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Comparative outcomes and characteristics of biliary, alcoholic and drug-induced pancreatitis based on the National Inpatient Sample (2016-2021)

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Abstract

Background Pancreatitis outcomes vary significantly depending on etiology. We compared biliary, alcoholic and drug-induced pancreatitis, focusing on mortality, complications and healthcare resource utilization to inform etiology-specific management strategies.

Methods A nationwide retrospective analysis was conducted using the National Inpatient Sample (NIS) database from 2016-2021. Patients with biliary, alcoholic and drug-induced pancreatitis were identified using International Classification of Diseases, 10th Revision (ICD-10) codes. Logistic regression models were used to compare mortality, complications and healthcare utilization, with biliary pancreatitis as the reference. Adjusted odds ratios (aORs) and regression coefficients were calculated.

Results A total of 287,050 biliary, 451,730 alcoholic, and 27,465 drug-induced pancreatitis hospitalizations were identified. Patients with alcoholic pancreatitis were younger and predominantly male, while those with drug-induced pancreatitis had higher comorbidity burdens, including diabetes, dyslipidemia and hypertension. Mortality was higher in alcoholic pancreatitis (aOR 1.19, 95% confidence interval [CI] 1.06-1.41; P=0.05), whereas drug-induced pancreatitis showed no significant difference. Alcoholic pancreatitis was associated with greater odds of pseudocyst formation (aOR 3.54, 95%CI 3.32-3.79), bleeding (aOR 1.52, 95%CI 1.41-1.63), and mechanical ventilation (aOR 2.06, 95%CI 1.84-2.31), all with P<0.001. In contrast, drug-induced pancreatitis was linked to lower odds of bleeding (aOR 0.69, 95%CI 0.57-0.84; P<0.001) and percutaneous drainage (aOR 0.23, 95%CI 0.09-0.63; P=0.004). Both alcoholic and drug-induced pancreatitis had shorter hospital stays and lower total charges compared with biliary pancreatitis.

Conclusions Alcoholic pancreatitis is associated with higher mortality and complication rates, while drug-induced pancreatitis demonstrates fewer complications but greater comorbidity. These findings highlight the importance of etiology-based management in optimizing pancreatitis outcomes.

Keywords Pancreatitis, biliary, alcoholic, drug-induced, outcomes

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Introduction

Acute pancreatitis is one of the leading causes of gastrointestinal-related hospital admissions, with a rising incidence of 2-5% annually [1,2]. In the USA, pancreatitis is estimated to account for approximately 300,000 of the total hospital admissions yearly, representing around 1 million days in hospital and over 2.5 billion dollars of estimated cost. About one fifth of the patients develop complications and the overall mortality is estimated to be around 2% [1,3,4].

The clinical course and outcomes of pancreatitis are strongly influenced by the underlying etiology [5,6]. Biliary and alcohol-induced pancreatitis are 2 of the most common etiologies,

while drug-induced pancreatitis (DIP) is relatively uncommon. These etiologies vary widely in their epidemiological patterns, risk profiles and clinical trajectories [5-7]. The revised Atlanta Classification classifies acute pancreatitis based on the presence and duration of end-organ failure and the presence of complications [8].

Biliary pancreatitis (BP), due to gallstone migration causing ductal obstruction, continues to be the most common etiology, contributing to 40-70% of cases [1]. The initial presentation tends to be severe; however, the risk of recurrence, as well as complications and mortality, tend to be less when definitive management is sought through cholecystectomy [6,9,10].

Alcohol-related pancreatitis (ARP) occurs secondary to sustained heavy alcohol use, defined as exceeding 50 g/day for over 5 years. It is the second most common etiology, accounting for 25-35% of cases [1]. It tends to affect a younger population and is usually associated with other multiple comorbidities. ARP follows a more severe course, with a high incidence of complications, chronicity, recurrence rates and mortality, particularly when the alcohol use disorder has not been addressed [1,11-13].

DIP is a less common etiology, contributing to 0.1-5% of cases. Being a diagnosis of exclusion, it requires a high index of suspicion. It typically follows a more benign course, presenting as mild to moderate disease, and tends to be associated with other comorbidities [4,14].

The most recent guidelines from the American College of Gastroenterology highlight the importance of early identification of the etiology of acute pancreatitis, followed by etiology-specific management, which can significantly reduce morbidity, mortality and healthcare utilization [1]. We aimed to analyze nationwide data to evaluate the impact of different etiologies of pancreatitis on clinical outcomes, including morbidity, mortality, length of hospital stay (LOS) and healthcare costs. These findings may serve as a reference for developing etiology-based management strategies to improve patient outcomes and optimize resource utilization.

Materials and methods

Study design and data source

We conducted a retrospective cohort study using the National Inpatient Sample (NIS) for calendar years 2016-2021. The NIS, developed by the Healthcare Cost and Utilization Project (HCUP) and maintained by the Agency for Healthcare Research and Quality, is the largest publicly available all-payer inpatient database in the United States. It contains discharge-level data drawn from approximately 20% of all community hospital admissions nationwide (excluding rehabilitation and long-term acute care facilities) and employs a stratified sampling design that permits weighted analyses to generate nationally representative estimates of hospital utilization, costs, demographics and outcomes.

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Study population and variables

We identified adult hospitalizations (≥18 years) with acute pancreatitis (AP) using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes K85.x. Etiology was determined from ICD-10 AP etiologic codes recorded during the hospitalization and categorized as biliary acute pancreatitis (K85.1), alcohol-induced pancreatitis (K85.2) or DIP (K85.3). Hospitalizations coded as other or unspecified acute pancreatitis (e.g., K85.8, K85.9)—which may include rarer etiologies, such as idiopathic pancreatitis, hypertriglyceridemia- or hypercalcemia-associated pancreatitis—were not included in the etiologic comparisons. We did not analyze hypertriglyceridemia- or hypercalcemia-induced pancreatitis as separate etiologies because the dataset does not include laboratory triglyceride or calcium values, and does not allow consistent identification of these causes beyond other/unspecified coding. To ensure mutually exclusive groups, admissions with more than 1 etiologic code were assigned according to a prespecified hierarchy, prioritizing the principal diagnosis; encounters with unresolved overlap were excluded from the analysis. Admissions with chronic pancreatitis (K86.0/1), pancreatic malignancy (C25.x), pregnancy-related hospitalizations, or missing key demographics (age or sex) were excluded. Patient demographics included age, sex, race/ethnicity, primary payer, and ZIP-code–based median household income quartile. Hospital characteristics comprised region (Northeast, Midwest, South, West), size (small, medium, large), and location/teaching status (rural, urban non-teaching, urban teaching) using HCUP definitions. Comorbidities were captured via ICD-10-CM codes and summarized both individually (e.g., hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, chronic obstructive pulmonary disease, obesity, tobacco/cannabis use disorders, heart failure) and with the Charlson Comorbidity Index (CCI) as an overall measure of disease burden.

Outcomes

The primary outcome was in-hospital all-cause mortality, indicated by the NIS variable "DIED." Secondary outcomes were AP-related complications and resource utilization: pancreatic pseudocyst/cyst, gastrointestinal bleeding, packed red blood cell transfusion, percutaneous pancreatic drainage, need for invasive mechanical ventilation, shock, and acute kidney injury. Pancreatic pseudocyst and pancreatic cyst were identified using their respective ICD-10-CM diagnosis codes recorded during the index hospitalization; the NIS does not

provide imaging or pathology to further highlight cyst type. LOS (days) and total hospital charges (USD) were analyzed as continuous measures of healthcare utilization.

Statistical analysis

All analyses incorporated the NIS complex survey design, using discharge weights, strata and clustering to produce nationally representative estimates. Baseline characteristics were summarized as weighted means with standard errors for continuous variables, and weighted frequencies with percentages for categorical variables; between-group comparisons used survey-adjusted linear regression for continuous variables and Rao-Scott χ^2 tests for categorical variables. Multivariable survey-weighted logistic regression estimated adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for binary outcomes, with BP serving as the reference. For LOS and total charges, survey-weighted linear regression estimated adjusted mean differences relative to biliary AP. Covariates were selected *a priori* based on clinical relevance and prior literature, and included age, sex, race/ethnicity, income quartile, insurance type, hospital region, hospital size (beds), location/teaching status, CCI, and the individual comorbidities listed above. A 2-sided P-value ≤0.05 denoted statistical significance.

Ethical considerations

Because the NIS is a publicly available, de-identified dataset compliant with the Health Insurance Portability and Accountability Act, institutional review board approval and informed consent were not required.

Results

Demographic and socioeconomic characteristics

From 2016 to 2021, we identified 766,245 adult AP hospitalizations that met the inclusion criteria. The etiology distribution was 287,050 biliary (37.5%), 451,730 alcohol-induced (59.0%), and 27,465 drug-induced (3.6%). Patients with ARP were younger (mean age 45.04 years) and more frequently male (69.02%), whereas those with BP were older on average; DIP patients had age profiles similar to BP. Across etiologies, distributions of race/ethnicity, payer, and income quartile differed significantly, ARP being more commonly associated with lower income quartiles and public insurance, and BP occurring more frequently among older, Medicare-insured patients. Table 1 shows the baseline characteristics of patients with ARP, DIP and BP.

Hospital and regional characteristics

Most admissions in all groups occurred at urban teaching hospitals, though the proportional distribution across size and geographic region differed by etiology. ARP was more frequent in large, urban teaching centers and in Southern hospitals, while BP demonstrated broader representation across regions and hospital sizes. These differences were statistically significant on survey-adjusted comparison (Table 1).

Comorbidities

Comorbidity profiles varied across etiologies. DIP exhibited higher prevalences of cardiometabolic conditions, including diabetes, dyslipidemia and hypertension, and generally higher overall comorbidity by CCI. Substance-use patterns diverged markedly: ARP showed the highest prevalence of tobacco and cannabis use disorders. BP had comparatively lower rates of substance-use diagnoses, but a greater burden of age-related comorbidities. Full distributions are presented in Table 1.

Post-admission complications and mortality

In adjusted analyses using the BP cohort as the reference, ARP was associated with higher in-hospital mortality (aOR 1.19, 95%CI 1.06-1.41; P=0.05). ARP also carried significantly greater adjusted odds of pancreatic pseudocyst (aOR 3.54, 95%CI 3.32-3.79; P<0.001), pancreatic cyst (aOR 2.17, 95%CI 1.92-2.45; P<0.001) and invasive mechanical ventilation (aOR 2.06, 95%CI 1.84-2.31; P<0.001); bleeding (aOR 1.52, 95%CI 1.41-1.63; P<0.001), and acute kidney injury (aOR 1.41, 95%CI 1.36-1.47; P<0.001) were likewise elevated after covariate adjustment. By contrast, DIP demonstrated lower adjusted odds of gastrointestinal bleeding (aOR 0.69, 95%CI 0.57-0.84; P<0.001), blood transfusion (aOR 0.76, 95%CI 0.59-0.98; P=0.034) and percutaneous drainage (aOR 0.23, 95%CI 0.09-0.63; P=0.004) relative to BP. The direction and magnitude of effects for other complications (e.g., shock) were consistent with these patterns and are detailed in Table 2.

Healthcare utilization

Resource utilization differed significantly by etiology after multivariate adjustment. Relative to BP, ARP had a modestly shorter LOS (coefficient -0.324 days, P<0.001) and substantially lower total charges (-$19,102, P<0.001). DIP showed even greater differences in LOS and charges (coefficients -1.058 days and -$26,687, both P<0.001). These findings persisted in sensitivity analyses and aligned with the observed complication profiles (Table 3).

Table 1 Baseline characteristics of acute pancreatitis patients by etiology

Characteristics	Biliary	Alcoholic	Drug induced	P-value*
Number of patients	287050	451730	27465	
Mean age (years)	57.02	45.04	57.07	<0.001
Sex				<0.001
Male	40.69%	69.02%	45.52%	
Female	59.31%	30.98%	54.48%	
Race				<0.001
White	64.01%	60.84%	66.92%	
Black	10.09%	23.52%	15.80%	
Hispanic	18.56%	10.42%	11.60%	
Asian or Pacific Islander	2.92%	1.30%	2.19%	
Native American	0.87%	1.27%	0.58%	
Other	3.50%	2.62%	2.90%	
Median household income				<0.001
0-25th percentile	28.83%	32.79%	29.64%	
26th-50th percentile	26.73%	25.79%	26.63%	
51st-75th percentile	24.41%	23.83%	24.32%	
76th-100th percentile	20.02%	17.59%	19.42%	
Hospital teaching status				<0.001
Rural	8.57%	10.04%	12.68%	
Urban nonteaching	22.69%	24.37%	22.82%	
Urban teaching	68.74%	65.59%	64.50%	
Hospital size (beds)				<0.001
Small	22.63%	27.20%	25.04%	
Medium	29.99%	30.57%	29.03%	
Large	47.38%	42.23%	45.94%	
Hospital region				<0.001
Northeast	17.81%	18.16%	19.54%	
Midwest	20.55%	23.51%	22.40%	
South	38.91%	37.89%	41.50%	
West	22.73%	20.44%	16.55%	
Insurance status				<0.001
Medicare	39.35%	13.14%	41.79%	
Medicaid	17.24%	36.46%	15.91%	
Private insurance	33.64%	30.42%	35.38%	
Self-Pay	6.74%	15.07%	4%	
Charlson Comorbidity Index				<0.001
Mild (score 1-2)	25.33%	36.23%	27.16%	
Moderate (score 3-4)	12.18%	12.18%	18.27%	
Severe (score≥5)	15.78%	9.55%	28.74%	
Comorbidities	33.35%	21.08%	45.65%	<0.001
Dyslipidemia	23.16%	14.98%	43.68%	<0.001
Diabetes	28.10%	9.97%	24.19%	<0.001
Obesity	10.30%	3.30%	14.73%	<0.001
Chronic renal failure	1.44%	8.05%	2.73%	<0.001
Cannabis	54.52%	54.29%	70.39%	<0.001
Hypertension	9.42%	16.04%	13.69%	<0.001
Depression	13.49%	35.49%	13.15%	<0.001
Liver disease	3.50%	0.90%	2.60%	<0.001
Dementia				

* Given the large sample size, P-values in Table 1 may reflect statistically significant differences of small magnitude; therefore, clinical relevance and effect size should be prioritized when interpreting these comparisons

Discussion

This retrospective national study, which employed data from over 760,000 hospitalizations, represents one of the most extensive investigations into the diverse outcomes of BP, ARP and DIP. The etiologic distribution in our cohort (37.5% biliary, 59.0% alcohol-induced, 3.6% drug-induced) should be interpreted in light of the hospitalization-based nature of

Table 2 Adjusted odds ratios, confidence intervals, and *P* values for various complications in pancreatitis types

Mortality	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	1.19	1.06-1.41	0.05
Drug induced pancreatitis	0.78	0.56-1.13	0.204
Pancreatic cyst	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	2.17	1.92-2.45	<0.001
Drug induced pancreatitis	0.93	0.68-1.28	0.651
Pancreatic pseudocyst	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	3.54	3.32-3.79	<0.001
Drug induced pancreatitis	0.92	0.76-1.12	0.408
Percutaneous drainage	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	0.94	0.75-1.17	0.55
Drug induced pancreatitis	0.23	0.09-0.63	0.004
Mechanical ventilation	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	2.06	1.84-2.31	<0.001
Drug induced pancreatitis	0.62	0.45-0.87	0.005
Bleeding	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	1.52	1.41-1.63	<0.001
Drug induced pancreatitis	0.69	0.57-0.84	<0.001
Blood transfusion	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	0.99	0.88-1.11	0.866
Drug induced pancreatitis	0.76	0.59-0.98	0.034
Cardiogenic shock	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	1.37	0.81-2.31	0.243
Drug induced pancreatitis	1.51	0.67-3.41	0.321
Acute renal failure	aOR	95%CI	P-value
Biliary pancreatitis (baseline)			
Alcoholic pancreatitis	1.41	1.36-1.47	<0.001
Drug induced pancreatitis	1.04	0.96-1.14	0.352

CI, confidence interval; aOR, adjusted odds ratio

the NIS (encounters rather than unique patients), which may overrepresent recurrent alcohol-related admissions, and the reliance on ICD-10 coding for etiologic classification, which may under-capture some biliary cases.

Our analysis demonstrated that ARP is the most severe form, characterized by an elevated incidence of devastating complications and mortality, and occurs in a younger patient demographic. In contrast, DIP presents a clinical dilemma: it occurs in a population with considerable preexisting comorbidities, yet demonstrates relatively benign in-hospital characteristics and fewer sequelae. Meanwhile, BP occupies a moderate position in terms of clinical severity, although it demands the greatest healthcare resources, evidenced by prolonged hospitalizations and elevated overall costs.

This study identified several baseline traits that are more closely connected with a specific type of pancreatitis. For instance, Black patients with pancreatitis exhibit a greater probability of an alcohol-related etiology [15]. A previous study by Yang *et al* determined that this ethnic group has a 2- to 3-fold higher incidence of ARP compared to white individuals [16]. Nevertheless, the underlying processes require further investigation, as factors such as nutritional, genetic, epigenetic or metabolic variations may account for this discrepancy [16]. Concurrently, this study demonstrated results similar to prior findings reported by Zhu *et al* and Gunsahin *et al*, indicating that men had a greater susceptibility to ARP [17,18]. This association with sex disparities in social drinking indicates that males are more prone to higher rates of alcoholism than women; hence, this result may be attributable to a greater rate of male alcoholism and its dose-dependent involvement [18].

Our study found that cannabis use was significantly more prevalent among patients with ARP (8.05%) compared to BP (1.44%) and DIP (2.73%). This cross-sectional observation reflects the distribution of cannabis use across etiologic categories among patients already hospitalized with acute pancreatitis, and does not assess whether cannabis increases the risk of developing pancreatitis. Prior research conducted by Adejumo *et al* reported that simultaneous cannabis and excessive alcohol consumption were associated with a lower occurrence of acute pancreatitis and chronic pancreatitis (aOR 0.50, 95%CI 0.48-0.53, and 0.77, 95%CI 0.71-0.84, respectively) [19]. However, mechanistically, alcohol consumption may exhibit synergistic effects when combined with cannabis use. Both drugs can individually trigger CB1 receptors in the pancreas, probably intensifying their proinflammatory properties when administered simultaneously, hence increasing the likelihood of pancreatitis [20,21].

A central finding of this study is the confirmation that ARP is associated with a more severe clinical trajectory compared to BP, the most common etiology of AP in many regions, as demonstrated by the significantly greater odds of in-hospital mortality (aOR 1.19, 95%CI 1.00-1.41; P=0.05). However, since the P-value rests at the threshold of statistical significance, the result should be interpreted with caution. This suggests that, while a trend toward higher mortality exists within this large national cohort, the effect size is modest, and may be susceptible to residual confounding from unmeasured variables. This is also presented in prior studies that found conflicting results; some studies reported a higher mortality rate in ARP, while others stated no significant difference in mortality [12,22].

The apparently paradoxical finding of shorter LOS in ARP despite higher complication rates warrants careful interpretation. This may reflect several factors. First, patients with BP typically require procedural interventions, such as endoscopic retrograde cholangiopancreatography (ERCP) and/or cholecystectomy before discharge, which may

Table 3 Comparison of length of stay and total hospital charges among biliary, alcoholic and drug-induced pancreatitis

LOS (days)	Coefficient	95%CI		P-value
Biliary pancreatitis (baseline)				
Alcoholic pancreatitis	-0.324	-0.386	-0.262	<0.001
Drug induced pancreatitis	-1.058	-1.200	-0.915	<0.001
Total health charges (USD)	Coefficient	95%CI		P-value
Biliary pancreatitis (baseline)				
Alcoholic pancreatitis	-19102.86	-20022.28	-18183.4	<0.001
Drug induced pancreatitis	-26687.06	-28839.56	-24534.5	<0.001

LOS, length of stay; CI, confidence interval

prolong hospitalization regardless of disease severity. Second, complications such as pseudocyst formation in ARP often develop later in the disease course, and may not necessarily prolong the index hospitalization; these patients may be discharged and subsequently readmitted for management of complications. Third, it is possible that patients with severe ARP who develop life-threatening complications may have higher early mortality, resulting in shorter measured lengths of stay. Finally, socioeconomic factors and differences in discharge planning may contribute to earlier discharge in the alcohol-induced cohort. These findings highlight the limitation of LOS as a sole measure of disease severity, and emphasize the importance of examining multiple outcome metrics.

The association between ARP and the emergence of both local and systemic adverse effects was significantly more evident than in other acute pancreatitis types. Patients with ARP had a significantly higher chance of experiencing pancreatic pseudocysts, pancreatic cysts, gastrointestinal bleeding and acute renal failure (ARF). They were also more than twice as likely to need mechanical ventilation (aOR 2.06, 95%CI 1.84-2.31; P<0.001). Injury to the pancreatic ducts following prolonged alcohol consumption may cause pancreatic cysts and pseudocysts to form, by allowing pancreatic fluid to leak out of the ducts. In certain cases, this fluid consolidates into a distinct collection, enclosed by the walls of neighboring organs, including the stomach, omentum, small intestine and colon, resulting in a pseudocyst [23,24]. Meanwhile, the significant requirement for mechanical ventilation may indicate a heightened prevalence of severe systemic inflammatory response syndrome and its progression to acute respiratory distress syndrome, both of which are recognized contributors to mortality in severe acute pancreatitis [25]. Meanwhile, there are several ways in which ARP could affect ARF, such as higher levels of reactive oxygen species, overproduction of immunoglobulin A, changes in the renal microcirculation, and injury to skeletal muscle [26]. Meanwhile, a higher rate of bleeding is linked to several mechanisms, including premature activation of pancreatic enzymes (e.g., elastase, trypsin, and phospholipase A2), release of cytokines (e.g., interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor-α), increased vascular permeability, and pancreatic microcirculatory disorder, along with fibrin deposition which increases the risk of hemorrhage [27,28].

The greater severity of ARP is probably due to a mix of different pathophysiological processes and patient-level elements that contribute to its complexity. Chronic alcohol consumption causes direct, cumulative damage to the pancreas, which is different from the acute ductal obstruction that initiates most instances of BP. Ethanol and its metabolites, including fatty acid ethyl esters, exhibit direct toxicity to pancreatic acinar cells [29,30]. This toxicity disturbs cellular calcium homeostasis and accelerates the intracellular stimulation of digestive proenzymes such as trypsinogen, triggering a sequence of autodigestion, inflammation and oxidative stress that is intrinsically distinct from other causes [29,31].

It is important to note that the DIP group had considerably more preexisting comorbidities than the biliary and alcoholic groups, in particular hypertension (70.4%), dyslipidemia (45.7%), and diabetes (43.7%). The CCI further demonstrated this finding, with 28.7% of DIP patients receiving a "severe" classification, compared to only 15.8% of BP and 9.6% of ARP patients. However, it should be noted that the comorbidities are not the independent risk factors for severe pancreatitis in the studied population; rather, they express the underlying cause. DIP is a diagnosis of exclusion, usually chosen after ruling out gallstones and alcohol abuse, occurring particularly among individuals on polypharmacy [32]. The drugs that are most often thought to cause AP are the same ones that are most often given to people with the comorbidities we saw in the DIP group. These encompass diuretics, calcium-channel blockers and angiotensin-converting enzyme inhibitors for hypertension, statins for dyslipidemia, and multiple diabetes medications (e.g., glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors) [33,34].

Our study also revealed that the BP cohort exhibited the highest mean overall expenditures and a longer average LOS. In contrast, ARP (charges coefficient: -$19,102; LOS coefficient: -0.32 days) and DIP (charges coefficient: -$26,687; LOS coefficient: -1.06 days) were associated with lower costs and shorter hospitalization durations (all P<0.001). The greater resource utilization observed in BP probably reflects the procedural components of its definitive management. The conventional treatment approach for BP involves eliminating the underlying obstruction, typically achieved through ERCP to remove common bile duct stones, followed by cholecystectomy [35]. These invasive procedures, especially

ERCP, may prolong hospitalization and elevate provider and consulting costs [36]. Meanwhile, the primary approach for treating ARP and DIP is through supportive care, including intensive fluid resuscitation, effective pain control, nutritional assistance and, most importantly, the discontinuation of the causative agent (alcohol or any specific medicine) [37]. The disparity between BP's procedure-oriented cost framework and ARP and DIP's severity-based, albeit less procedural, cost structure effectively elucidates our findings regarding resource utilization.

The key strength of this study lies in its utilization of the NIS, the most extensive all-payer inpatient care database in the United States, coupled with an enormous sample size. This methodology offers exceptional statistical power to identify significant variance in outcomes, and enhances the external validity and generalizability of our results at a national level. However, despite the robust nature of the NIS database, the study is subject to several limitations. First, this retrospective analysis relies on the accuracy of ICD-10-CM coding; therefore, miscoding may result in etiologic misclassification. In addition, etiologic classification is limited by the predefined ICD-10-CM acute pancreatitis codes and the absence of key clinical and laboratory data in the dataset. As a result, metabolic causes of acute pancreatitis, such as hypertriglyceridemia- or hypercalcemia-associated pancreatitis, could not be reliably identified as a separate cohort because the dataset does not provide laboratory values. Moreover, idiopathic pancreatitis and other rare etiologies are not reliably distinguishable in the NIS and are typically captured under other/unspecified acute pancreatitis codes (e.g., K85.8/9); therefore, these hospitalizations were not included in our statistical comparison. Second, the NIS database lacks granular clinical detail, such as laboratory values (e.g., lipase levels), imaging results, and severity scores (e.g., Acute Physiology and Chronic Health Evaluation II and Bedside Index for Severity in Acute Pancreatitis), which limits the ability to fully adjust for disease severity at presentation. Third, the etiologic distribution observed in our NIS analysis differs from many clinical cohorts in which BP is often the most common etiology. This difference probably reflects key features of administrative, hospitalization-level data. The NIS captures hospitalizations (encounters), not unique patients; therefore, etiologies associated with recurrent admissions, particularly for ARP, may be proportionally overrepresented. Furthermore, etiologic classification in the NIS depends on specific ICD-10 etiologic acute pancreatitis codes. Consequently, in routine practice, some biliary-related presentations may be coded as unspecified acute pancreatitis with separate biliary diagnoses, rather than coded explicitly as biliary acute pancreatitis (K85.1); this could contribute to relative under-capture of biliary etiology when restricting etiologic comparisons to K85.1/2/3.

Finally, the NIS captures only in-hospital outcomes, meaning we could not assess long-term outcomes, readmission rates or the progression to chronic pancreatitis, which are particularly relevant for ARP.

In conclusion, our study confirms significant differences in patient demographics, comorbidity profiles, clinical outcomes and resource utilization across the 3 major etiologies of acute pancreatitis. ARP is associated with the highest morbidity and mortality, driven by a significantly higher risk of local and systemic complications. Conversely, DIP presents a milder in-hospital course, despite a high burden of preexisting comorbidities. BP, while moderate in severity, is associated with the highest healthcare resource utilization. These findings underscore the critical importance of early and accurate etiologic diagnosis to guide tailored, etiology-specific management strategies aimed at reducing complications, improving patient outcomes, and optimizing healthcare resource allocation. Further prospective studies with detailed clinical data are warranted to validate these findings and explore the long-term trajectories of these distinct patient populations.

Summary Box

What is already known:

- The etiology of acute pancreatitis significantly influences its clinical presentation, complication profile, and overall outcomes
- Biliary and alcohol-induced pancreatitis represent the 2 most common causes, whereas drug-induced pancreatitis remains rare and under-investigated
- Prior studies have produced inconsistent results regarding the relative severity, mortality, and healthcare utilization associated with different etiologies

What the new findings are:

- Alcohol-induced pancreatitis was associated with the highest risk of in-hospital mortality and complications, including pseudocyst formation, bleeding, and need for mechanical ventilation
- Drug-induced pancreatitis occurred in patients with a higher comorbidity burden, but demonstrated fewer in-hospital complications
- Biliary pancreatitis, though moderate in severity, accounted for the greatest healthcare costs and length of hospital stay due to its procedural management
- These findings emphasize the importance of the early identification of etiology and adopting tailored, etiology-specific treatment approaches to improve outcomes and optimize healthcare use

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