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Original Article

The impact of opioid use in chronic pancreatitis from 2004–2024: A propensity-matched analysis of 183,214 individuals

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ABSTRACT

Background: Chronic pancreatitis is a progressive inflammatory disease causing exocrine and endocrine dysfunction, frequently leading to severe, recurrent pain necessitating treatment with opioid analgesics. The impact of opioid use on chronic pancreatitis outcomes is poorly understood.
Objective: This study's objective was to evaluate the effect of opioid use on mortality and healthcare utilization in patients with chronic pancreatitis using real-world data.
Design: We conducted a retrospective cohort study using the TriNetX research network, identifying U.S. adults (≥18 years) with chronic pancreatitis from a 121-million-patient database (2005–2025). Patients were stratified into opioid users and non-users (controls) and propensity score matched (1:1) for demographics, body mass index, comorbidities, laboratory parameters, and treatments. Primary outcomes included acute-on-chronic pancreatitis, all-cause mortality, emergency department (ED) visits and hospitalizations. Outcomes were analyzed using Cox regression and time-stratified methods, reported as adjusted hazard ratios (aHR).
Results: Of 252,130 patients with chronic pancreatitis, 143,758 opioid users and 108,372 non-users were propensity-matched. Opioid users were older, with higher rates of alcohol use, pancreatitis risk factors, psychiatric disorders, substance use disorder, malnutrition, and analgesic use (all $p < 0.0001$). Opioids were associated with increased risks of acute-on-chronic pancreatitis (aHR = 1.45, 95 % CI: 1.36–1.54), all-cause mortality (aHR = 1.90, 95 % CI: 1.80–2.00), and ED visits (aHR = 1.28, 95 % CI: 1.22–1.36).
Conclusion: Opioid use in chronic pancreatitis is associated with higher morbidity, mortality, and healthcare utilization, likely reflecting underlying disease severity and complications. These patients represent a high-risk group warranting greater attention, and prospective studies are needed to clarify causal relationships and guide optimized pain management strategies.

1. Background

Chronic pancreatitis (CP) is a progressive inflammatory condition that leads to both exocrine and endocrine dysfunction. Despite various, often repeated, interventions, including endoscopic and pharmacological, many patients remain symptomatic and develop complications such as chronic pain, diabetes, and malnutrition [1]. Currently, the treatment of CP primarily focuses on managing complications, with pain being the most frequent and bothersome, affecting around 90 % of patients with CP [2]. Prototypically, abdominal pain in CP is usually located in the epigastric or right upper abdominal quadrant. Although multifactorial in nature, pain putatively results from pancreatic

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inflammation, hyperstimulation, and neuropathy, causing a significant diminution in the patient's quality of life [3,4]. A step-up approach, beginning with medical management—including opioid analgesics—and escalating to endoscopic or surgical interventions as necessary, is endorsed by both U.S. and international medical societies [5,6]. In fact, escalation to opioid analgesics often occurs rather quickly due to the debilitating nature of the pain. As a result, patients suffering from CP are at particularly high risk of developing opioid use disorder (OUD) [7]. As excessive alcohol and tobacco use are the most important reasons for developing CP, the addictive potential associated with this misuse also predisposes to OUD.

Opioid-induced hyperalgesia is a complication of treatment with narcotics, and therefore, albeit seemingly paradoxically, opioids used to manage the severe pain associated with CP can worsen CP pain. Additionally, opioids may negatively impact the clinical course of CP by their associated morbidity, including opioid induced bowel dysfunction, falls and fractures, cognitive decline [8], along with depression and social isolation, particularly in elderly [9]. One single-center retrospective study showed that opioid-dependent CP patients had poorer outcomes, including higher rates of acute pancreatitis reccurences, along with a higher resource utilization [10]. However, opioids association with adverse outcomes, such as acute-on-chronic pancreatitis, mortality, and healthcare resource utilization, has not been extensively studied in large populations. Previous studies have been limited by small sample sizes often derived from tertiary centres. Other studies primarily focused on alcohol use, smoking, and substance use disorders, with only a few addressing opioid use in the context of readmission rates due to CP rather than broader outcomes [11–14]. In this study, we aim to address these knowledge gaps by leveraging large-scale real-world data to assess the effects of opioid use on the outcomes of CP.

2. Design

Data source – This retrospective cohort study utilized the TriNetX Analytics Network Platform (Cambridge, MA, USA), a global federated research network encompassing de-identified electronic health records (EHRs) from 121 million patients across 68 U S. health care organizations (HCOs) [15]. This platform supports real-time cohort selection and propensity score matching (PSM) application for comparative analysis of outcomes while accounting for potential confounders [15]. Data integrity maintained through a rigorous quality assurance process is enforced during EHR extraction, ensuring standardized formatting prior to database inclusion. This study employed publicly available de-identified data and is therefore exempt from Institutional Review Board (IRB) approval, as per the National Human Research Protections Advisory Committee guidelines [16]. De-identification is performed at the network level by TriNetX experts, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule standards [17].

Study population and variables – A real-time search and analysis of the U.S. Collaborative Network in the TriNetX platform were conducted through April 18th, 2025. We analyzed records of adults ($\geq$18 years) who were diagnosed with CP, using the International Classification of Diseases, Tenth Edition, Clinical Modification codes (ICD-10-CM: K86.0, K86.1), see Supplementary Table 1. Prescription opioid use was defined as the presence of TriNetX codes corresponding to opioid analgesics within 90 days after the initial diagnosis of CP (National Library of Medicine (NLM) code: VA:CN101), see Figs. 1 and 2. Additionally, OUD was defined by the presence of the ICD-10-CM code F11 during the same time period. To mitigate potential bias and enhance the granularity of our findings regarding the association between opioid use and CP outcomes, we conducted a comprehensive series of analyses. The primary analysis examined the overall impact of opioid use, encompassing both prescription opioid use and OUD, on CP outcomes. Additionally, we performed two subgroup analyses to independently evaluate the isolated impact of prescription opioid use and the combined impact of prescription opioid use and OUD, see Fig. 1. Patients with OUD without records of prescription opioid use were excluded from this analysis. Finally, we conducted an aetiology-stratified subgroup analyses based on CP subtype, categorizing patients into alcohol-related CP and non-alcohol-related CP, and the latter encompassing all non-alcohol-related aetiologies of CP. This approach allowed us to account for the different risk profiles and healthcare utilization patterns between these groups, as well as to address potential biases arising from studying OUD populations [18–20]. To minimize misclassification and cohort overlap, patients with diagnostic codes for both alcohol-related and non-alcohol-related CP were excluded from the sub-group analyses. We aimed to provide more targeted insights into how different types of opioid analgesic use may impact CP outcomes.

Patient and hospital characteristics – We retrieved data within the TriNetX database on demographic data, including age (mean with standard deviation (SD)), sex (male, female), and race/ethnicity (White, Black or African American, Hispanic or Latino). Additionally, we included data on pancreatitis risk factors, including history of acute pancreatitis, alcohol use, smoking, cholelithiasis, pancreatic cancer, hypertriglyceridaemia (>1000 mg/dL), hypercalcaemia (>10.5 mg/dL), spasm of the sphincter of Oddi, congenital malformations of the pancreas and pancreatic duct, and medications (e.g. glucocorticoids, thiazide diuretics, sodium valproate, and azathioprine, Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA), and Dipeptidyl Peptidase-4 (DPP-4) inhibitors) [21,22]. Alcohol use was captured using combined codes for alcohol use disorder, alcoholic liver disease, laboratory markers for alcohol use (e.g. mean corpuscular volume >100 fL, AST/ALT ratio >2:1, GGT elevation), history of alcohol use disorder counseling, and treatment (e.g. disulfiram, naltrexone, acamprosate). Additional comorbid conditions associated with increased healthcare utilization in patients with CP were captured, including psychiatric comorbidities (e.g. depression, anxiety, psychotic disorders, and substance use disorders) [7,23–25], along with the presence of exocrine insufficiency and malnutrition. Furthermore, we retrieved data on analgesic therapy (e.g. non-opioid analgesics, gabapentinoids, tricyclic antidepressants, nerve block) to adjust for underlying pain severity and treatment pathways, and reduce potential bias from confounding by indication. Furthermore, pancreatic insufficiency treatment (metformin, insulin, enzyme supplementation). Lastly, we accounted for social determinants of adverse health outcomes; defined by a set of validated ICD-10-CM codes known as 'Z codes' (Z55-Z65), which are endorsed by the American Hospital Association Coding Clinic to capture social and economic factors that may lead to heightened social needs and impact various health and life outcomes) [26,27], see Supplementary Table 1. Using one-to-one (1:1) PSM based on these covariates, we matched patients within the CP with opioid use cohort to those who did not use opioids (e.g. control group), see Table 1 and Supplementary Table 3. Additionally, we matched patients in the subgroups (e.g. CP patients using prescription opioids without OUD, and those with a combination of both, alcohol-related CP, non-alcohol-related CP) to controls, see Supplementary Tables 4–7.

Study aims and outcomes – The primary endpoint of this study was the incidence of acute-on-chronic pancreatitis (ICD-10-CM: K85) over a one-year follow-up period, see Fig. 2. Secondary endpoints were identified with Current Procedural Terminology (CPT) codes and TriNetX codes, see Supplementary Table 1. These

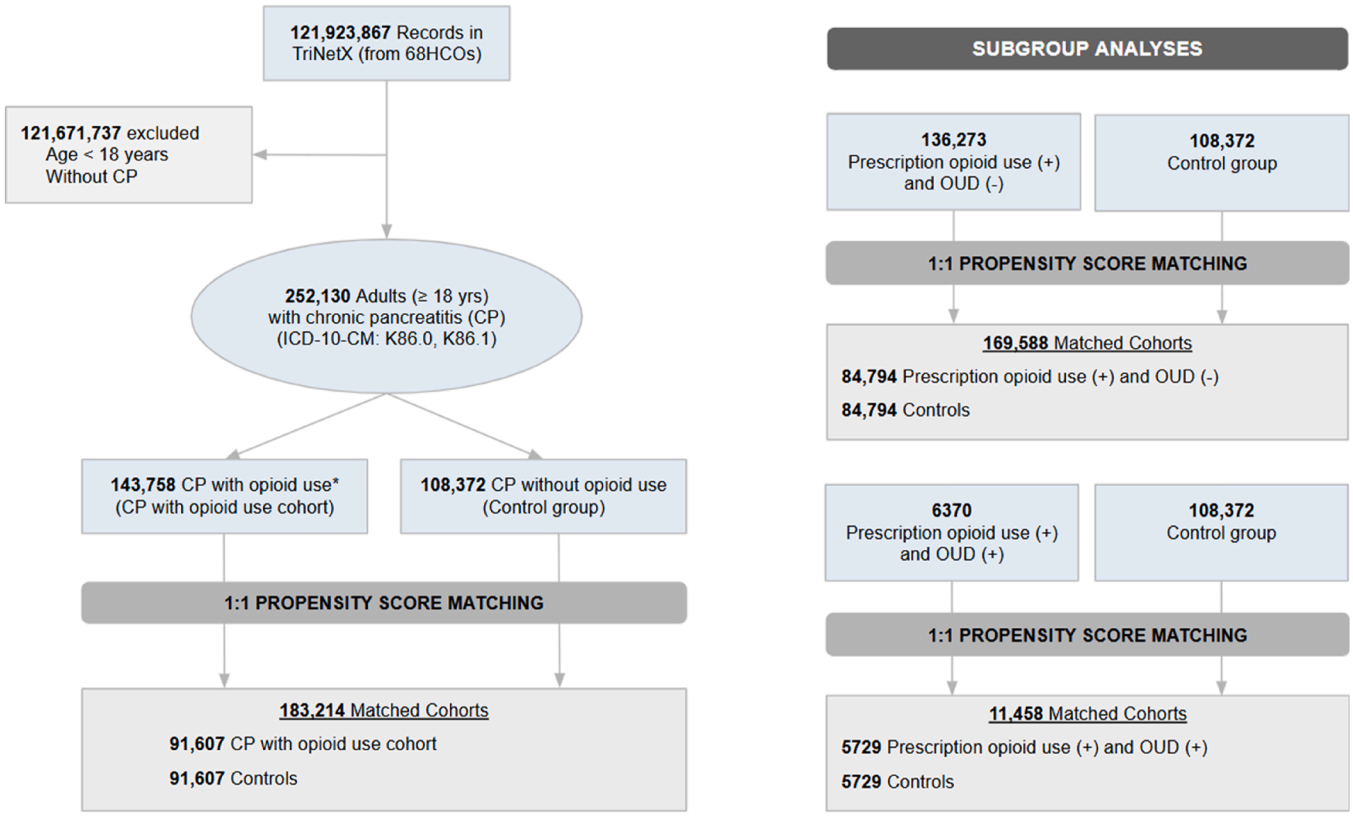

Fig. 1. Flowchart of the study population.
*Opioid use referred to prescription opioid use or opioid use disorder (OUD)
Abbreviations: CP, chronic pancreatitis, OUD, opioid use disorder.

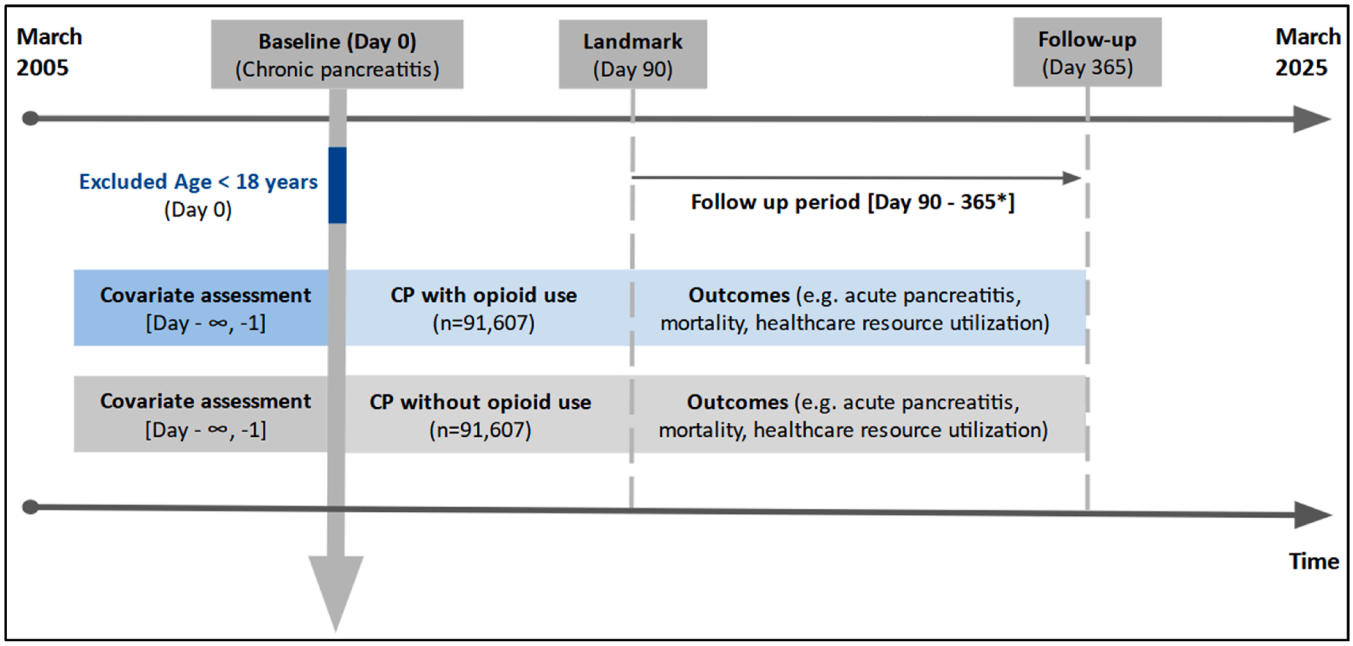

Fig. 2. Study design and follow-up timeline for patients with chronic pancreatitis (CP): comparison of cohorts with and without opioid use following initial CP diagnosis.
*Outcomes were assessed from Day 90 to Day 365 or censored at death or loss to follow-up.

outcomes included the one-year all-cause mortality (TriNetX: Deceased), along with all-cause emergency department visits (CPT: 1013711), hospitalizations (CPT: 1013659), and intensive care unit (ICU) admissions (CPT: 1013729). Given the potential overlap between acute-on-chronic pancreatitis events and emergency department visits, these outcomes were analyzed in separate

Table 1
Baseline characteristics when comparing individuals with chronic pancreatitis (CP) using prescription opioid analgesics or diagnosed with opioid use disorder (CP with opioid use cohort, n = 143,758) compared to those without opioid exposure (control group, n = 108,372). Matching based on demographics, comorbidities, social determinants of adverse health outcomes, and treatment resulted in 91,607 matched pairs.

Baseline characteristics	Before propensity matching					After propensity matching				
	CP with opioid use		Controls		p	CP with opioid use		Controls		p
	N	%	N	%		N	%	N	%	
Age (Mean ± SD)	55.3 ± 16.2	–	56.7 ± 18.1	–	<0.0001	56.1 ± 16.4	–	55.9 ± 18.1	–	0.001
Sex										
Male	71,378	51.0 %	51,226	48.1 %	<0.0001	45,267	49.4 %	45,314	49.5 %	0.826
Female	63,321	45.3 %	50,032	47.0 %	<0.0001	42,568	46.5 %	42,593	46.5 %	0.907
Race or Ethnicity										
White	92,779	66.3 %	70,053	65.8 %	0.003	61,172	66.8 %	61,352	67.0 %	0.372
Black or African American	24,385	17.4 %	14,599	13.7 %	<0.0001	13,657	14.9 %	13,636	14.9 %	0.890
Hispanic or Latino	9101	6.5 %	7504	7.0 %	<0.0001	6307	6.9 %	6265	6.8 %	0.698
Social determinants of adverse health outcomes	6423	4.6 %	2959	2.8 %	<0.0001	2731	3.0 %	2806	3.1 %	0.306
Alcohol use										
Alcohol use disorder	25,520	18.3 %	10,491	9.9 %	<0.0001	10,295	11.2 %	10,354	11.3 %	0.663
Alcoholic liver disease	9000	6.4 %	3394	3.2 %	<0.0001	3306	3.6 %	3325	3.6 %	0.812
MCV >100 fL	18,385	13.1 %	8461	7.9 %	<0.0001	8196	8.9 %	8108	8.9 %	0.470
AST/ALT ratio >2:1	683	0.5 %	192	0.2 %	<0.0001	227	0.2 %	192	0.2 %	0.087
GGT elevation	9097	6.5 %	4402	4.1 %	<0.0001	4172	4.6 %	4172	4.6 %	1.000
AUD counseling	795	0.6 %	280	0.3 %	<0.0001	258	0.3 %	275	0.3 %	0.461
AUD treatment	2835	2.0 %	1256	1.2 %	<0.0001	1246	1.4 %	1215	1.3 %	0.529
Pancreatitis risk factors[a]										
History of acute pancreatitis	46,677	33.4 %	23,077	21.7 %	<0.0001	22,112	24.1 %	22,147	24.2 %	0.848
Smoking	35,696	25.5 %	15,157	14.2 %	<0.0001	14,763	16.1 %	14,877	16.2 %	0.470
Cholelithiasis	16,042	11.5 %	8057	7.6 %	<0.0001	7681	8.4 %	7628	8.3 %	0.655
Malignant neoplasm of pancreas	10,087	7.2 %	2924	2.7 %	<0.0001	3109	3.4 %	2924	3.2 %	0.015
Hypertriglyceridemia > 1000 mg/dL	1873	1.3 %	939	0.9 %	<0.0001	864	0.9 %	893	1.0 %	0.487
Hypercalcemia > 10.5 mg/dL	10,700	7.7 %	5560	5.2 %	<0.0001	5200	5.7 %	5239	5.7 %	0.694
Spasm of sphincter of Oddi	508	0.4 %	214	0.2 %	<0.0001	201	0.2 %	211	0.2 %	0.622
Congenital malformations of pancreas and pancreatic duct	1900	1.4 %	964	0.9 %	<0.0001	971	1.1 %	931	1.0 %	0.357
Drugs inducing pancreatitis										
Glucocorticoids	57,386	41.0 %	31,572	29.6 %	<0.0001	29,795	32.5 %	29,736	32.5 %	0.769
Thiazide diuretics	20,626	14.8 %	12,072	11.3 %	<0.0001	11,324	12.4 %	11,204	12.2 %	0.393
Valproate	2444	1.7 %	1133	1.1 %	<0.0001	1091	1.2 %	1095	1.2 %	0.931
Azathioprine	976	0.7 %	478	0.4 %	<0.0001	466	0.5 %	454	0.5 %	0.692
GLP-1 analogues	2344	1.7 %	1702	1.6 %	0.130	1549	1.7 %	1506	1.6 %	0.433
DPP-4 inhibitors	3503	2.5 %	2388	2.2 %	<0.0001	2162	2.4 %	2149	2.3 %	0.841
Other comorbid conditions										
Exocrine pancreatic insufficiency	2490	1.8 %	898	0.8 %	<0.0001	921	1.0 %	883	1.0 %	0.369
Malnutrition	14,231	10.2 %	4818	4.5 %	<0.0001	4834	5.3 %	4765	5.2 %	0.469
Anxiety disorders	33,613	24.0 %	17,972	16.9 %	<0.0001	16,636	18.2 %	16,688	18.2 %	0.753
Mood disorders	33,479	23.9 %	17,759	16.7 %	<0.0001	16,518	18.0 %	16,539	18.1 %	0.898
Psychotic disorders	3977	2.8 %	2221	2.1 %	<0.0001	2041	2.2 %	2021	2.2 %	0.751
Substance use disorder	49,683	35.5 %	21,916	20.6 %	<0.0001	21,308	23.3 %	21,483	23.5 %	0.334
BMI	27.1 ± 7.0		27.2 ± 6.8		0.0003	27.1 ± 6.9		27.3 ± 6.8		0.377
< 18 kg/m^2	9157	6.5 %	5000	4.7 %	<0.0001	4681	5.1 %	4665	5.1 %	0.865
18–25 kg/m^2	43,466	31.1 %	25,095	23.6 %	<0.0001	23,397	25.5 %	23,239	25.4 %	0.397
25–30 kg/m^2	42,854	30.6 %	25,407	23.9 %	<0.0001	23,493	25.6 %	23,285	25.4 %	0.265
≥ 30 kg/m^2	37,658	26.9 %	21,554	20.2 %	<0.0001	20,166	22.0 %	20,134	22.0 %	0.857
Analgesic therapy										
Non-opioid analgesics	84,952	60.8 %	42,735	40.1 %	<0.0001	41,996	45.8 %	41,813	45.6 %	0.391
NSAIDs	28,077	20.1 %	13,970	13.1 %	<0.0001	13,441	14.7 %	13,441	14.7 %	1.000
Gabapentinoids	29,891	21.4 %	13,030	12.2 %	<0.0001	12,822	14.0 %	12,775	13.9 %	0.751
Tricyclic antidepressants	10,090	7.2 %	4477	4.2 %	<0.0001	4360	4.8 %	4360	4.8 %	1.000
Nerve block	5182	3.7 %	2596	2.4 %	<0.0001	2546	2.8 %	2502	2.7 %	0.530
Pancreatic insufficiency management										
Metformin	16,043	11.5 %	9896	9.3 %	<0.0001	9147	10.0 %	9042	9.9 %	0.412
Insulin	33,979	24.3 %	16,037	15.1 %	<0.0001	15,842	17.3 %	15,545	17.0 %	0.066
Enzyme supplementation	17,277	12.4 %	9947	9.3 %	<0.0001	9389	10.2 %	9214	10.1 %	0.176

Abbreviations: BMI, Body Mass Index, CP, chronic pancreatitis, DPP-4, Dipeptidyl peptidase 4, GLP-1, Glucagon-like peptide-1, NSAID, non-steroid anti-inflammatory drug, SD, standard deviation.

[a] Pancreatitis risk factors included risk factors for both acute and chronic pancreatitis.

models to minimize collinearity and isolate their respective associations with opioid exposure. Adjustments for confounders, including demographics, comorbid conditions, treatments, and social determinants for adverse health outcomes were made to account for potential confounding effects. Furthermore, we assessed the trends of prevalence of opioid use in patients with CP, see Fig. 3 and Supplementary Table 2.

Statistical analysis – Statistical analyses were conducted using the TriNetX Advanced Analytics Platform. Continuous variables were reported as mean ± SD and compared using t-tests, while categorical variables were presented as absolute frequencies and corresponding percentages and compared using Chi-square tests, with statistical significance set at two-sided $p < 0.05$. To minimize confounding, 1:1 PSM was employed using logistic regression of all

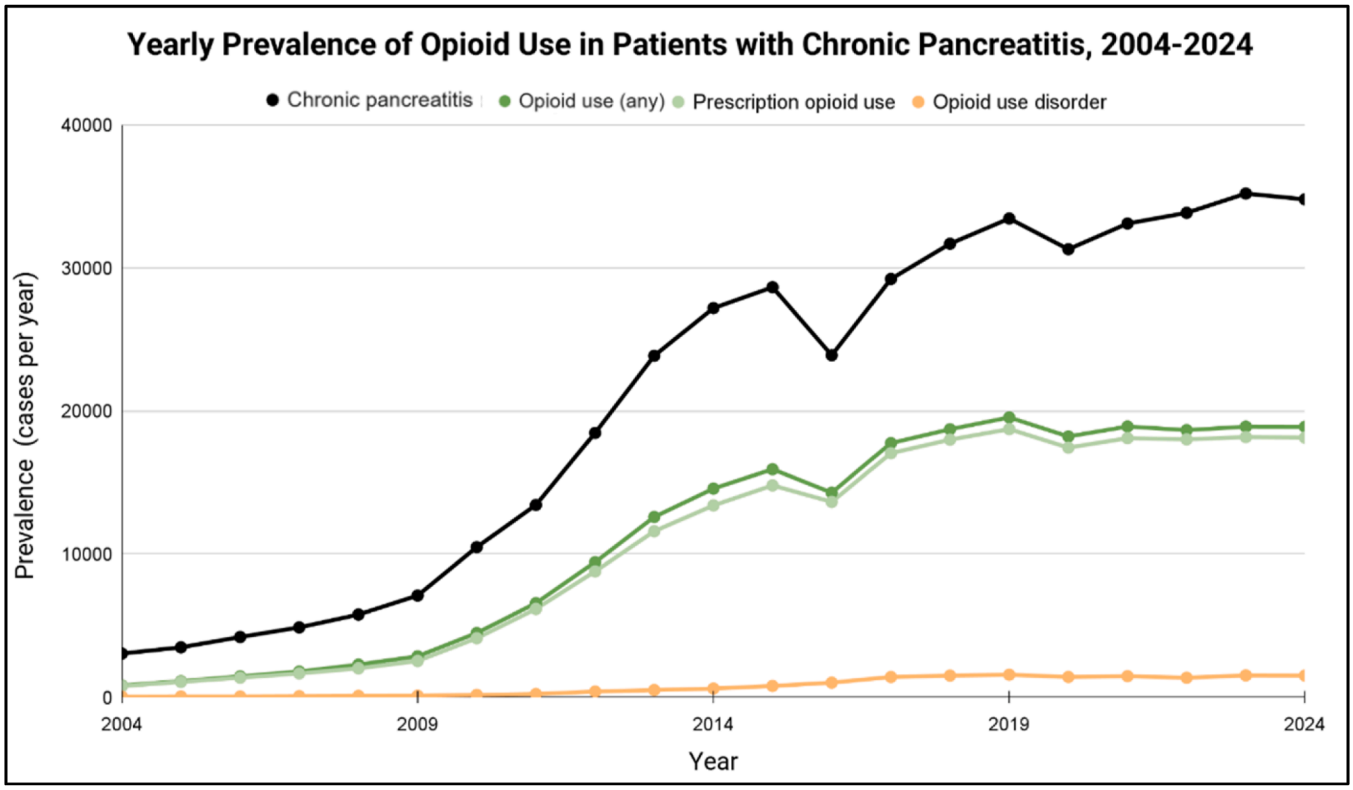

Fig. 3. Trends of opioid use in patients with chronic pancreatitis, from 2004 to 2024.

baseline covariates, greedy nearest-neighbor algorithm without replacement, and a caliper of 0.1 SD of the logit of the propensity score. PSM was preferred over weighting or stratification to enhance clinical interpretability and enable patient-level comparisons [28,29]. Balance was evaluated post-matching using standardized mean differences (SMDs), with values < 0.1 indicating adequate balance. Comparative analyses were performed between matched cohorts (e.g. CP with opioid use vs. controls; prescription opioid use vs. controls; prescription opioid use with OUD vs. controls).

To mitigate immortal time bias and ensure temporal comparability, a landmark analysis was performed at Day 90 following the index diagnosis of CP. Patients who died, were lost to follow-up, or experienced the primary outcome before this time point were excluded. Eligible patients were then stratified based on opioid use status at Day 90 (CP + opioid vs CP–opioid). Follow-up extended from Day 90 to Day 365 or until censoring (death or loss to follow-up).

Separately, temporal trends in early post-diagnosis opioid exposure were evaluated across calendar years 2004–2024. For each year, patients with incident CP were identified, and the proportion with opioid exposure within 90 days of diagnosis was estimated. This fixed observation window was employed to minimize bias related to differential follow-up or early mortality. Opioid exposure was defined as either an opioid prescription or OUD diagnosis during this interval, irrespective of prior use, see Fig. 3 and Supplementary Table 2.

For all-cause mortality, cumulative event probabilities were estimated using Kaplan-Meier methods and compared using the log-rank test. For non-mortality outcomes, we applied a competing risks framework using the Aalen-Johansen estimator to account for death as a competing event. Adjusted hazard ratios (aHRs) with 95 % confidence intervals (CIs) were estimated using Cox proportional hazards regression. Assumptions of proportionality were evaluated using Schoenfeld residuals; a p-value>0.05 was interpreted indicative of no violation of the proportionality assumption. Violations were addressed through stratified models where appropriate. Incidence rates were reported as percentages alongside absolute event counts. All analyses were performed using R (survival package, version 3.2–3), with variance estimates for competing risks derived using the infinitesimal jackknife method.

To assess opioid analgesic treatment patterns, we analyzed time to treatment initiation, treatment duration, and retention using the TriNetX Treatment Pathways function, see Supplementary Methods and Supplementary Fig. 1. All analyses were conducted within the TriNetX platform. The reporting of this study adheres to the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) reporting guidelines, see Supplementary Table 9 [30].

3. Results

Study population – A total of 121,923,867 records were identified within the U.S. Collaborative Network. Amongst these, 252,130 adult individuals (≥18 years) were diagnosed with CP. Of this cohort, 143,758 (57 %) were exposed to opioids within 90 days of CP diagnosis (e.g. either prescription opioid analgesics or OUD) (CP with opioid use cohort), whereas 108,372 (43 %) were not (control group), see Figs. 1 and 2.

Within the CP with opioid use cohort, 136,273 (95 %) patients received prescription opioid analgesics without a documented history of OUD, while 6370 (4 %) had a combination of prescription opioid use and OUD, see Fig. 1. Each subgroup was propensity-matched with 108,372 controls (e.g. patients in the CP without opioid use within one year after the first index diagnosis of CP),

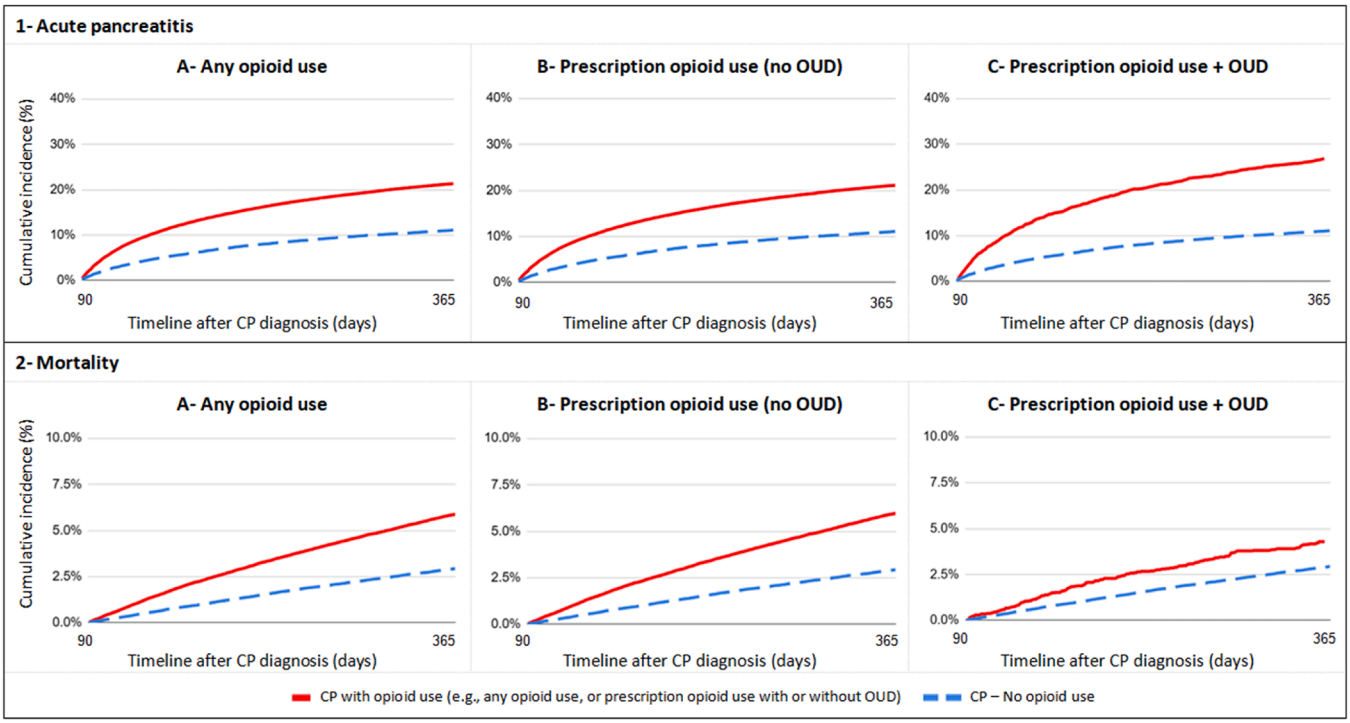

Fig. 4. Cumulative incidence of acute pancreatitis episodes and mortality within one year following chronic pancreatitis (CP) diagnosis, stratified by opioid use.
(A) CP patients with any opioid use vs. no opioid use.
(B) CP patients using prescription opioids without opioid use disorder (OUD) vs. no opioid use.
(C) CP patients using prescription opioids with OUD vs. no opioid use.
At one year, cumulative incidence of acute pancreatitis was 21.3 % (A), 21.1 % (B), and 26.7 % (C) among opioid-exposed groups, compared with 11.0 % in the opioid-unexposed group. One-year mortality was 5.9 % (A), 5.9 % (B), and 4.3 % (C) among opioid-exposed groups, compared with 2.9 % in the opioid-unexposed group.
Abbreviations: CP, chronic pancreatitis, OUD, opioid use disorder.

resulting in matched pairs of 91,607 (CP with opioid use vs. control), 84,794 (CP with prescription opioid use vs. control), and 5729 records (CP with prescription opioid use and OUD vs. control), see Fig. 1.

Additionally, patients were stratified based upon the aetiology of their CP. As a result, 6507 individuals with alcohol-related CP using opioids were matched with 4404 controls, resulting in 4035 matched pairs. Furthermore, 121,053 patients with non-alcohol-related CP using opioids were matched with 99,964 non-opioid users with non-alcohol related CP, resulting in 80,872 matched pairs.

Between 2004 and 2024, the prevalence of opioid use in the first 90 days of CP diagnosis increased steadily, rising from 27.1 % (n = 826) to 54.3 % (n = 18,890), see Fig. 3 and Supplementary Table 2. This trend was reflected in the prevalence of opioid analgesic prescriptions, which increased from 25.6 % (n = 783) to 52.1 % (n = 18,136). Similarly, the prevalence of OUD increased from 1.6 % (n = 48) to 4.4 % (n = 1523) over the same period.

Patient characteristics – Among the unmatched samples, individuals in the CP with opioid use cohort (n = 143,758) were younger than those in the control group (n = 108,372) and were more likely to identify as White or Black/African American (all $p < 0.0001$). Furthermore, opioid users were more likely to have evidence of alcohol use, pancreatitis risk factors, psychiatric comorbidities, malnutrition, Charlson comorbidities, analgesic therapy, and pancreatic insufficiency treatment utilization compared to controls (all $p < 0.0001$), see Table 1 and Supplementary Table 3. A similar distribution of baseline characteristics was observed across subgroups with prescription opioid use with or without OUD, compared to controls, see Supplementary Tables 4 and 5, and with subgroups with alcohol-related and non-alcohol-related CP, see Supplementary Table 6 and 7 We matched cohorts using PSM to eliminate the influence of confounders on study outcomes, ensuring a balanced distribution of covariates, as indicated by non-significant p-values ($p > 0.05$) across matched variables, enhancing the comparability between treatment and control cohorts, see Table 1 and Supplementary Tables 3–7.

Among CP patients who received opioids at any time during follow-up (n = 189,373), 66 % (n = 124,360) initiated opioid therapy within one month of diagnosis, including 44 % who started within 24 h. Furthermore, among those prescribed opioids within 90 days of CP diagnosis (n = 143,758), the median duration of opioid use was 810 days, and a mean of 912 ± 899 days. Retention analysis revealed distinct patterns based on the reason for discontinuation: median survival was 1378 days overall, with 1997 days for those who electively discontinued treatment, see Supplementary Fig. 1.

Acute-on-chronic pancreatitis incidence – The one-year cumulative incidence of acute-on-chronic pancreatitis in patients with CP was higher in opioid users (21.3 % vs. 11.0 %) in the full unmatched cohort. Notably, patients with prescription opioid use and OUD had a higher incidence (26.7 %) compared to those without OUD (11.0 %), see Fig. 4. Among matched samples, the risk of acute-on-chronic pancreatitis was significantly higher in CP patients using opioids (n = 91,607) compared to controls (n = 91,607) (4.1 % vs. 3.2 %, aHR 1.451, 95 % CI 1.365–1.543), with proportional hazards assumptions met. Risk stratification revealed even greater associations in those with prescription opioid use and OUD (6.2 % vs. 3.7 %, aHR 1.910, 95 % CI 1.495–2.442) than those without OUD (4.1 % vs. 3.1 %, aHR 1.497, 95 % CI 1.404–1.596)

compared to controls. However, when stratified by CP aetiology, patients with alcohol-related CP did not exhibit a significant difference in acute-on-chronic pancreatitis rates between opioid users and controls (3.3 % vs. 3.2 %, aHR 1.181, 95 % CI 0.825–1.690). In contrast, patients with non-alcohol-related CP showed a significantly increased risk of acute-on-chronic pancreatitis among opioid users compared to controls (3.4 % vs. 2.9 %, aHR 1.341, 95 % CI 1.253–1.436), see Table 2 and Supplementary Table 8. Subgroup proportionality tests were non-significant for all subgroups ($p > 0.05$, except alcohol-related CP patients), indicating stable hazard ratios over time.

Mortality – The one-year cumulative mortality among CP patients was higher among opioid users (5.9 %) compared to non-users (2.9 %). Notably, patients with OUD had a lower, yet still elevated, mortality rate (4.3 %) compared to non-users, see Fig. 4. The one-year survival was significantly lower among CP patients with opioid exposure (94.5 %) compared to non-users (97.0 %, $p < 0.0001$), see Supplementary Table 8. In a matched cohort (n = 91,607 pairs), opioid-exposed patients demonstrated nearly a twofold increased risk of one-year mortality (4.2 % vs. 2.4 %, aHR 1.897, 95 % CI 1.799–2.001), an association that persisted across prescription opioid subgroups regardless of OUD status (without OUD: 4.2 % vs. 2.4 %, aHR 1.871, 95 % CI 1.771–1.978; with OUD: 3.7 % vs. 2.3 %, aHR 1.718, 95 % CI 1.378–2.141), with non-proportional hazards observed overall but proportionality met within the OUD subgroup. Furthermore, stratified analyses revealed no significant mortality difference in alcohol-related CP (2.5 % vs. 2.1 %, aHR 1.320, 95 % CI 0.986–1.766), whereas non-alcohol-related CP was associated with a two-fold increase in mortality risk (3.4 % vs. 2.9 %, aHR 2.009, 95 % CI 1.900–2.124), again with proportional hazards violation, suggesting time-varying effects, see Table 2 and Supplemental Table 8.

Healthcare resource utilization – The one-year cumulative incidence of healthcare resource utilization was markedly higher in CP patients using opioids compared to non-opioid users, including emergency department visits (26.3 % vs. 14.4 %), hospitalizations (9.7 % vs. 5.3 %), and ICU admissions (1.5 % vs. 0.7 %). The highest utilization (35.6 % hospitalizations) was recorded in the OUD subgroup, see Fig. 5. Among matched samples, opioid use in CP patients (n = 91,607) was strongly associated with higher healthcare resource utilization, including emergency department visits (5.0 vs. 4.3 %, 95 % CI 1.217–1.356), hospitalizations (5.7 % vs. 4.0 %, 95 % CI 1.499–1.666), and ICU admissions (2.8 % vs. 1.6 %, 95 % CI 1.804–2.066). Proportional hazards assumptions were violated for all outcomes ($p < 0.049$) suggesting escalating risk with prolonged opioid exposure. Notably, patients with OUD exhibited the highest risk escalation for ICU admissions (5.2 % vs. 2.6 %, aHR 2.180, 95 % CI 1.747–2.719) and ED visits (6.5 % vs. 4.9 %, aHR 1.467, 95 % CI 1.157–1.861), while those without OUD showed disproportionately increased hospitalization rates (5.6 % vs. 4.0 %, aHR 1.534, 95 % CI 1.451–1.622), all with no violation of proportional hazards. In contrast, patients with alcohol-related CP showed no differences in healthcare resource utilization, where as those with non-alcohol-related CP demonstrated significantly increased

Table 2
Outcomes when comparing patients with chronic pancreatitis (CP) using prescription opioid analgesics or diagnosed with opioid use disorder (OUD) (CP with opioid use cohort, n = 91,607) to those without documented opioid use (control, n = 91,607, controls) after propensity score matching. Subgroup analyses comparing patients with alcohol-related CP, non-alcohol-related CP, prescription opioid use with or without OUD, all compared to controls were performed. Patients with pre-inclusion outcomes were excluded from the analysis.

Outcomes	Incidence % (N)		Cox regression		Proportional Hazards Assumption	
	CP with opioid use	Control group	aHR[a]	95 % CI	χ^2	P**
A. Main analysis						
Acute-on-chronic pancreatitis	4.1 % (2125)	3.2 % (1991)	1.451	(1.365–1.543)	0.087	0.768
Mortality	4.2 % (3656)	2.4 % (2145)	1.897	(1.799–2.001)	8.433	0.004
All-cause ED visits	5.0 % (2553)	4.3 % (2691)	1.284	(1.217–1.356)	27.854	<0.0001
All-cause Hospitalizations	5.7 % (2797)	4.0 % (2709)	1.580	(1.499–1.666)	3.879	0.049
All-cause ICU admissions	2.8 % (2180)	1.6 % (1344)	1.931	(1.804–2.066)	7.499	0.006
B. Prescription opioid use (No OUD)						
Acute-on-chronic pancreatitis	4.1 % (1959)	3.1 % (1786)	1.497	(1.404–1.596)	0.232	0.630
Mortality	4.2 % (3361)	2.4 % (2014)	1.871	(1.771–1.978)	6.116	0.013
All-cause ED visits	5.6 % (2504)	4.5 % (2546)	1.408	(1.332–1.487)	14.101	0.0002
All-cause Hospitalizations	5.6 % (2496)	4.0 % (2489)	1.534	(1.451–1.622)	3.058	0.080
All-cause ICU admissions	2.7 % (1995)	1.6 % (1247)	1.911	(1.780–2.051)	6.460	0.011
C. Prescription opioid use + OUD						
Acute-on-chronic pancreatitis	6.2 % (152)	3.7 % (110)	1.910	(1.495–2.442)	0.275	0.600
Mortality	3.7 % (206)	2.3 % (128)	1.718	(1.378–2.141)	0.711	0.399
All-cause ED visits	6.5 % (137)	4.9 % (135)	1.467	(1.157–1.861)	2.224	0.136
All-cause Hospitalizations	5.5 % (110)	4.4 % (142)	1.369	(1.067–1.756)	0.015	0.904
All-cause ICU admissions	5.2 % (214)	2.6 % (124)	2.180	(1.747–2.719)	1.453	0.228
D. Alcohol-related CP						
Acute-on-chronic pancreatitis	3.3 % (51)	3.2 % (72)	1.181	(0.825–1.690)	5.617	0.018
Mortality	2.5 % (97)	2.1 % (85)	1.320	(0.986–1.766)	2.135	0.144
All-cause ED visits	2.9 % (55)	3.4 % (85)	1.002	(0.714–1.407)	0.570	0.450
All-cause Hospitalizations	3.5 % (68)	3.0 % (82)	1.370	(0.994–1.890)	0.107	0.744
All-cause ICU admissions	2.4 % (76)	2.3 % (82)	1.184	(0.867–1.618)	0.330	0.566
E. Non-Alcohol-related CP						
Acute-on-chronic pancreatitis	3.4 % (1663)	2.9 % (1638)	1.341	(1.253–1.436)	0.048	0.826
Mortality	4.5 % (3463)	2.4 % (1945)	2.009	(1.900–2.124)	8.662	0.003
All-cause ED visits	4.8 % (2221)	4.4 % (2381)	1.252	(1.181–1.326)	18.891	<0.0001
All-cause Hospitalizations	5.4 % (2359)	4.0 % (2367)	1.508	(1.424–1.597)	10.695	0.001
All-cause ICU admissions	2.7 % (1867)	1.5 % (1163)	1.927	(1.791–2.074)	8.182	0.004

Abbreviations: aHR, adjusted hazard ratio, CP, chronic pancreatitis, ED, emergency department, ICU, intensive care unit, OUD, opioid use disorder.
** p-value assesses the validity of the proportional hazards assumption and should not be interpreted as indicator of statistical significance.
[a] Adjusted for demographics, comorbid conditions and treatment.

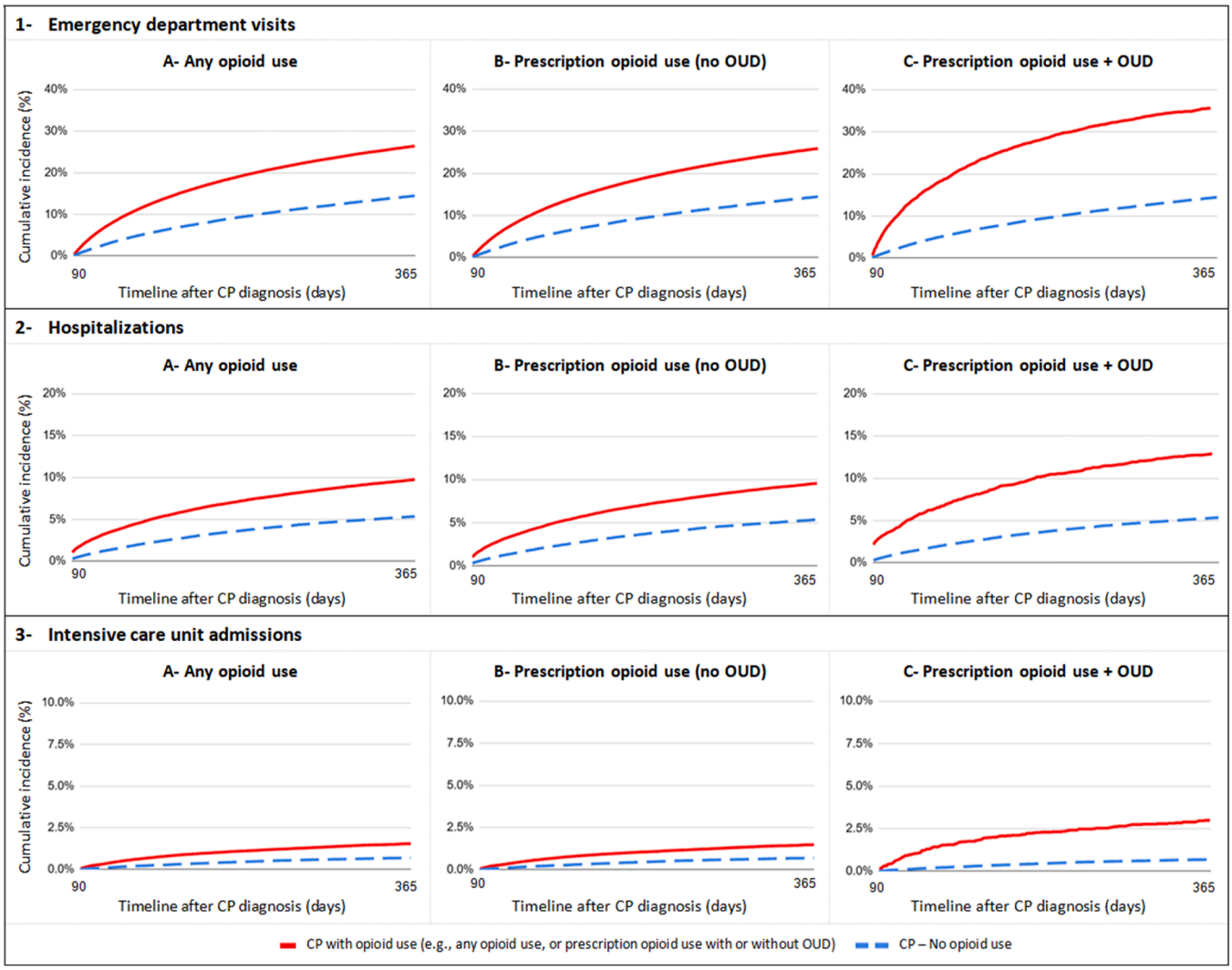

Fig. 5. Cumulative incidence of emergency department (ED) visits, hospitalizations, and intensive care unit admissions within one year following chronic pancreatitis (CP) diagnosis, stratified by opioid use.
(A) CP patients with any opioid use vs. no opioid use.
(B) CP patients using prescription opioids without opioid use disorder (OUD) vs. no opioid use.
(C) CP patients using prescription opioids with OUD vs. no opioid use.
At one year, cumulative incidence of ED visits was 26.3 % (A), 25.8 % (B), and 35.6 % (C) among opioid-exposed groups, compared with 14.4 % in the opioid-unexposed group. Hospitalization rates were 9.7 % (A), 9.5 % (B), and 12.9 % (C) among opioid-exposed groups, versus 5.3 % in the unexposed group. ICU admission rates were 1.5 % (A), 1.5 % (B), and 3.0 % (C), compared with 0.7 % in the opioid-unexposed group.
Abbreviations: CP, chronic pancreatitis, OUD, opioid use disorder.

healthcare resource utilization, with significant violations of proportionality across all utilization outcomes (all $p < 0.05$), suggesting time-dependent risk amplification, see Table 2 and Supplemental Table 8.

4. Discussion

This cohort study investigated the trends and clinical outcomes associated with opioid use in patients with CP using real-world data from a comprehensive U.S.-based healthcare database. Our results demonstrate that prescription opioid use, whether or not associated with OUD, significantly associates with increased healthcare resource utilization and adverse clinical outcomes.

The observed increase in opioid use among patients with CP reflects broader national trends in opioid consumption and prescription practices. Over the past two decades, opioid use has risen dramatically in these patients, driven by increased prescribing for chronic pain management and, subsequently, a rise in OUD [23,31–33]. Between 2004 and 2024, the prevalence of opioid use among patients with CP increased from 27.1 % to 54.3 %, with prescription opioids accounting for the majority of cases. This trend has been shaped by the chronic debilitating pain associated with CP, often leading to long-term opioid therapy despite concerns about dependence and adverse outcomes [31]. The growing prevalence of OUD—now affecting 10.7 % of CP patients—underscores the urgent need for alternative pain management strategies, including multimodal analgesia and non-opioid therapies.

Our study found that even after adjusting for other potential confounders such as demographics, comorbid conditions, and treatment, opioid use in patients with CP was associated with a nearly 1.5-fold increase in acute-on-chronic pancreatitis rates. Although these findings should be interpreted as associations

rather than causal relationships given the potential for reverse causation and confounding by indication, previous studies suggested that opioid analgesics may worsen acute pancreatitis by increasing inflammation, gut permeability, and impairing macrophage healing [12], with prolonged use (e.g. more than 6 days) associated with an increased risk of severe pancreatitis [10]. Furthermore, some studies have hypothesized that opioids may contribute to increased pancreatic ductal pressure or sphincter of Oddi dysfunction, potentially aggravating pancreatic inflammation [1,22]; however, these mechanisms remain controversial and are supported by limited or inconsistent evidence. However, a recent study using peripherally restricted opioid antagonists did not influence the severity of acute pancreatitis [34]. Adequate analgesia in CP is critical, not only to enhance patient quality of life but also to mitigate associated morbidity such as malnutrition and functional decline. Given the often persistent and debilitating nature of pain, current evidence supports a stepwise, multimodal analgesic approach, reserving opioids for refractory cases unresponsive to non-opioid therapies.

Furthermore, there is a concerning increase in all-cause mortality among opioid users with CP. In fact, opioid use has been identified as the strongest predictor of mortality in patients with following surgical intervention, where opioid-dependent patients were four times more likely to expire than opioid-free patients [35]. Although a recent study reported lower mortality in patients receiving combination analgesic therapy with opioids and acetaminophen, it was associated with longer hospital stays in ICU patients hospitalized with acute pancreatitis [36].

The increased healthcare resource utilization among opioid users with CP was previously observed by Phillips et al. and Bilal et al., who reported that opioid-dependent CP patients experience increased hospitalization rates and disability, higher healthcare costs, and worsened quality of life [23, 31]. Similarly, higher opioid use was also associated with persistent OUD and a higher 30-day readmission risk [7,25]. Additionally, a nationwide analysis demonstrated that 3.5 % of CP admissions had OUD, with affected patients having significantly longer hospitalizations (4.4 vs. 3.9 days) and a 25 % increased risk of readmission [11].

Given the growing body of evidence highlighting the risks of opioid therapy, including opioid withdrawal symptoms, opioid induced bowel dysfunction, and worsening pancreatitis symptoms [37], there is a pressing need for alternative pain management strategies in CP. Other options include targeted drug delivery through intrathecal opioid therapy, central sensitization, and neural remodeling that includes neuromodulators (e.g., pregabalin, antidepressants), interventional procedures (e.g. celiac plexus block), and, in refractory cases, endoscopic or surgical interventions [4,38]. Lastly, a recent trial (e.g., the ESCAPE Trial) demonstrated that early surgical intervention resulted in superior pain control, higher patient satisfaction, and greater cost-effectiveness compared to an endoscopy-first approach, without adversely affecting quality of life or pancreatic function in patients with painful obstructive CP and a dilated pancreatic duct [39–41]. Both the American College of Gastroenterology and the American Gastroenterological Association recommend interventional treatment (surgical or endoscopic) for symptomatic patients, particularly those with pain due to ductal obstruction [42,43].

The strength of this study includes the use of a large-scale, real-world dataset, facilitating an analysis of over 252,130 patients with CP. This ensures the external validity of our findings compared to previous small-scale studies. PSM allowed for adjustment for potential confounders, including demographics, comorbid conditions, and treatments, ensuring that the differences observed were associated with opioid use rather than other risk factors. Lastly, our comprehensive analysis of the differential effects of opioid use across CP subgroups offered additional insights into opioid-associated outcomes. Despite its strengths, our study has several limitations. First, the retrospective and observational design of this study precludes causal inference; while associations can be identified, causality cannot be established without prospective or randomized data. Second, this study was based on data from U.S. healthcare systems, which may limit the generalizability of findings to other countries due to differences in healthcare delivery, opioid prescribing practices, and chronic pancreatitis management. Additionally, our reliance on ICD-10 coding may introduce the risk of misclassification bias; in fact, the observed prevalence of alcohol-related CP in our cohort was lower than previously reported (e.g., 42–77 %) [44], likely due to limitations in diagnostic coding and insurance-related documentation. Furthermore, patients with overlapping alcohol-related and non-alcohol-related CP codes were excluded to reduce misclassification, which may have further contributed to underestimation. Additionally, our findings may be influenced by confounding by indication and reverse causation, as patients receiving opioids likely represent a more severe phenotype of CP, characterized by greater baseline pain and a higher burden of complications—factors that are themselves associated with poorer outcomes. In fact, among unmatched samples, patients prescribed opioids in our cohort had a significantly higher prevalence of pancreatic malignancy, which likely reflects greater underlying disease severity and symptom burden. This limits the comparability between groups and precludes causal interpretations. Imaging findings and validated scoring systems (e.g., M-ANNHEIM, COPPS, others) were not available within the TriNetX platform, therefore, proxy indicators of disease severity – such as previous non-opioid analgesic therapy and pancreatic insufficiency treatment – were utilized. Although PSM reduced confounding, residual confounding may persist from unmeasured variables, such as opioid dosing, pain severity, and adherence to non-opioid therapies. Furthermore, the TriNetX platform does not specify indications for medication use, which may result in an overestimation of opioid prescriptions by encompassing cases related to both acute and CP as well as other chronic pain conditions. In time-to-event analyses for non-mortality outcomes, treating death as a censoring event rather than a competing risk may have underestimated non-mortality event probability. However, competing risk analysis allowed us to adjust the incidence of non-mortality outcomes accordingly, providing more realistic estimates in our unmatched samples. Currently, the TriNetX analytics platform does not support competing risk analyses on propensity score–matched samples. It is important to note that a higher incidence of acute-on-chronic pancreatitis or healthcare utilization among opioid users does not necessarily reflect increased disease severity, as TriNetX but lacks clinical markers such as pain scores, imaging findings, or hospitalization severity. In fact, one recent study found no definitive association between opioid doses and the severity of acute pancreatitis, challenging earlier findings that suggested a potential dose-dependent risk [45]. Another limitation of this study is that opioid exposure was characterized using annual incidence and prevalence rates derived from aggregated population-level data rather than individual-level, time-varying measures, due to constraints within the TriNetX platform. As such, the exposure variable does not capture the timing, duration, or frequency of prescriptions at the patient level, which may limit the precision of temporal associations and the ability to assess causal relationships. Future studies leveraging longitudinal data and advanced modeling are needed to better capture dynamic treatment effects. Furthermore, the smaller size of the OUD and alcohol-related subgroups had less statistical power, thereby contributing to non-significant differences in outcomes, whereas the larger main

cohort allowed more reliable assessment of associations between opioid use and outcomes in chronic pancreatitis. Additionally, our analysis lacked stratification by opioid class, potency, or route of administration. This precludes the ability to discern differential risk profiles, particularly for agents such as enteral, long-acting, weak opioids (e.g. tramadol), which may exhibit distinct safety and addiction profiles. Interventional therapies for CP (e.g. endoscopic, surgical) were not included in this study to maintain the focus on pharmacologic management and avoid confounding from heterogeneous treatment pathways. Lastly, our study focused on short-term outcomes, and the long-term effects of opioid therapy—such as dependence, withdrawal, and quality of life were not assessed.

5. Conclusion

In conclusion, although patients on opioid therapy may represent a selected group with more pain and co-morbidity, our findings are consistent with prior literature. As opioid therapy may potentially be harmful, clinicians should minimize opioid exposure where possible and intensify the use of multimodal pain management strategies. Future prospective studies should further investigate the long-term efficacy of opioid-sparing approaches in CP to optimize treatment guidelines and improve patient outcomes. Clinical decision-making should carefully weigh potential risks against the ethical obligation to provide adequate pain control and maintain quality of life in this patient population.

Guarantor of the article

Professor Adam D Farmer, MD PhD FRCP.

Specific author contributions

Yassine Kilani – collection, analysis, and interpretation of the data and writing the manuscript.

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Ayah Obeid – analysis and interpretation of the data and writing the manuscript.

Farah Heis – analysis and interpretation of the data and writing the manuscript.

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Tarek Nammour - revising the manuscript for important intellectual content, drafting the manuscript.

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Søren S Olesen - revising the manuscript for important intellectual content, drafting the manuscript.

Adam D Farmer – study supervision, revising the manuscript for important intellectual content, drafting the manuscript.

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Appendix A. Supplementary data

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