Does Etiology of Pancreatitis Matter? Differences in Outcomes Among Patients With Post–Endoscopic Retrograde Cholangiopancreatography, Acute Biliary, and Alcoholic Pancreatitis

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Objectives: We compared outcomes of acute alcoholic pancreatitis (AAP), acute biliary pancreatitis (ABP), and post–endoscopic retrograde cholangiopancreatography pancreatitis (PEP).

Methods: This was a retrospective cohort study conducted at a tertiary care center between June 2007 and June 2012.

Results: A total of 300 (68%) patients were diagnosed with AAP, 88 (20%) with ABP, and 55 (12%) with PEP. Longer length of hospital stay (LOHS) was more common in ABP (23%) as compared with AAP (10%) and PEP (7%, $P = 0.025$). Pseudocyst ($P = 0.048$), organ failure (OF) ($P = 0.01$), need for interventions ($P \leq 0.001$), and mortality ($P = 0.002$) occurred more in ABP as compared with other groups. Systemic inflammatory response syndrome was associated with LOHS of more than 10 days ($P = 0.01$) and multi-OF ($P = 0.05$). Chronic pancreatitis was associated more with pseudocyst ($P < 0.001$) and mortality ($P = 0.03$). Serum urea nitrogen of greater than 25 g/dL predicted LOHS of more than 10 days ($P = 0.02$), OF ($P < 0.001$), multi-OF ($P < 0.001$), and persistent OF ($P < 0.001$).

Conclusions: Acute biliary pancreatitis is a more severe disease compared with PEP and AAP. Chronic pancreatitis, systemic inflammatory response syndrome, and high serum urea nitrogen are important predictors of morbidity.

Key Words: biliary pancreatitis, alcoholic pancreatitis, ERCP, organ failure, persistent

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Acute pancreatitis (AP) is an inflammation of pancreas, which in severe cases involves surrounding tissues and at times remote organs as well.[1] Acute pancreatitis is one of the most common gastrointestinal problems that caused approximately 275,000 hospitalizations in 2009 in United States leading to an annual incidence of AP of 13 to 45 cases per 100,000 persons.[2,3] Approximately 40% of all cases of AP results from impaction of migratory gallstone at the ampulla causing obstruction and inflammation.[4–6] Alcohol is the most common toxin and the second leading cause of pancreatitis, accounting for approximately 20% to 35% of all the cases of AP.[5] Post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) accounts for 1% to 5% of all cases[4,5] and is the most common complication of ERCP and occurs in 2% to 15% of procedures.[7,8]

In approximately 85% of cases of AP, disease is local and mild that resolves on its own with supportive treatment.[9] A more serious disease involving pancreatic necrosis and organ failure (OF) develop in the remaining cases of AP leading to a more protracted length of hospital stay (LOHS).[10,11] Etiology can be an important determinant of severity as well as recurrence of AP.[12] Post–endoscopic retrograde cholangiopancreatography pancreatitis has been shown to have a milder course as compared with acute biliary or alcoholic pancreatitis (AAP).[1,13] Recurrence is common in acute biliary pancreatitis if cholecystectomy is delayed or not performed.[12,14] Previous studies have shown alcohol as an important determinant of developing pancreatic necrosis in acute pancreatitis.[11] However, there has been no single study comparing different types of pancreatitis to determine the effect of etiology on developing complications.

The aim of this study was twofold. First was to compare the patient characteristics, outcomes, severity, complications, and mortality among acute biliary, alcoholic, and post-ERCP pancreatitis. Second was to study the association between etiology and other relevant predictors and severity of acute pancreatitis.

MATERIALS AND METHODS

The study was approved by the institutional review board for Human Research of Johns Hopkins Hospital.

Study Design and Population

A retrospective cohort study was conducted in which all patients with a history of acute pancreatitis were identified using the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* diagnosis code 577.0-based query of Johns Hopkins Administrative database from June 2007 to June 2012. Patients with alcoholic, acute biliary, and post-ERCP pancreatitis were identified from detailed paper and electronic chart review based on clinical symptoms, laboratory findings, and computer tomographic findings.

Exclusion Criteria

All patients who were transferred from another hospital to Johns Hopkins Hospital for the initial evaluation or treatment were

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excluded because of unavailability of reliable clinical data on initial presentation.

Definitions

Acute pancreatitis was diagnosed in patients with 2 of the following 3 features: sudden onset of upper abdominal pain, serum amylase and/or lipase levels greater than three times the upper limit of normal, and/or findings on computed tomography (CT)/contrast-enhanced CT, or transabdominal ultrasonography characteristic of AP.[15]

Acute alcoholic pancreatitis was defined as pancreatitis associated with daily alcohol intake of 50 or greater to 80 g (~4–7 standard drinks per day) for several years.[16]

Acute biliary pancreatitis (ABP) was defined as the pancreatitis caused by obstruction of the ampulla of Vater by a gallstone resulting in increased pancreatic ductal pressure and reflux of bile into the pancreatic duct that activates pancreatic enzymes and the inflammatory cascade.[17,18]

Post-ERCP pancreatitis was defined as new or increased epigastric abdominal pain with amylase or lipase 3 or more times the upper limit of normal 24 hours after the ERCP and hospitalization or prolongation of existing hospitalization for at least 24 hours.[19]

Severity of the pancreatitis was assessed in terms of LOHS, development of pancreatic necrosis/pseudocyst, need for intervention, systemic inflammatory response syndrome (SIRS) onset, single/multiple OF (MOF), persistent OF (POF), and mortality within 30 days of admission. Intervention used was either percutaneous/endoscopic drainage or surgery. SIRS was defined as 2 or more of the following: temperature >38°C or <36°C; respiratory rate >20 breaths per minute or $PaCO_2$ < 32 mm Hg; pulse >90 beats per minute; white blood cells < 4000 cells/mm^3 or 12,000 cells/mm^3 or >10% immature bands. Persistent SIRS was defined as presence of SIRS of more than 48 hours.[20] Organ failure was characterized according to Marshall Scoring System in which score 1 to 4 was given for the failure of respiratory, renal, and cardiovascular system based on patient's symptoms.[21] If there was MOF, these scores were added. Persistent OF was defined as the presence of OF persisting more than 48 hours.[21,22]

Statistical Analysis

Statistical analysis was performed using SPSS 22 statistical software package (IBM Analytics, Armonk, NY). Categorical variables were compared between 3 groups by univariate analysis using the Pearson χ^2 test or Fisher exact tests as appropriate. Continuous variables were compared using the 1-way analysis of variance test. In multivariable analysis, logistic regression was performed to identify predictors for each outcome of interest. The results are presented as estimated odds ratios (ORs) with P values. A two-sided P value of <0.05 was considered statistically significant.

RESULTS

Initially, 941 patients with acute pancreatitis were identified based on the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification*, code 577.0. After detailed electronic and paper chart review incorporating clinical symptoms, laboratory data, and radiological findings, 443 patients were included. Based on etiology, 300 patients with AAP, 88 with acute biliary pancreatitis, and 55 with post-ERCP pancreatitis were found.

On comparing the demographics, the mean (standard deviation [SD]) age of patients with PEP, ABP, and AAP was 49.7 (14.7), 49.4 (18.9), and 46.4 (11.8) years respectively (Table 1). Post–endoscopic retrograde cholangiopancreatography pancreatitis (69%) and ABP (51%) occurred more frequently among female white population as compared with AAP (39%). Seventy percent of patients with AAP were black. Fifty-three percent of PEP patients previously had a history of post-ERCP pancreatitis. Forty-two percent of AAP and 45% of PEP patients had chronic pancreatitis as

TABLE 1. Demographic Comparison Between PEP, AAP, and ABP Group

Variable, n (%)	Post-ERCP Pancreatitis (n = 55)	Acute Biliary Pancreatitis (n = 88)	Acute Alcoholic Pancreatitis (n = 300)	*P*
Age, y				
0–20	1 (2)	7 (8)	3 (1)	**<0.0001**
21–40	14 (25)	17 (19)	83 (27)	0.445
41–60	27 (49)	38 (43)	175 (59)	**0.031**
≥60	13 (24)	26 (30)	39 (13)	**0.001**
Age, mean (SD), y	49.7 (14.7)	49.4 (18.9)	46.4 (11.8)	0.08
Sex, female	38 (69)	45 (51)	118 (39)	**<0.0001**
Race				
White	42 (76)	44 (50)	51 (17)	**<0.0001**
African American	6 (11)	37 (42)	209 (70)	**<0.0001**
Hispanic/other	7 (13)	7 (8)	40 (13)	**<0.0001**
Clinical characteristics				
History of CP	25 (45)	20 (23)	127 (42)	**0.004**
History of PEP	29 (53)	1 (1)	2 (1)	**0.001**
History of recurrent pancreatitis	27 (49)	26 (30)	110 (37)	0.062
SIRS, h				
0–24	9 (16)	20 (23)	61 (20)	0.656
24–48	0	1 (1)	44 (15)	**0.001**

Bold values indicate statistically significant results.

CP indicates chronic pancreatitis.

compared with 23% in ABP. Recurrent pancreatitis history was present more frequently in PEP (49%) and AAP (37%) than ABP (30%).

Complications such as pseudocyst formation occurred in 87 (19.6%), pancreatic necrosis in 26 (5.9%), single OF in 55 (12.4%), MOF in 13 (2.9%), and POF in 23 (5.2%) patients (Table 2). A total of 35 (7.9%) patients required an intervention because of complications. The overall mortality rate was 8.8% (PEP = 4%, ABP = 11%, AAP = 9%, $P = 0.002$, reference = PEP). Prolonged LOHS of more than 10 days was more common in ABP patients (23%) as compared with AAP (10%) and PEP (7%, $P = 0.025$). Complications such as pseudocyst ($P = 0.048$), OF ($P = 0.01$), need for interventions to treat complications ($P = 0.001$), and mortality ($P = 0.002$) occurred more commonly in ABP patients as compared with the other groups.

On multivariable analysis, using PEP a reference, SIRS on the second day of hospitalization was associated with LOHS of more than 10 days (OR, 2.57, $P = 0.01$) and MOF (OR, 5.3, $P = 0.05$) (Table 3). History of chronic pancreatitis was associated with an increased risk of pseudocyst formation (OR, 3.87, $P = 0.0001$) and mortality (OR, 3.79, $P = 0.03$). Serum urea nitrogen (SUN) >25 g/dL predicted LOHS of more than 10 days (OR, 2.43, $P = 0.02$), OF (OR, 33.9, $P = 0.0001$), MOF (OR, 21.6, $P = 0.0001$), and POF (OR, 45.02, $P = 0.0001$).

DISCUSSION

We performed a retrospective study of patients with AP investigating the etiology of acute pancreatitis as an important determinant of the morbidity and mortality. We found that ABP is a more severe disease compared with PEP and AAP, with a higher risk of complications. Systemic inflammatory response syndrome, chronic pancreatitis, and high SUN are important predictors of morbidity.

Gallstones are the number 1 cause of pancreatitis worldwide.[23,24] However, our cohort has more patients with alcoholic etiology. This may be due to geographical location of our institute and increased incidence of alcohol use in the local population.[25] However, ABP was more common in the younger and older population as compared with AAP. Seventy percent of people affected with AAP were African American, among whom 60% were males. These demographical results are consistent with previous studies.[3,26] Postendoscopic retrograde cholangiopancreatography pancreatitis affected young female patients more as female sex and age less than 50 years are recognized risk factors for developing post-ERCP pancreatitis.[7,27] Recurrent and chronic pancreatitis were more common in patients with AAP similar to previously published studies.[28,29] Patients with AAP who have a history of chronic pancreatitis have shown increased frequency of ED visits in a recent study.[30]

Complications such as extended length of stay, pseudocyst formation, necrosis, OF, and mortality were seen more in ABP patients as compared with alcoholic and post-ERCP pancreatitis in our study.[31,32] The longer length of stay in our hospital may be due to tertiary nature of our institute where patients might have stayed longer so that gallstones can be treated within the same hospital stay by ERCP or cholecystectomy.[6] Another factor, which leads to increased severity in ABP, might be recurrent episodes of pancreatitis in the absence of definite treatment of gallstones before discharge.[33] Previous studies have shown reduction in complication of pancreatitis if ERCP was performed to treat

TABLE 2. Clinical Comparison Between PEP, AAP, and ABP Group

Outcome, N (%)	PEP (n = 55)	ABP (n = 88)	AAP (n = 300)	*P*
Length of hospital stay, d				
1–2	11 (20)	21 (24)	91 (30)	0.974
3–10	40 (73)	47 (53)	179 (60)	**0.005**
>10	4 (7)	20 (23)	30 (10)	**0.025**
Complications				
Pancreatic pseudocyst	4 (7)	19 (22)	64 (21)	**0.048**
Pancreatic necrosis	1 (2)	6 (7)	19 (6)	0.387
Single OF				
Respiratory (PaO_2/FiO_2)	1 (2)	7 (8)	6 (2)	**0.016**
Renal (serum creatinine), mg/dL	3 (5)	13 (15)	17 (6)	**0.014**
Cardiovascular (systolic BP), mm Hg	1 (2)	3 (3)	4 (1)	0.171
MOF	0 (0)	0 (0)	13 (4)	**0.001**
POF	2 (4)	8 (9)	13 (4)	0.164
Interventions to treat complications				
Percutaneous drainage	0 (0)	6 (7)	7 (2)	**0.035**
Surgical drainage	0 (0)	1 (1)	0 (0)	0.133
Necrosectomy	0 (0)	1 (1)	0 (0)	0.133
Debridement	0 (0)	1 (1)	0 (0)	0.133
Laparoscopic cholecystectomy	1 (2)	7 (8)	0 (0)	**0.001**
Open cholecystectomy	0 (0)	8 (9)	1 (0.3)	**0.001**
Exploratory laparotomy	0 (0)	1 (1)	1 (0.3)	0.534
Mortality				
Within hospital stay	0 (0)	1 (1)	5 (2)	0.607
Within 30 d of diagnosis	0 (0)	5 (6)	3 (1)	**0.002**
After 30 d of diagnosis	2 (4)	4 (5)	19 (6)	0.735

Bold values indicate statistically significant results.

TABLE 3. Association Between Clinical Predictors and Measured Outcomes

Predictors	LOHS (>10 d)	Pancreatic Necrosis	Pancreatic Pseudocyst	OF	MOF	POF	Mortality
Age	1.00 (0.96)	0.99 (0.47)	1.01 (0.54)	1.00 (0.82)	1.01 (0.82)	1.01 (0.41)	1.01 (0.77)
Sex, female	0.74 (0.31)	**0.14 (0.002)**	0.83 (0.48)	0.75 (0.53)	0.52 (0.41)	0.97 (0.95)	1.83 (0.28)
Etiology							
PEP	Reference	Reference	Reference	Reference	Reference	Reference	Reference
ABP	1.01 (0.97)	0.51 (0.52)	**0.28 (0.02)**	1.64 (0.46)	0.001 (0.997)	1.04 (0.97)	0.001 (0.99)
AAP	0.001 (2.88)	1.05 (0.93)	1.41 (0.31)	0.47 (0.19)	2.43 (0.26)	0.76 (0.68)	1.65 (0.43)
SIRS day 1	1.76 (0.09)	1.34 (0.57)	1.81 (0.06)	0.92 (0.87)	0.10 (0.07)	1.86 (0.29)	1.77 (0.39)
SIRS day 2	**2.57 (0.01)**	0.69 (0.60)	**0.15 (0.014)**	2.50 (0.14)	**5.3 (0.05)**	0.64 (0.63)	0.96 (0.97)
CP	1.71 (0.072)	0.52 (0.18)	**3.87 (<0.001)**	0.42 (0.08)	0.33 (0.21)	1.32 (0.62)	**3.79 (0.03)**
SUN, g/dL	**2.43 (0.02)**	0.37 (0.23)	0.66 (0.35)	**33.9 (<0.001)**	**21.6 (<0.001)**	**45.02 (<0.001)**	3.55 (0.06)

Data presented as OR (*P*).

Bold values indicate statistically significant results.

gallstones.[34] Recurrent episodes can increase the concurrent damage to pancreatic tissue leading to increase in the incidence of necrosis and subsequent intervention to treat the necrosis. Obesity might be another factor increasing the severity of ABP because the obesity leads to increased gallstones formation.[35] Jin et al[24] showed increase in severity and mortality of pancreatitis in patients with higher body mass index.

This study showed SIRS on the second day of hospitalization as a predictor of extended LOHS and multi-OF. Systemic inflammatory response syndrome has been shown as predictor of moderate and severe acute pancreatitis.[36] It is an important tool because it can help the physician in differentiating mild from severe pancreatitis and recognizing early severe pancreatitis.[37] This further influences decision-making in performing further intervention during the clinical course of AP such as CT and endoscopy as well as predicting long-term outcomes.[38] History of chronic pancreatitis was associated with an increased risk of pseudocyst formation in our study. Our results support previous studies, which have shown that 70% of pseudocysts arose in patients with chronic pancreatitis.[35,39] Most pseudocysts resolved on their own but some required drainage. Serum urea nitrogen of greater than 25 g/dL predicted LOHS of more than 10 days and POF in our study. Persistent OF is an important parameter determining the severity of acute pancreatitis.[40] Renal failure is the most common OF associated with severe acute pancreatitis and has been shown important determinant of severity and mortality in previous studies as well as in the present study.

Our study has several strengths. This is the first study to compare outcomes of patients with 3 major kinds of pancreatitis. We screened all acute pancreatitis patients to correctly identify the etiology of the pancreatitis. Secondly, all transferred patients were excluded, because clinical information in patients transferred from other hospitals is often incomplete and tend to enrich the study with patients who have more severe disease.[41] This study has several potential limitations. First, its design was retrospective. However, we tried to overcome this drawback by obtaining consecutive data using a standard approach and enrolling a large number of patients. Secondly, it is a single-center study conducted at a tertiary site, and thus, the results may not be generalizable because of referral bias.

In conclusion, our study shows that the etiology of acute pancreatitis is an important determinant of morbidity and mortality. Acute biliary pancreatitis is a more severe disease compared with PEP and AAP, with a higher risk of complications. Systemic inflammatory response syndrome, chronic pancreatitis, and high SUN are important predictors of morbidity.

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