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ORIGINAL RESEARCH—CLINICAL

Natural History, Clinical Characteristics, and Outcomes in Idiopathic Chronic Pancreatitis

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BACKGROUND AND AIMS: Chronic pancreatitis (CP) is a fibroinflammatory syndrome of the pancreas associated with pain and poor quality of life. It has toxic and genetic risk factors but can also be idiopathic. The natural history of idiopathic CP (ICP) is not well-known. Therefore, we studied clinical characteristics and outcomes of these patients followed in our Pancreas Center. **METHODS:** Review of CP patients between January 1, 2016, and April 30, 2021. Patients were divided into 2 groups based on diagnosis, ICP vs non-ICP. CP patients with a smoking history were placed in the non-ICP group. Statistical analysis was performed to identify differences in demographics, comorbidities, complications, controlled medications, and resource utilization. **RESULTS:** Out of 450 patients, 101 (22%) were diagnosed with ICP and 349 (78%) were non-ICP. ICP patients were mainly female (59.4% vs 40.5%; $P = .005$), had less comorbid anxiety (10.5% vs 22.1%; $P = .002$), depression (24.2% vs 35.8%; $P < .001$), disability (13% vs 16.3%; $P = .021$), exocrine pancreatic insufficiency (45.3% vs 62.6%; $P = .004$), splanchnic vein thrombosis (1.04% vs 14.9%; $P < .001$), pseudocysts (16.7% vs 41.6%; $P < .001$), and biliary obstruction (3.12% vs 19.2%; $P < .001$). They underwent less abdominal imaging (2.63 vs 3.42; $P = .048$) and endoscopic retrograde cholangiopancreatography (0.88 vs 1.32; $P = .030$). They also had less opioid use (29.6% vs 54.4%; $P < .001$), gabapentinoid use (34% vs 52.3%; $P = .002$), and celiac blocks (7.22% vs 16.1%; $P < .041$). **CONCLUSION:** Our study demonstrates that the clinical course of ICP is less morbid compared to non-ICP. This study specifically removes smoking, a significant risk factor for CP, to study a truly idiopathic cohort.

Keywords: Idiopathic Chronic Pancreatitis; Smoking; Natural History; Clinical Outcomes

Introduction

Chronic pancreatitis (CP), as defined by an international consensus group, is a syndrome of progressive and irreversible fibroinflammatory injury to the pancreatic parenchyma characterized by abdominal pain, exocrine and endocrine insufficiency occurring in individuals with underlying metabolic, genetic, and environmental risk factors.[1] In the United States, the annual incidence of CP ranges from 5 to 8 per 100,000 persons, while the prevalence is 42–73 per 100,000 persons.[2,3] For most cases of CP, there is an identifiable, underlying etiology. The risk factors for CP are commonly categorized by the *TIGAR-O* (Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive) classification.[4] In the toxic category, alcohol consumption accounts for 42%–77% of CP cases.[2] Tobacco smoking acts synergistically with alcohol to damage the pancreas and is also noted to independently account for nearly 25% of the attributable risk of CP.[5] However, when CP is diagnosed in the absence of any recognized risk factors, a patient is determined to have idiopathic CP (ICP), accounting for 28%–80% of CP diagnoses depending on geographic location.[2,6]

Although the clinical features of CP typically include debilitating abdominal pain, along with exocrine and endocrine deficiency,[7] the level of burden of each component can differ between CP types. Because ICP has no identifiable and therefore no modifiable risk factors, it is important to assess if its clinical course differs from non-ICP to provide optimal care for these patients. Hence, our study aimed to evaluate the clinical characteristics, outcomes, and healthcare utilization of ICP patients compared to those with non-ICP.

Methods

Patient Selection and Study Design

We performed a retrospective review of all adult patients with established CP followed at the Pancreas Center in our tertiary care hospital between January 1, 2016, and April 30, 2021.

Abbreviations used in this paper: **CP, chronic pancreatitis; ICP, idiopathic chronic pancreatitis; RAP, recurrent acute pancreatitis; TIGAR-O, Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive.**

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Diagnosis of the CP

The diagnosis of CP was made based on the presence of clinical symptoms and radiologic features consistent with CP seen on computed tomography or magnetic resonance cholangiopancreatography, or by endosonographic criteria. Clinical features used for diagnosis included presence of at least one of the following: abdominal pain, symptoms of exocrine pancreatic insufficiency (diarrhea and weight loss along with low fecal elastase level), or new-onset diabetes (confirmed via hemoglobin A1C testing). Detailed history, including alcohol and tobacco use, prior acute pancreatitis (AP), genetic testing (performed when feasible for patients <35 years of age), and family history of CP, were obtained for each patient. Cross-sectional imaging criteria included pancreatic calcifications, ductal irregularity with or without pancreatic atrophy. Patients diagnosed with CP via combination of clinical symptoms and endoscopic ultrasound were only included if they met the Rosemont criteria for definitive diagnosis of CP.[8] While attributing etiology, patients were designated to have ICP only after a thorough evaluation of risk factors as outlined above. Patients not meeting any of the above clinical criteria, who had nonspecific imaging or endosonographic findings suggestive of CP, were not included in the study.

Data Collection, Study Groups, and Outcomes of Interest

We divided our cohort of CP patients into 2 groups based on the etiology of their CP: idiopathic and non-idiopathic. We defined patients with ICP as those patients with no established cause of CP despite thorough evaluation for risk factors, including smoking, and including negative genetic testing, when indicated, especially in patients less than 35 years of age. Non-ICP patients were those patients in whom an underlying etiology/risk factor was identified, including smoking.

Clinical data were collected for all qualifying patients. These included demographic characteristics such as age, sex, body mass index, etiology of disease, prior AP, and comorbidity profile. We also collected data regarding comorbid psychiatric conditions such as anxiety and depression. Information regarding these diagnoses was obtained from review of primary care and psychiatry notes. Only those patients who were being treated with medications for anxiety and/or depression were designated a definitive diagnosis of these conditions. Patients with disability were those with mental or physical impairment due to CP which limited one or more major activities of life and resulted in confirmed receipt of social security benefits per chart review. We also collected data on complications of CP, including exocrine and endocrine insufficiency, as well as anatomical complications such as pancreatic pseudocyst, splanchnic vein thrombosis and biliary obstruction, and information on concurrent use of controlled medications obtained from the state-wide prescription monitoring program, and noncontrolled medications. Lastly, we obtained data related to health care utilization in these patients, including average number of CP flares requiring hospitalization in the preceding 24 months, endoscopic procedures and surgeries for CP, average number of imaging studies such as computed tomography and magnetic resonance cholangiopancreatography and recurrent emergency department visits for abdominal pain resulting in an opioid prescription. We then compared clinical characteristics, outcomes, and healthcare utilization between the 2 groups.

Statistical Analysis

All outcomes were evaluated for normality. Categorical variables were presented as proportions and continuous variables as means with range, standard deviations, and 95% confidence intervals. All analyses were performed using the R software (version 3.6.1, R Core Team 2018a) within RStudio (version 1.1463, RStudio, Inc).

Ethical Considerations

Our institutional review board approved this study.

Results

In the study period, 450 patients with established CP followed in our Pancreas Center met criteria for inclusion. Of these patients, 101 (22%) were diagnosed with ICP and 349 (78%) were non-ICP. The etiology/risk factor in the non-ICP cohort were as follows: alcohol (n = 150, 42.9%), recurrent biliary obstruction (n = 32, 9.17%), smoking only (n = 131, 37.5%), and other (n = 37, 10.6%). Within the "other" category, patients with genetic (cystic fibrosis transmembrane conductance regulator in 14 patients and PRSS1 in 2 patients) and structural causes (anatomic obstruction from prior complications of prior recurrent AP (RAP) such as stricture (n = 11), disconnected duct (n = 6), and iatrogenic injury from prior procedures (n = 4)) of CP were included. Table 1 further compares the demographic characteristics, complications, and comorbidities of these 2 groups. The mean follow-up was similar in both groups and was approximately 8 years. There were no statistically significant differences in the age, race, Charlson comorbidity index or body mass index. A significantly larger proportion of ICP patients were female (59.4% vs 40.5%; $P = .005$). In the non-ICP group, there was significantly more recreational tetrahydrocannabinol (THC) (23.5% vs 3.16%; $P < .001$), as well as preceding RAP (68.6% vs 53.1%; $P = .007$). ICP patients had less comorbid anxiety (10.5% vs 22.1%; $P = .002$), depression (24.2% vs 35.8%; $P < .001$), and less disability (13% vs 16.3%; $P = .021$). In regards to symptoms of CP, there was no statistically significant difference in weight loss, loss of appetite, or chronic abdominal pain between the 2 groups. A significantly lower proportion of ICP patients had exocrine pancreatic insufficiency (based on fecal elastase testing and/or characteristic symptoms of malabsorption such as steatorrhea and weight loss) (45.3% vs 62.6%; $P = .004$). However, there was no difference in rates of developing diabetes or pancreatic cancer between the 2 groups. When comparing anatomic complications of CP, ICP patients had significantly less splanchnic vein thrombosis (1.04% vs 14.9%; $P < .001$), pseudocysts (16.7% vs 41.6%; $P < .001$), and biliary obstruction (3.12% vs 19.2%; $P < .001$).

Table 2 compares the medication and healthcare resource utilization in CP patients. Patients with ICP underwent fewer average abdominal imaging scans (2.63 vs 3.42; $P = .048$) and endoscopic retrograde

Table 1. Demographic Characteristics, Clinical Presentation, and Complications of Idiopathic and Non-idiopathic CP

Demographic characteristics and comorbidities	Idiopathic CP N = 101	Non-idiopathic CP N = 349	*P*-value
Mean age, y (SD)	56.1 (17.1)	59.0 (14.3)	.129
Mean BMI, kg/m^2 (SD)	24.9 (4.66)	26.0 (5.50)	.087
Mean follow-up in pancreas center, y (SD)	7.56 (4.56)	8.52 (6.07)	.140
Sex			.005
Female	60 (60.0%)	151 (43.5%)	
Male	41(41.0%)	196 (56.5%)	
Race			.257
White	71 (71.7%)	259 (74.9%)	
Black	8 (8.08%)	39 (11.3%)	
Hispanic	5 (5.05%)	18 (5.20%)	
Other	15 (15.2%)	30 (8.67%)	
Individual etiology of non-ICP group			<.001
Alcohol	0 (0.00%)	150 (42.9%)	
Recurrent biliary	0 (0.00%)	32 (9.17%)	
Purely smoking (no concurrent alcohol or other risk factors)	0 (0.00%)	131 (37.5%)	
Other	0 (0.00%)	37 (10.6%)	
Mean CCI (SD)	0.79 (1.01)	1.11 (1.10)	.61
Recreational marijuana use	3 (3.16%)	81 (23.5%)	<.001
Recurrent acute pancreatitis	51 (53.1%)	236 (68.6%)	.007
Disability	13 (13%)	57 (16.3%)	.021
Anxiety	10 (10.5%)	76 (22.1%)	.002
Depression	23 (24.2%)	123 (35.8%)	<.001
CP-related symptoms and complications			
Daily abdominal pain	25 (25%)	128 (36.6%)	.273
Weight loss	25 (26.3%)	111 (32.3%)	.325
Early onset diabetes	7 (6.93%)	44 (12.6%)	.111
Late-onset diabetes	6 (5.94%)	23 (6.59%)	.17
Exocrine pancreatic insufficiency	43 (45.3%)	214 (62.6%)	.004
Splanchnic vein thrombosis	1 (1.04%)	51 (14.9%)	<.001
Pseudocyst	16 (16.7%)	143 (41.6%)	<.001
Biliary obstruction	3 (3.12%)	65 (19.2%)	<.001
Pancreatic cancer	5 (5.26%)	12 (3.52%)	.547

BMI, body mass index; CCI, Charlson comorbidity index; SD, standard deviation.

cholangiopancreatography (0.88 vs 1.32; $P = .030$). There was no significant difference in medical THC use or non-opioid controlled medication use. ICP patients had significantly less opioid use (29.6% vs 54.4%; $P < .001$), gabapentinoid use (34% vs 52.3%; $P = .002$), and celiac blocks (7.22% vs 16.1%; $P < .041$) overall. There was no

Table 2. Medication Use and Resource Utilization in Patients With Idiopathic and Non-idiopathic CP

	Idiopathic CP N = 101	Non-idiopathic CP N = 349	*P*-value
Mean number of flares requiring hospitalization (SD)	1.71 (3.64)	2.45 (3.29)	.085
Recurrent ED visits with opioid prescription	2 (2.04%)	28 (8.24%)	.056
Mean number of CTs since diagnosis (SD)	2.63 (3.02)	3.42 (3.08)	.029
Mean number of MRIs since diagnosis (SD)	2.07 (2.15)	2.22 (1.91)	.547
Mean number of ERCPs since diagnosis (SD)	0.88 (1.64)	1.32 (1.97)	.030
Non-opioid controlled medication use	21 (21.6%)	101 (29.4%)	.166
Medical marijuana use	5 (5.49%)	34 (10.4%)	.220
Gabapentinoid use	33 (34.0%)	179 (52.3%)	.002
Opioid use	29 (29.6%)	187 (54.4%)	<.001
Celiac plexus block	7 (7.22%)	55 (16.1%)	.041
Pancreatic surgery for pain	14 (14.4%)	45 (13.2%)	.884

CT, computed tomography; ED, emergency department; ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; SD, standard deviation.

significant difference in the number of flares requiring hospitalization, emergency department visits for opioid prescriptions, or surgery for CP-related pain.

Discussion

In this study, we compare the clinical course of ICP and non-ICP patients followed longitudinally in our Pancreas Center over 8 years. We found that ICP patients were more likely to be female. They had less recreational THC use, preceding RAP, disability, and psychiatric illness (including anxiety and depression). They had less CP-related complications such as exocrine pancreatic insufficiency, splanchnic vein thrombosis, pseudocysts, and biliary obstruction. ICP patients underwent less abdominal imaging, endoscopic retrograde cholangiopancreatography, and had less gabapentinoid use, opioid use, and celiac plexus blocks for pain control. These findings possibly can be explained by the absence or decreased frequency in proinflammatory insults from ongoing alcohol use, tobacco use, and RAP, resulting in slower progression of ICP and with comparatively milder CP manifestations.

The exclusion of smokers in our ICP group presents one of several important distinctions to our study when compared to another similar retrospective study conducted in China comparing ICP to alcoholic CP patients.[9] There are substantial data to suggest that tobacco use not only accelerates disease progression of CP but also acts as an independent risk factor for the development of CP in itself.[10] Clear distinction of this risk factor has been challenging to ascertain given the high coexistence of smoking and alcohol use in CP patients. The North American Pancreatitis Study 2 (NAPS2) showed that although heavy smokers tended to be heavy drinkers, smoking itself seemed to be a significant risk factor for pancreatitis and had a dose-dependent association with CP.[11] Additionally, we chose to compare ICP with CP of all etiologies, not just alcoholic CP, thereby highlighting the clinical outcomes that specifically set ICP patients apart from all other CP patients, irrespective of known primary cause.

Our study included a well characterized cohort of established CP patients followed longitudinally over many years in our multidisciplinary Pancreas Center, allowing us access to records of clinical care, pain management, nutrition, surgery, and psychosocial support. Hence, unlike prior publications performed predominantly in Asia,[9,12] we were able to build a natural history more representative of patients residing in western countries. Despite these strengths, we recognize that there are several limitations to our study. Chiefly, our results may not be generalizable to all medical settings as our study was performed at a single tertiary care center at an academic institution located in a large urban city. Due to referral bias, the patients seen at our Pancreas Center were more complex. Additionally, our study is naturally limited by its entirely retrospective nature of design, forcing us to rely on electronic medical records to ascertain data. Lastly, given that we did not have any statistically significant demographics to control for based on results of our univariate analysis, we did not perform multivariate analysis to find independent predictors, making our analysis very qualitative.

Conclusion

In conclusion, our study demonstrates that the clinical course of ICP is less morbid, with lower rates of CP-related complications and lower healthcare utilization compared to non-ICP patients. This study adds to the sparse literature available characterizing true ICP patients longitudinally, specifically removing smoking as a possible confounding cause of CP within the ICP group. Further research is needed to continue exploring the natural history of this disease with this specific selection criteria.

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Study concept and design: Sheth. Acquisition of data: Shah, Bocchino. Analysis and interpretation of data: Liyen Cartelle, Shah, Bocchino, Ahmed, Freedman, Sheth. Drafting of the manuscript: Liyen Cartelle, Sheth, Bocchino. Critical revision of the manuscript for important intellectual content: Shah, Liyen Cartelle, Bocchino, Ahmed, Freedman, Sheth. Study supervision: Sheth.

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
The data sets generated and/or analyzed during the current study are not publicly available due to their nature as private health information but are available from the corresponding author on reasonable request.

Reporting Guidelines:
STROBE.