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Original Article

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Prevalence and Impact of Acute Pancreatitis on Hospitalization Outcomes in a Cohort of Patients With Crohn's Disease

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Abstract

Background: Few studies evaluated the risk of acute pancreatitis (AP) in patients with Crohn's disease (CD). It's controversial if AP can be considered as an extraintestinal manifestation of CD. We studied this potential association in a retrospective cohort of patients with CD.

Methods: We draw our cohort from the Nationwide Readmission Databases 2016 - 2018. We used the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes to identify all adult patients admitted with a diagnosis of CD. Patient with a comorbid AP were identified. We analyzed the significant impact of AP on hospitalization outcomes. A multivariate regression analysis was used to identify factors associated with AP.

Results: We included 214,622 patients discharged from an index hospitalization for CD, 1.1% had AP. AP was independently associated with higher odds of inpatient mortality (odds ratio (OR): 1.831; 95% confidence interval (CI): 1.345 - 2.492, P < 0.001), gallstone disease (OR: 4.047; 95% CI: 3.343 - 4.9, P < 0.001), nonalcoholic fatty liver disease (NAFLD) (OR: 3.568; 95% CI: 3.08 - 4.133, P < 0.001), and hypercalcemia (OR: 1.964; 95% CI: 1.302 - 2.965, P = 0.001). Thirty-day readmission analysis showed that CD patients with AP were more commonly to be readmitted for AP than for any other reason.

Conclusions: In our nationwide cohort of CD patients, there was a significant association between AP and worse hospitalization outcomes. Additionally, we found independent associations for having AP that may help identify patients at high risk.

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Introduction

Acute pancreatitis is an inflammation of the pancreas that varies in severity but is usually associated with significant morbidity [1]. It is the most common gastrointestinal cause of hospital admissions in the USA, with over 270,000 hospital admission and up to $2.6 billion per year in cost [2, 3]. Crohn's disease (CD) is a chronic transmural inflammation that can affect the entire gastrointestinal tract with relapsing and remitting symptoms and has been associated with multiple extraintestinal manifestations (EIMs). CD is more prevalent in developed countries with the USA having one of the highest prevalence worldwide at 214 per 100,000 [4].

While the intestine is the most commonly involved organ in patients with CD, inflammation can occur outside the intestine [5]. Specific EIMs that are known to occur with CD include arthritis, spondylitis, sacroiliitis, primary sclerosing cholangitis, uveitis, erythema nodosum, and pyoderma gangrenosum [6].

Whether acute pancreatitis can be considered an extraintestinal manifestation of CD or not, remains a controversial topic [7-9]. Mucin-1 (MUC-1) is expressed in an abnormal, hyperglycosylated form on the colonic epithelium of humans with inflammatory bowel disease (IBD) and contributes to inflammation. Animal studies have shown the migration of MUC-1 specific T cells to the colon and pancreas of IBD patients, suggesting potential susceptibility to a T cell-mediated injury of the pancreas [10]. One-third of patients with CD have antibodies against pancreatic juice, which may contribute to the development of acute pancreatitis. Some studies showed that patients with CD have a four-fold increase in the risk of developing acute pancreatitis compared to patients without CD [7].

Previous studies have shown that CD patients tend to have an increased risk of gallstones compared to patients without CD, with a reported prevalence of gallstones in CD ranging from 13% to 34% based on data from recent studies [11-13]. Weersma et al showed that the occurrence of acute pancreatitis in CD patients who are taking azathioprine (AZA) is signifi-

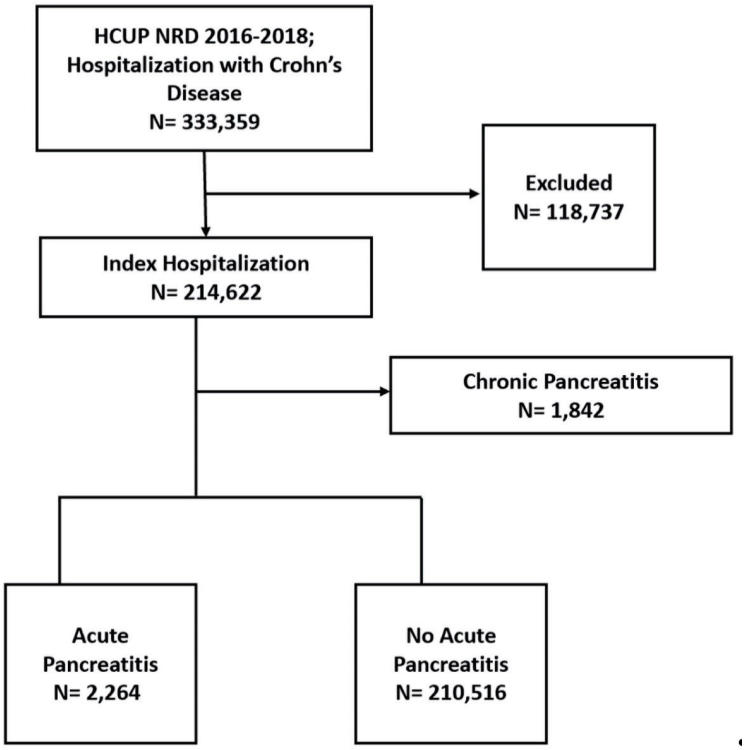

Figure 1. Case selection flowchart. HCUP: the Healthcare Cost and Utilization Project; NRD: Nationwide Readmissions Database.

cantly increased compared to patients taking AZA for other autoimmune conditions like systemic lupus erythematosus [14].

Recent studies showed that IBD patients have a three-fold higher health care cost than patients without IBD. Some of the biggest cost drivers include anemia, mental health disorders, chronic steroid or opioid use, emergency department (ED) visits, and nonelective readmissions [15].

This is the first study to evaluate the burden and associated outcomes of acute pancreatitis in a large nationwide cohort of CD patients. We, therefore, aimed to estimate the prevalence of acute pancreatitis among patients with CD, and demographic and clinical factors associated with acute pancreatitis in this patient population. We also evaluated hospitalization outcomes including inpatient mortality, costs of hospitalizations, hospital length of stay (LOS), and readmission rates.

Materials and Methods

Data source and study design

We utilized the Healthcare Cost and Utilization Project (HCUP) Nationwide Readmissions Database (NRD) which is drawn from HCUP State Inpatient Databases (SID) and contains verified patient linkage numbers that can be used to track a person's hospitalizations within a state while adhering to strict privacy guidelines [16]. This is a retrospective cohort study of patients discharged with a diagnosis of CD between 2016 and 2018. The study was performed in accordance with the 1963 Helsinki Declaration and is exempt from an Institutional Review Board due to the lack of any identifying patient information [17, 18].

Study population and groups

Inclusion criteria: NRD records between 2016 and 2018 with discharge diagnosis of CD. We excluded patients younger than 18 years old and records with missing information. We used the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes to identify diagnoses of interest.

CD patients with a comorbid diagnosis of acute pancreatitis were identified. We compared CD patients with and without acute pancreatitis. Before comparing CD patients with and without acute pancreatitis, we first excluded those with chronic pancreatitis (Fig. 1).

Study variables

We collected data on age, gender, income status, hospitals' bed size, and insurance. NRD categorizes income status into four groups according to the average household income of the zip code where the patient lives. Comorbid conditions of interest were identified using ICD-10-CM codes (Supplementary Material 1, www.jocmr.org). Index hospitalization discharges occurring in the month of December were excluded from the 30-day readmission analysis. Elective readmissions and patients

who died in the index hospitalization were excluded from the readmission analysis.

Our primary outcomes were the prevalence of acute pancreatitis among patients with CD and the factors independently associated with having acute pancreatitis in this patient population. Secondary outcomes included inpatient mortality, the LOS, all-cause 30-day nonelective readmission rate, and total cost of hospitalization. We calculated the rates for the most common causes of 30-day nonelective readmission.

Statistical analysis

We extracted and analyzed the data using SPSS Version 25 (IBM Corporation, Armonk, NY, USA). Median and interquartile ranges (IQR) were used to summarize numeric variables (not normally distributed) and then compared using the Mann-Whitney test. Categorical variables were summarized with percentages and compared using the Pearson χ^2 test. The factors that were significant in univariate analyses at $P < 0.05$ were included in the multivariate regression analysis to estimate the odds ratio (OR) and 95% confidence interval (CI) for factors associated with acute pancreatitis among patients with CD. We also used multivariate regression analysis to evaluate the effect of acute pancreatitis on inpatient mortality. A P value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of CD patients with and without acute pancreatitis

We extracted 333,359 hospital discharge records with a diagnosis of CD. We excluded records with missing information or age < 18. We analyzed 214,622 index hospital discharges with CD, of whom 2,264 (1.1%) patients had acute pancreatitis, and 1,842 (0.9%) patients had chronic pancreatitis.

CD patients with acute pancreatitis were younger (51; IQR: 38 - 64 vs. 53; IQR: 36 - 68, P = 0.003) compared to CD patients without acute pancreatitis. CD patients with acute pancreatitis were more commonly to belong to the lowest income category (25.5% vs. 23.2%, P = 0.015) and less commonly to the highest income category (21.4% vs. 23.7%, P = 0.015) compared to CD patients without acute pancreatitis.

CD patients with acute pancreatitis had higher prevalence of hypertension (34.2% vs. 30%, P < 0.001), diabetes mellitus (18.7% vs. 15.4%, P < 0.001), and obesity (13.7% vs. 11.8%, P = 0.005) compared to CD patients without acute pancreatitis. CD patients with acute pancreatitis were more commonly to have gallstone disease (5.3% vs. 1.2%, P > 0.001) and nonalcoholic fatty liver disease (NAFLD) (9.6% vs. 2.3%, P < 0.001) compared to CD patients without acute pancreatitis. Demographic and clinical characteristics of CD patients with and without acute pancreatitis are summarized in Table 1.

Of CD patients with acute pancreatitis, 360 (15.9%) had biliary acute pancreatitis and 252 (11.1%) had alcohol-induced acute pancreatitis. The etiology of acute pancreatitis among patients with CD is summarized in Table 2.

Hospitalization outcomes for CD patients with and without acute pancreatitis

CD patients with acute pancreatitis had higher inpatient mortality (1.9% vs. 1.2%, P = 0.002) and increased median LOS (4; IQR: 2 - 6 vs. 3; IQR: 2 - 6, P < 0.001) compared to CD patients without acute pancreatitis. After adjusting for sex, age, insurance type, hospital bed size, and comorbid conditions, acute pancreatitis was associated with increased odds of inpatient mortality (hazard ratio (HR): 1.831; 95% CI: 1.345 - 2.492, P < 0.001).

There was no significant difference in median total charges ($29,562; IQR: $16,593 - $58,424 vs. $30,803; IQR: $16,884 - $58,708, P = 0.418) between CD patients with and without acute pancreatitis, respectively. There was no significant difference in all-cause 30-day nonelective readmission rate (9.7% vs. 9.9%, P = 0.709) between CD patients with and without acute pancreatitis, respectively. CD patients with chronic pancreatitis had a statistically significant higher rate of all-cause 30-day nonelective readmissions (15.7% vs. 9.9%, P < 0.001) compared to CD patients without chronic pancreatitis.

The most common cause of 30-day nonelective readmission among CD patients with acute pancreatitis was another episode of acute pancreatitis. CD flare, sepsis, acute kidney failure, and *Clostridium difficile* enterocolitis were among the most common causes of 30-day readmission in CD patients with acute pancreatitis (Table 3).

Multivariate analysis for factors associated with acute pancreatitis in patients with CD

Multivariate analysis demonstrated that gallstone disease (OR: 4.047; 95% CI: 3.343 - 4.9, P < 0.001), NAFLD (OR: 3.568; 95% CI: 3.08 - 4.133, P < 0.001), and hypercalcemia (OR: 1.964; 95% CI: 1.302 - 2.965, P = 0.001) had increased odds of having acute pancreatitis. Age ≥ 65 was associated with decreased odds of having acute pancreatitis (OR: 0.639; 95% CI: 0.567 - 0.72, P < 0.001).

Hepatic failure (OR: 1.505; 95% CI: 1.086 - 2.086, P = 0.014), acute kidney failure (OR: 1.288: 95% CI: 1.149 - 1.444, P < 0.001), and thrombocytopenia (OR:1.236; 95% CI: 1.024 - 1.49, P = 0.031) were independently associated with acute pancreatitis (Table 4).

Discussion

There are few studies to evaluate an association between acute pancreatitis and CD. Our study is significant as we used a nationally representative database to study the association between acute pancreatitis and CD.

The reported incidence of acute pancreatitis in the USA ranges around 43.8 cases per 100,000 adults [19]. In our co-

Table 1. Demographic and Clinical Characteristics of Crohn's Disease Patients With and Without Acute Pancreatitis

	AP absent (n = 210,516)	AP present (n = 2,264)	P value
Median age, n (IQR)	53 (36 - 68)	51 (38 - 64)	0.003
Age group, n (%)			
18 - 44	77,815 (37)	814 (36)	< 0.001
45 - 64	68,780 (32.7)	923 (40.8)	
65 or older	63,921 (30.4)	527 (23.3)	
Sex, n (%)			
Male	88,798 (42.2)	972 (42.9)	0.471
Female	121,718 (57.8)	1,292 (57.1)	
Median household income for patient's ZIP code, n (%)			
0 - 25th percentile	48,943 (23.2)	577 (25.5)	0.015
26th - 50th percentile	55,798 (26.5)	616 (27.2)	
51st - 75th percentile	55,910 (26.6)	586 (25.9)	
76th - 100th percentile	49,865 (23.7)	485 (21.4)	
Bed size of the hospital, n (%)			
Small	33,286 (15.8)	421 (18.6)	< 0.001
Medium	58,752 (27.9)	689 (30.4)	
Large	118,478 (56.3)	1,154 (51)	
Insurance, n (%)			
Medicare	84,990 (40.4)	784 (34.6)	< 0.001
Medicaid	30,336 (14.4)	393 (17.4)	
Private insurance	80,711 (38.3)	904 (39.9)	
Self-pay	7,620 (3.6)	111 (4.9)	
No charge	5,788 (2.7)	61 (2.7)	
Other	1,071 (0.5)	11 (0.5)	
Hypertension, n (%)	63,054 (30)	774 (34.2)	< 0.001
Diabetes mellitus, n (%)	32,457 (15.4)	423 (18.7)	< 0.001
Obesity, n (%)	24,818 (11.8)	310 (13.7)	0.005
Dyslipidemia, n (%)	44,761 (21.3)	516 (22.8)	0.077
ESRD, n (%)	3,041 (1.4)	30 (1.3)	0.635
Acute kidney failure, n (%)	28,608 (13.6)	404 (17.8)	< 0.001
NAFLD, n (%)	4,894 (2.3)	218 (9.6)	< 0.001
PBC, n (%)	133 (0.1)	3 (0.1)	0.194
PSC, n (%)	53 (0.03)	2 (0.1)	0.063
Gallstone disease, n (%)	2,467 (1.2)	121 (5.3)	< 0.001
Hepatic failure, n (%)	1,604 (0.8)	41 (1.8)	< 0.001
Thrombocytopenia, n (%)	7,825 (3.7)	127 (5.6)	< 0.001
Hypercalcemia, n (%)	1,029 (0.5)	24 (1.1)	< 0.001
Hypokalemia, n (%)	34,391 (16.3)	606 (26.8)	< 0.001

AP: acute pancreatitis; IQR: interquartile range; ESRD: end-stage renal disease; NAFLD: nonalcoholic fatty liver disease; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis.

hort, 1.1% (1,100 per 100,000) of hospitalized CD patients had acute pancreatitis, and 0.9% had chronic pancreatitis. While our study cohort included only hospitalized CD patients, the observed high prevalence of acute pancreatitis supports the studies suggesting an increased risk of developing acute pancreatitis in patients with CD [7-9]. Even after adjusting for sex,

Table 2. Etiology of Acute Pancreatitis in Patients With Crohn's Disease

Etiology	Acute pancreatitis (n = 2,264)
Idiopathic acute pancreatitis	89 (3.9%)
Biliary acute pancreatitis	360 (15.9%)
Alcohol-induced acute pancreatitis	252 (11.1%)
Drug-induced acute pancreatitis	183 (8.1%)
Unspecified acute pancreatitis	1,380 (61%)

age, insurance type, hospital bed size, and comorbid conditions, our study showed that patients with CD and acute pancreatitis had increased odds of in-hospital mortality compared to CD patients without acute pancreatitis.

CD patients with acute pancreatitis were younger than CD patients without acute pancreatitis. An age ≥ 65 years was associated with lower odds of having acute pancreatitis. There was no significant difference in the distribution of gender between the two groups, although patients in both groups were more commonly females; this supports previous studies from Europe that showed a similar risk of developing acute pancreatitis in both genders [8].

Gallstone disease, alcoholism, medications, and postoperative complications are among the most commonly suggested etiologies for acute pancreatitis in patients with CD [5, 20, 21]. In our study, patients with acute pancreatitis had a higher prevalence of gallstone disease, and the presence of gallstones was associated with a greater than four-fold increased odds of having acute pancreatitis. After a gallstone pancreatitis episode, it is recommended to perform a cholecystectomy as soon as possible to eliminate the risk of future attacks [3]. Given the significantly higher odds of developing acute pancreatitis and the associated morbidity and mortality, further prospective studies would be needed to estimate the benefits of closer monitoring and elective management of gallstone disease in patients with CD.

Liver diseases of various etiologies have been associated with risk of acute pancreatitis [10, 22]. We found that NAFLD was independently associated with acute pancreatitis in hospitalized CD patients. Hepatic failure and acute kidney failure were independently associated with acute pancreatitis. Acute kidney failure is a common complication of severe acute pancreatitis and is associated with a poor prognosis [23].

Hypercalcemia is associated with acute pancreatitis in patients with breast cancer, multiple myeloma, or primary hyperparathyroidism [24, 25]. Our data showed that hypercalcemia was independently associated with increased odds of having acute pancreatitis in patients with CD. We also showed an independent association between acute pancreatitis and thrombocytopenia, an observation that has been suggested by previous studies [26].

Preventable nonelective readmissions possess a significant burden on the healthcare system. Readmission analysis showed that having another episode of acute pancreatitis was the most common cause for nonelective 30-day readmission in CD patients with acute pancreatitis. Management and elimination of modifiable risk factors are recommended to improve clinical outcomes. We provide clinicians with multiple factors associated with having acute pancreatitis in patients with CD that might benefit from more aggressive monitoring.

Several limitations should be considered while interpreting the results of this study. NRD contains inpatient records

Table 3. Most Common Causes of 30-Day Nonelective Readmission Among CD Patients With Acute Pancreatitis

30-day readmission primary diagnosis	Rate
Acute pancreatitis	27.1
Crohn's disease	13
Sepsis	9.7
Acute kidney failure	5.8
Clostridium difficile enterocolitis	1.9
Pseudocyst of pancreas	1.4
Ileus	1.4
Dehydration	1.4
Urinary tract infection	1
Peritoneal adhesions	1

Table 4. Multivariate Analysis for Factors Associated With Acute Pancreatitis in Patients With Crohn's Disease

Predictor	P value	Odds ratio	95% CI	
			Lower	Upper
Age (years)				
18 - 44	Reference			
45 - 64	0.404	1.045	0.944	1.155
≥ 65	< 0.001	0.639	0.567	0.72
Diabetes mellitus	0.002	1.196	1.069	1.337
Hypertension	< 0.001	1.199	1.092	1.316
Gallstone disease	< 0.001	4.047	3.343	4.9
NAFLD	< 0.001	3.568	3.08	4.133
Hepatic failure	0.014	1.505	1.086	2.086
Acute kidney failure	< 0.001	1.288	1.149	1.444
Hypercalcemia	0.001	1.964	1.302	2.965
Hypokalemia	< 0.001	1.741	1.583	1.915
Thrombocytopenia	0.031	1.236	1.024	1.49

CI: confidence interval; NAFLD: nonalcoholic fatty liver disease.

only, and no outpatient records were included. The NRD file does not track patients hospitalized in one state and readmitted or transferred to a hospital in another state [27]. NRD does not provide data on prescribed medications and several CD medications have been associated with development with acute pancreatitis. NRD does not provide data on habitual alcohol consumption, smoking, or prescribed medications yet we were able to classify acute pancreatitis based on etiology. NRD does not provide data on laboratory test results, and we were unable to report data on pertinent continuous variables including lipase and amylase. The use of administrative codes (ICD-10-CM) is subject to misclassification. The study population has a high prevalence of gallstones and elevated calcium, both of which are known to cause acute pancreatitis. However, our study has several strengths. We used a large database, which is nationally representative of the US population. The NRD is a validated database used in clinical and epidemiological research and includes discharge data from 30 geographically dispersed states.

In conclusion, we observed a significant association between acute pancreatitis and worse hospitalization outcomes in our national cohort of CD patients. CD patients with acute pancreatitis were more likely to experience in-hospital mortality, hepatic failure, acute kidney failure, thrombocytopenia, and longer LOS. Gallstone disease, NAFLD, and hypercalcemia were associated with increased odds of having acute pancreatitis in patients with CD. As we aspire to control healthcare expenditure in CD patients, it becomes a priority to study comorbidities associated with worsening morbidity and mortality and to apply preventive measures to eliminate causes of nonelective preventable readmissions.

Supplementary Material

Suppl 1. International Classification of Diseases, Tenth Revision, Clinical Modification codes.

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Financial Disclosure

No financial relationships to be declared.

Conflict of Interest

Authors had no conflict of interest to be declared.

Informed Consent

No consent was required for the analysis as there were no patient-specific identifiers.

Author Contributions

Concept and design of the study: Ahmed Abomhya. AA, EC, FK, ZA, and HH contributed to the literacy search. All authors contributed to the analysis and interpretation of data. All authors contributed to drafting the manuscript and revising it critically for intellectual content: All authors approved the final version of the manuscript to be published.

Data Availability

The NRD is available at: https://www.hcup-us.ahrq.gov/nrdoverview.jsp.

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