, nutritional status, alcohol and smoking exposure, disease morphology, surgical candidacy, early post-procedural complications, and center-level practice variation are not fully captured in this type of dataset. The study therefore does not support a statistically significant all-cause mortality difference during the reported analysis window, but it cannot determine comparative procedural safety or early complication-related mortality.

The strengths of this study include a large multicenter real-world dataset and the use of propensity score matching to reduce measured baseline imbalance between treatment groups. However, several limitations remain and should be considered for interpretation. First, residual confounding by indication is a major limitation: treatment allocation in CP is influenced by ductal anatomy, stone burden, inflammatory mass, disease duration, symptom severity, nutritional status, surgical candidacy, alcohol and smoking intensity, center expertise, and patient preference, many of which were not available in the database. Matching therefore reduced the measured imbalance, but cannot establish causality or treatment superiority. Second, exposure misclassification remains possible. The endoscopic cohort was restricted to ERCP-based stent and ductal dilation/sphincteroplasty codes, but surgical codes still included heterogeneous resection procedures and CPT 48148, which is not specific to CP-directed treatment. Third, outcome misclassification is possible, because diagnoses, procedures, medications, emergency department visits and death status were identified from structured EHR codes. Pain was assessed using coded proxies, rather than validated patient-reported instruments such as visual analog, numeric rating or Izbicki scores. Chronic opioid prescriptions did not capture dose, duration, morphine milligram equivalents or persistent use. Acute pancreatitis could not be separated into post-ERCP pancreatitis and disease-related flares, which may bias interpretation of this endpoint against endoscopic therapy. Diabetes definitions included type 2 diabetes, and therefore did not isolate pancreatogenic diabetes. Fourth, although patients with prior recorded outcomes were excluded from outcome-specific analyses, no fixed washout period was applied; some post-index outcomes may represent previously undocumented disease progression rather than definite treatment-induced complications. Fifth, the 6-month CP diagnosis-to-intervention window may have introduced heterogeneity and time-window bias. Sixth, early procedural complications severe enough to limit subsequent follow up may be under-captured, and all-cause mortality cannot be attributed to CP or the intervention. Finally, we cannot provide the total number of endoscopic procedures per patient; after excluding patients with prior repeat-intervention records, the repeat-intervention endpoint was not estimable, limiting interpretation of comparative treatment durability.

Taken together, these findings support a pragmatic and individualized approach to CP management. Early multidisciplinary review, involving endoscopy, surgery, pain management, nutrition and endocrinology, remains appropriate. The present data suggest that patients managed with an endoscopy-first strategy may warrant close attention to recurrent pancreatitis, exocrine functional decline, celiac plexus block/neurolysis and escalation of opioid exposure, but these associations should be interpreted alongside the limitations of EHR coding and residual confounding by indication. Surveillance for diabetes remains important after both endoscopic and surgical treatment pathways. These observations also reinforce the importance of structured opioid stewardship and proactive screening for both EPI and diabetes as part of longitudinal CP care [12,17,18].

In conclusion, in this study comparing endoscopic therapy to pancreatic surgery for CP, endoscopic therapy was associated with higher rates of new chronic opioid prescriptions, celiac plexus block/neurolysis, acute pancreatitis and EPI during follow up. No significant between-group differences were observed for opioid use disorder, endocrine pancreatic insufficiency, emergency department utilization or all-cause mortality. Pain documentation was not significantly different on risk analysis, although the Kaplan-Meier analysis for this coded proxy reached statistical significance and should be interpreted cautiously. The need-for-repeat-intervention endpoint was not estimable after exclusion of patients with prior outcome records. Overall, these results highlight clinically relevant tradeoffs between endoscopic and surgical strategies in real-world practice, but they remain associative and hypothesis-generating. Careful multidisciplinary patient selection, structured opioid stewardship, and surveillance for pancreatic functional decline remain important. Prospective studies with granular disease-phenotype data, procedure counts, early complication capture and patient-reported outcomes are needed to better define which patients benefit most from early surgery vs. an endoscopy-first approach.

Summary Box

What is already known:

- For symptomatic obstructive chronic pancreatitis (CP), endoscopic therapy is commonly used as a less invasive strategy, particularly when pancreatic duct drainage, stent therapy, stone management or sphincter intervention is considered appropriate
- Patients with painful obstructive CP and a dilated pancreatic duct have better pain outcomes with early surgery than with an endoscopy-first strategy

What the new findings are:

- In the matched cohorts, endoscopic therapy was associated with higher rates of new chronic opioid prescriptions, celiac plexus block/neurolysis, acute pancreatitis, and exocrine pancreatic insufficiency
- Opioid use disorder, endocrine pancreatic insufficiency, emergency department utilization and all-cause mortality were not significantly different between groups on risk-based or Kaplan-Meier analyses

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