





ORIGINAL ARTICLE

Comparative study of the outcome between alcohol and gallstone pancreatitis in a high-volume tertiary care center

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Key words

acute pancreatitis, alcohol, biliary, etiology, gallstone.

Accepted for publication 4 February 2019.

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Declaration of conflict of interest: The authors declare that they have no conflict of interest.

Abstract

Background and Aim: The two most common etiologies of acute pancreatitis (AP) are alcohol and gallstone. Whether etiology contributes to the outcome in patients with AP is an unresolved issue, more so in the severe form of the disease. The aim is to study the effects of the etiological factors of alcohol and gallstone on the disease course and the role of etiology in the subgroup of severe AP.

Methods: Consecutive patients of AP with alcohol or gallstone etiology were included. Various severity parameters and various outcome measures, such as need for organ support, intensive care, surgical or radiological intervention, hospital stay, and mortality, were evaluated between the two groups.

Results: Of the 759 patients, alcoholic pancreatitis was seen in 368 (48.5%), while gallstone disease was observed in 246 (32.4%). Gallstone pancreatitis occurred in older age ($P < 0.0001$), had a higher female predilection ($P < 0.001$), and a higher body mass index ($P = 0.002$) compared to alcohol pancreatitis. Both groups were similar in terms of development of various organ failures and various severity assessment scores. Alcoholic AP had higher rates of necrosis ($P = 0.05$) and the need for percutaneous catheter drainage ($P = 0.02$). Outcome measures such as length of hospital stay, need for intensive care, organ support, surgical intervention, or mortality were similar between the two groups. Subset analysis of severe AP (303 patients) showed no difference between the two etiologies with regard to outcome.

Conclusion: The outcome of AP was independent of the etiology of the disease, alcohol or gallstone, and more so in the severe form of the disease. The number of local complications tends to be slightly higher in the alcoholic group.

Introduction

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas that cascades into varying degrees of damage to the pancreas and extrapancreatic organs, sometimes resulting in subsequent dysfunction and failure. The worldwide incidence of AP has been on the rise.^{1–3} Although a majority of the cases resolve with conservative management, 10–20% of the patients might experience severe disease, with a mortality risk as high as 25%.⁴

Although various etiologies have been described to cause AP, the two most common etiologies accounting for 70–80% of all the cases are gallstones (GSs) and alcohol.^{5,6} Identification of the etiology may help in the better formulation of treatment strategies or prevention of recurrence, although the pattern of conservative management of the ongoing attack of AP is similar across etiologies. Whether etiology contributes to the outcome in patients with AP is an unresolved issue. Considering the two main etiologies, GS and alcohol, different studies have reported different outcomes based on etiology. Older studies, prior to the

revised Atlanta Classification, 2012,⁷ had differing reports of outcome based on etiology. While some had reported higher mortality and severity with biliary pancreatitis,^{8–10} others had found more complications and mortality rates with alcohol,^{11–13} and some had reported no difference.^{14–16} In recent times, some studies have shown more local complications^{17,18} and higher mortality in the alcohol group,¹⁸ while others found no difference.¹⁹ The basic pathophysiology of pancreatitis, irrespective of the etiology, is premature activation of the digestive enzymes within the acinar cell, causing autodigestion. However, the triggering event for the two etiologies varies, with alcohol having reduced blood flow with free radical damage²⁰ and GS having obstruction of ampulla of Vater, causing retention of pancreatic juice and bile reflux.²¹ Moreover, baseline pancreatic damage is expected to be present in patients with alcoholic AP due to long-standing alcohol intake.²² Hence, a difference in the course of the two different etiology-induced AP might be expected theoretically. In recent times, change in the management of pancreatitis in the form of radiological intervention, more efficient

target-approached fluid management, and interventions like endoscopic sphincterotomy might have altered the clinical outcomes compared to the past.

In AP, the outcome depends on the severity of the disease. The more concerning outcome parameters, such as mortality and morbidity, assume greater importance on the more severe end of the spectrum of the disease. Thus, whether any difference in the outcome parameters occurs in the subset of patients having severe AP depending on the etiology would be an interesting observation to make. In all the studies till date with a substantial number of patients, the range of severe AP was 8–30%^{17–19,23} of the total included patients, but the subset of patients with severe AP was never analyzed separately for any difference based on etiology.

The current study was designed to study the effects of the two main etiological factors, alcohol and GS, on the disease course and outcome of AP and also to investigate the role of etiology in the subgroup of AP having severe disease.

Methods

Patients. Between January 2010 and June 2018, all consecutive patients presenting to the gastroenterology and surgical services of a tertiary care center in North India with a diagnosis of AP were screened for inclusion in the study. A total of 759 patients with AP were screened, and 614 patients presenting with AP secondary to alcohol or GSs were included in the study. The demographic, radiographic, and laboratory data of these patients were collected prospectively as per institute protocol, and the data were analyzed retrospectively. Patients with a history of pre-existing chronic pancreatitis or patients with other or overlapping etiologies of AP were excluded from the study. The study was approved by the institute ethics committee. Written informed consent was obtained from all patients.

Definitions. The diagnosis of AP was made if a patient had two or more of the following three findings: typical abdominal pain, elevation of serum enzymes (amylase and/or lipase) to more than three times the upper limit of the normal level, and findings on imaging (ultrasonography or computed tomography [CT]) suggestive of AP.⁷

Alcohol-related pancreatitis was defined as the consumption of 50–80 g/day of alcohol, irrespective of gender, for five or more years or alcoholic binge drinking 1 week before the onset of the disease with a lack of evidence of other causes. Biliary AP was considered when imaging findings were suggestive of GS or biliary sludge on ultrasonography, CT, or endoscopic ultrasound. AP was labeled idiopathic when no definitive etiological agent could be identified on history or investigations for etiological work-up.

Severity assessment. Severity assessment was conducted as per the revised Atlanta Classification,⁷ divided into mild, moderately severe, and severe. The absence of organ failure (OF) or local or systemic complications was labeled mild AP. Moderately severe AP was defined by the presence of transient OF or local complications such as fluid collection or necrotic collection or exacerbation of comorbid illness. Severe AP was used when there was persistent OF for more than 48 h.

OF was defined using the modified Marshall scoring system.²⁴ Severity parameters such as the Acute Physiology and Chronic Health evaluation (APACHE)-II,²⁵ Systemic Inflammatory Response Syndrome (SIRS), and Bedside Index for Severity in AP (BISAP)²⁶ were calculated. The CT severity index (CTSI) was calculated for patients undergoing CT. Necrosis was defined using the CTSI.²⁷ Pancreatic pseudocyst or walled-off necrosis was defined as a well-formed collection beyond 4 weeks following an episode of acute edematous or necrotizing pancreatitis, respectively.⁷

Management. Patients were managed as per the standard recommendations, including adequate fluid resuscitation, organ system support, pain management, and nutritional support (enteral or parenteral).^{28,29} Extrapaneatic infections and suspected infected pancreatic necrosis (IPN) were managed with antibiotics. IPN was suspected based on the deteriorating clinical course of the patient and was diagnosed by culture positivity of the drain output or Contrast enhanced computed tomography (CECT) abdomen showing gas within the necrosis. In cases of persistent OF, suspected IPN, and/or pressure symptoms, the fluid collections were drained (endoscopically or percutaneous catheter). A dedicated unit comprising gastroenterologists and an interventional radiologist decided on the site and route of drainage based on the location, type, and extent of collection. Patients who did not show improvement or worsened on medical management and drainage of collection were subsequently taken for surgical necrosectomy.

Outcome measures. The various severity parameters documented at the time of presentation were compared between the two etiological groups. The parameters studied were SIRS, BISAP, and APACHE II scores, and the severity of AP was assessed as per revised Atlanta classification.

The various outcome measures included the duration of hospital stay, requirement of organ support (mechanical ventilation and dialysis), need for surgical necrosectomy, intensive care (ICU) admission, and drainage of collections and mortality in the patients' index hospital admission with AP.

Statistical analysis. All data were entered on a personal computer in Microsoft Excel 2010: Microsoft, Redmond, Washington, USA. The data were analyzed using SPSS software (version 22.0, IBM, Armonk, New York, USA). Data were explored for any outliers, errors, and missing values. The data were checked for normal distribution using the Kolmogorov–Smirnov test. For normally distributed data, the student *t* test was used for continuous variables, while for skewed data, nonparametric tests were used. Dichotomous variables were compared using the χ^2 test. Descriptive statistics were used wherever required. Quantitative data were described as mean and SD, with 95% confidence intervals. Categorical data were shown as proportions. Correlation studies were carried out using Pearson's correlation. A *P* value of less than 0.05 was considered statistically significant.

Results

A cohort of 759 patients of AP admitted to a tertiary care center in North India between January 2010 and June 2018 was included in the study. Of these 759 patients (525 males; 69.2%),

the etiology of pancreatitis was alcohol in 368 (48.5%) patients and was GS in 246 (32.4%) patients, while the remaining patients had other etiologies.

Hence, the 614 patients with an etiology of AP of either alcohol or GS were included in the final analysis.

Demographic parameters. Considerable differences were noted when comparing the basic demographic parameters between the two groups (Table 1). GS-related pancreatitis occurred in a significantly older population (43.29 ± 14.8 vs 37.08 ± 9.9 ; $P < 0.001$) compared to the alcohol group. Evidently significant female predilection was noted in the GS-related pancreatitis group ($P < 0.001$). The GS group had a significantly higher body mass index (BMI) (24.58 ± 3.6 vs 23.56 ± 3.8 ; $P = 0.002$). Repeat attacks of pancreatitis were noted to be significantly higher in the alcohol group.

Disease course. Comparing the disease course between the two groups (Table 2), it was noted that both the groups were similar in terms of development of OF, such as acute lung injury (ALI); acute kidney injury (AKI); shock; or development of collection, ascites, or need for surgery or dialysis. The patients with alcohol-related AP had significantly higher rates of necrosis (90.2 vs 84.1%; $P = 0.05$) compared to the patients with GS-related AP.

The various severity parameters, such as SIRS, BISAP, APACHE II at admission, CTSI, and the Atlanta classification, were compared between the two groups and were found to be similar.

Outcome parameters. Other outcome parameters, such as hospital stay, ICU need or ventilator need, and mortality, were similar between the two groups (Table 3). The need for percutaneous catheter drainage (PCD) (64.7 vs 56.1%; $P = 0.02$) was higher in the alcohol group, although the need for surgery or dialysis was similar between the two groups. Univariate analysis was carried out for factors such as age, gender, and BMI to determine if they had any effect on the outcome parameters. Age was found to only be significantly different as far as mortality was concerned (41.61 ± 14.3 vs 39.10 ± 12.0 ; $P = 0.05$). The rest of the demographic factors did not have any effect on the outcome parameters.

Table 1 Comparison of the basic demographic parameters

	Alcohol (n = 368)	Gall stone (n = 246)	P value
Age (mean \pm SD)	37.08 \pm 9.9	43.29 \pm 14.8	<0.001
Gender			
Male	358 (97.3%)	84 (34.1%)	<0.001
Female	10 (2.7%)	162 (93.7%)	
BMI (mean \pm SD)	23.56 \pm 3.8	24.58 \pm 3.6	0.002
Attack no			
Repeated	39 (11.4%)	12 (5.2%)	0.011

BMI, body mass index.

Table 2 Comparison of the disease course between alcohol and gallstone acute pancreatitis (AP)

	Alcohol (n = 368)	Gall stone (n = 246)	P value
Organ failure	224 (61.2%)	160 (65.0%)	0.28
Multiple organ failure	103 (44.4%)	73 (44.2%)	1.00
ALI	184 (50.4%)	143 (58.1%)	0.07
AKI	106 (29.0%)	75 (30.5%)	0.72
Shock	38 (10.4%)	37 (15.0%)	0.10
Necrosis	285 (90.2%)	191 (84.1%)	0.05
Collection	305 (83.1%)	207 (84.8%)	0.65
Ascites	215 (66.2%)	151 (65.4%)	0.57
SIRS	276 (77.3%)	189 (77.5%)	1.00
BISAP			
<2	110 (30.6%)	69 (28.3%)	0.59
≥ 2	250 (69.4%)	175 (71.7%)	
APACHE II admission	8.73 \pm 4.9	9.10 \pm 5.5	0.42
CTSI	7.76 \pm 2.5	7.45 \pm 2.7	0.16
Atlanta classification			
MAP	28 (7.7%)	31 (12.6%)	0.09
MSAP	157 (43.0%)	92 (37.4%)	
SAP	180 (49.3%)	123 (50%)	

Boldface indicates the statistically significant parameter. AKI, acute kidney injury; ALI, acute lung injury; APACHE, Acute Physiology and Chronic Health Evaluation; BISAP, Bedside index of severity of AP; CTSI, computed tomography severity index; MAP, mild AP; MSAP, moderately severe AP; SAP, severe AP; SIRS, Systemic Inflammatory Response Syndrome.

Outcome parameters in a subset of severe AP. The subset of patients with severe AP (303 patients) (Table 4) was analyzed for any differences in the outcome parameters. The various parameters, such as hospital stay, ICU need, ventilator need, need for pigtail dialysis, and mortality, were similar between the two groups.

Discussion

This study is a retrospective analysis of prospectively collected data comparing the various outcome parameters of the two main etiologies of AP, namely, GS and alcohol. These two etiologies

Table 3 Comparison of outcome parameters between alcohol and gallstone acute pancreatitis

	Alcohol (n = 368)	Gall stone (n = 246)	P value
ICU need	161 (43.8%)	123 (50%)	0.13
Hospital stay	24.4 \pm 18.5	27.4 \pm 22.0	0.09
Ventilator need	72 (19.6%)	60 (24.4%)	0.16
Mortality	62 (16.8%)	53 (21.5%)	0.17
Pigtail	238 (64.7%)	138 (56.1%)	0.02
Surgery	43 (12.4%)	22 (8.3%)	0.11
Dialysis	25 (6.9%)	19 (7.7%)	0.75

Boldface indicates the statistically significant parameter. ICU, intensive care unit.

Table 4 Comparison of the two etiologies in the subset of severe acute pancreatitis

	Alcohol (<i>n</i> = 180)	Gall stone (<i>n</i> = 123)	<i>P</i> value
Hospital stay	31.54 ± 20.6	36.77 ± 24.7	0.07
ICU need	128 (71.1%)	91 (74%)	0.60
Ventilator need	64 (35.6%)	52 (42.3%)	0.28
Dialysis	19 (12.5%)	15 (13.8%)	0.85
Mortality	55 (30.6%)	45 (36.6%)	0.32

ICU, intensive care unit.

account for 70–80% of all AP,^{5,6,15} as was also the case in the current study where 80.1% of the patients either had GS or alcohol as the etiology. The etiologies of alcohol- and GS-related AP have a clear gender bias as has been established in previous multiple studies, with males having a higher percentage of alcohol-related AP and females a higher percentage of GS-related AP.^{15,17,23} Similar results were observed in the current study, where 97.3% of males had alcohol-induced AP, while 93.7% females had GS-related AP. Alcohol-induced AP was found in a relatively younger population compared to the GS-related AP in this study (37.08 ± 9.9 vs 43.29 ± 14.8 ; $P < 0.001$), as also demonstrated in various other studies.^{15,18,23} Recurrent attacks of pancreatitis were evidently found in a higher percentage of patients with alcohol-related, than GS-related, AP (11.4 vs 5.2%, $P = 0.011$), as had been established in previous studies.³⁰ Alcoholic pancreatitis patients have a higher tendency of repeated attacks as a result of the recurrent insult due to ongoing alcohol intake compared to patients of GS-related AP.

Multiple studies have investigated the role of etiology on the disease course and outcome of AP. Older studies gave varying reports on the outcome, with some reporting greater severity with biliary pancreatitis,^{8–10} some with more complication rates with alcohol,^{11–13} and still others reporting no difference.^{14–16} Recent studies also demonstrate varying data. Cho *et al.*,¹⁸ in an analysis of 126 patients, found a significantly higher percentage of persistent OF in the alcohol group compared to the biliary group. Zhu *et al.*²³ reported differences between the two groups with regard to the young and middle-aged patients but not in the elderly. Similarly, in our study, no differences were noted between the two etiological groups in the elderly subset of patients (Table S1, Supporting information). In the current study, the development of OF, such as ALI, AKI, shock, and number of OFs, was similar between the two groups.

The various severity predictors for AP are routinely used to prognosticate the course of the disease during hospital stay. In the current study, no difference in the various severity markers, such as SIRS, BISAP, APACHE II, and CTSI, were found between the two groups. Cho *et al.*,¹⁸ however, pointed out a more severe disease course in the alcohol group but could not find any difference as far as these predictors were concerned, such as Ranson, BISAP, and APACHE II scores. Similar proportions of patients from the two groups were found to have severe AP and mild AP as per the revised Atlanta Classification.⁷ Zhu *et al.*²³ reported a higher proportion of severe AP in the hypertriglyceridemia (HTG) and alcohol groups compared to the biliary one, while Kim *et al.*¹⁷ demonstrated equal proportions of patients having severe AP with alcohol- and GS-related etiologies.

Although the development of collection and ascites showed no difference, development of necrosis was higher in the alcohol group (90.2 vs 84.1%, $P = 0.05$). Evidently, the need for pigtail drainage was also higher in the alcohol group (64.7 vs 56.1%, $P = 0.02$). The higher rates of development of local complications among the alcohol AP group has previously been pointed out by various studies. While Kim *et al.*¹⁷ found higher rates of peripancreatic fluid collection, Cho *et al.*¹⁸ highlighted greater pseudocyst formation in the alcohol group. Furthermore, Kim *et al.*¹³ compared the CT images of cases of AP between the two groups and found more aggressive CT findings in the alcohol group. Alcoholic AP is usually seen in heavy drinkers in whom substantial pancreatic damage has already set in by the time the patient develops AP.²² Therefore, underlying pancreatic ductal pathology, such as stricture or dilatation, are more prone in alcoholics, thus leading to the subsequent ductal disruption and higher probability of development of local complications in this group of patients. On the contrary, GS-related AP is a result of a single episode of ductal obstruction in a near normal pancreas.

The various other outcome parameters, such as length of hospital stay, need for ICU or ventilator, and need for surgery or dialysis, were found to be similar in the two groups. Cho *et al.*¹⁸ had a similar observation of nonsignificant difference between the two groups as far as hospital stay, Nil per oral (NPO) days, and alleviation of symptoms were concerned. As far as mortality is concerned, varying reports are available from the studies over the years. While some very initial studies had highlighted that mortality was higher with GS-related AP,^{8–10} later studies had shown that alcohol AP had higher mortality.^{3,11,12,17,18,23} This was possibly explained by the improved endoscopic techniques developed for early management of biliary AP, wherever needed, but most others have found no difference in the mortality as was found in the current study.^{15,16,31–33}

Factors such as morbidity and mortality for any disease usually assume importance at the more severe spectrum of the disease. Most of the studies studying the difference between the two groups included a small fraction of patients with severe AP, for example, Kim *et al.*¹⁷ had 8%, and Cho *et al.*¹⁸ had 10.3%, while Zhu *et al.*²³ had 14.4% of patients with AP. Moreover, none of the studies had studied the differences between the two groups in the subset of patients with severe AP. The current study had been carried out in a tertiary care center with a large referral base from three states, with approximately 150 patients of AP being reported annually at the center. Moreover, ours being a tertiary care center, a majority of the patients are referred from other centers and hence are on the more severe spectrum of the disease. Thus, nearly half of the patients ($n = 303$; 49.1%) had severe AP as per the Atlanta Classification. A subset analysis of these severe AP patients was carried out to find any difference between the two groups. It was observed that major outcome parameters, such as length of hospital stay, ICU need, and need for ventilator support or dialysis, were similar between the two groups. Mortality was also found to be similar between the two groups in this subset of patients. This can be explained by the fact that, once the inflammatory cascade sets in and severity of the disease increases, the outcome becomes independent of the basic etiology triggering the event. This phenomenon had been established in a proof-of-concept study by Novovic *et al.*³⁴

The basic pathophysiology of AP lies in the initiation of the cytokine storm and, in that study, no significant differences were observed between the two etiological groups in the cytokine levels of the patients with AP. This proves that, irrespective of the initial triggering factor based on the etiology, it is the degree of inflammatory burst that determines the course and the final outcome in patients with AP.

Whether etiology does play a role in the outcome of AP has been addressed in multiple studies. Some recent studies have found that alcohol has a more severe course with higher mortality compared to GS-related pancreatitis.^{3,17,18,23} Still further, few studies highlighted that the outcome of HTG-related AP has a more severe outcome. Li *et al.*³⁵ found higher rates of OF and complications in the HTG group compared to the biliary AP group, although no difference in the mortality was observed. While Zhu *et al.*²³ reported higher mortality in the HTG and alcohol groups compared to the biliary group, Zheng *et al.*¹⁹ showed lower mortality rates in the HTG and biliary groups. In a small study, Goyal *et al.*³⁶ found HTG to have a more severe course and outcome compared to the alcohol group. Our study comprehensively found that, except for local complications, the two etiologies of AP, namely, alcohol and GS, do not differ as far as severity, mortality, and other outcome measures were concerned.

Limitation. This study is conducted in a tertiary care center where a large number of patients is referred, rather than present at the first time, hence leading to the possibility of a referral bias. The study had a higher percentage of patients in the moderately severe and severe AP categories, and only 9.6% patients had mild AP. The detailed nature of the local complications, such as difference in the sites of necrosis and sites of collection, between the two groups needs to be studied.

In summary, the results of our study showed that the outcome of AP was mostly independent of the basic etiology of the disease, namely, alcohol or GS, and more so in the severe form of the disease. The number of local complications tends to be slightly higher in the alcoholic AP group. Further nationwide studies are required to validate these findings.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Outcome parameters in elderly subset of patients.