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Patients With Sentinel Acute Pancreatitis of Alcoholic Etiology are at Risk for Organ Failure and Pancreatic Necrosis: A Dual-Center Experience

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Abstract

Objectives—Assess the relationship between alcoholic etiology, tobacco use and severe acute pancreatitis (SAP).

Methods—Smoking and alcohol exposure were recorded upon admission in a cohort of acute pancreatitis patients within the United States (U.S.). Patients with first, “sentinel” attack of acute pancreatitis (AP) were identified for analysis.

Associations between alcohol, smoking and SAP were validated in an independent cohort of patients from Spain.

Results—U.S. cohort (n=222): Thirty-five% developed organ failure (OF), 35% Pancreatic Necrosis (PNec), and 7% died. OF (54% vs. 33%, p=0.03), PNec (62% vs. 31%, p=0.006), intensive care (ICU) admission (58% vs. 36%, p=0.03) and length of stay (LOS) (20 vs. 8 days, p=0.007) were greater in alcoholic when compared to other etiologies.

Spanish cohort (n=366): Similar differences in outcomes were also found with between alcoholic and non-alcoholic etiologies: OF (24% vs. 8%, p=0.001), PNec (38% vs. 14%, p<0.001), ICU admission (20% vs. 3%, p<0.001), and LOS (17 vs. 11 days, p=0.04).

Multivariable analysis confirmed alcoholic etiology to be independently associated with OF and PNec in both cohorts.

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Conclusions—Alcoholic etiology is independently associated with OF and PNec in patients with sentinel AP and is important when evaluating risk for severe disease in AP.

Keywords

acute pancreatitis; pancreatic necrosis; alcohol; tobacco

Introduction

Acute pancreatitis (AP) is the most common gastrointestinal diagnosis for inpatient hospitalization in the United States.¹ While majority of patients have an uncomplicated course and overall mortality is less than 5%; 15-20% of patients suffer a “severe” attack. Severe acute pancreatitis (SAP) is defined by the presence of organ failure (OF) and/or pancreatic necrosis (PNec); with mortality in SAP approaching up to 30%.²⁻⁵ Determination of risk factors for SAP is an area of intense research.

Alcohol is a known cause of AP, an independent risk factor for recurrent acute pancreatitis (RAP) and is associated with progression to chronic pancreatitis (CP).^{6,7} The results of an earlier prospective study by our group demonstrated that patients with heavy alcohol consumption were more likely to develop PNec in the setting of AP by any etiology.⁸ These results suggested that alcohol abuse may play a role in the natural history of SAP. However, the impact of alcohol consumption as a unique risk factor for SAP remains incompletely described in further retrospective studies.^{15,16}

Cigarette smoking is also associated with a higher risk of developing AP, recurrent AP, and progression to CP in clinical studies.⁹⁻¹² Studies have demonstrated smoking to be associated with elevated levels of pancreatic inflammatory cytokines, trypsinogen and the development of fibrotic parenchymal changes.¹³⁻¹⁶ While it is an exposure often paired with alcohol, smoking as a risk for acute and chronic pancreatic disease is now demonstrated to have a role that is independent of alcohol consumption.^{6,17,18} However, the impact of smoking as an environmental risk factor for severity in the context of AP also remains poorly studied.

The aims of this study are to explore the association of alcoholic etiology and smoking with organ failure (OF) and pancreatic necrosis (PNec) using a tertiary training cohort of patients with sentinel AP (training cohort). Subsequently, the above findings are validated in an independent cohort from a community hospital (validating cohort).

Methods

Training Cohort

The Severe Acute Pancreatitis Study (SAPS) at the University of Pittsburgh Medical Center (UPMC, U.S.A.) is an ongoing prospective observational study that has enrolled 344 patients with AP in four, one-year enrollment periods between June 2003 and May 2013. The diagnosis of AP was based on presence of at least two of the following three features: abdominal pain characteristic of AP, serum amylase and/or lipase at least three times the upper limit of normal, and characteristic findings of AP on abdominal computed

tomography (CT) scan. All patients are enrolled within 24 hours from the time of admission or transfer to our institution(s).¹⁹ The SAPS Study protocol has been approved by the Institutional Review Board of the University of Pittsburgh. Informed consent is obtained from all patients or appropriate surrogates before study enrollment. For the present study, we included SAPS patients who were admitted with their first attack of AP (sentinel) and excluded patients who had a prior history of AP.

Data Collection and Definitions

As previously described,²⁰ data collection in the SAPS study included detailed information on demographic, clinical, laboratory and radiographic parameters. For patients transferred to our institution, pertinent information from outside records was obtained by contacting the transferring center.

Alcohol Consumption and Cigarette Smoking

Data regarding alcohol consumption and cigarette smoking was collected prospectively in the form of a detailed questionnaire administered to patients by the study investigators during their hospitalization. Patients were classified as never drinkers, prior drinkers (abstinent for the past six months), or active drinkers (use within the past six months). Level of active alcohol consumption was defined as “light” when patients consumed less than four drinks per month. Patients with heavy alcohol consumption were either daily users reporting more than two drinks per day for men and one drink per day for women or binge drinkers reporting multiple days per month of consuming greater than five drinks per day for men and three drinks per day for women. Finally “moderate” drinkers were those patients with daily and/or episodic patterns of use quantified to a level greater than “light”, but less than “heavy.”²¹ Patients also identified the timing of their last drink prior to the attack of pancreatitis.

The etiology of AP was determined by the study physicians’ based on review of the prospectively collected questionnaires and the medical records. Biliary etiology was based on presence of gallstones and/or common bile duct stones on abdominal ultrasound, elevated serum alanine aminotransferase (ALT) concentration, especially more than threefold, and prior history of biliary colic.²² Alcoholic etiology was based on active moderate or severe alcohol consumption in the absence of evidence for other common etiologies, i.e. biliary or hypertriglyceridemic.

Cigarette smoking was assessed with the same enrollment questionnaire. Patients were classified as never smokers, former smokers (abstinent for six months leading to enrollment), or active smokers. Smoking was quantified as greater than or less than 1 pack per day.

Disease Severity

OF was defined by the Modified Marshal Score for cardiovascular, pulmonary, and/or renal dysfunction.⁵ OF was further sub-classified into transient (<48 hours) and persistent (≥ 48 hours). PNec was defined by a regional lack of parenchymal enhancement on contrast enhanced cross sectional imaging (CT or MRI scan). Other outcomes included ICU need,

length of hospitalization, and in-hospital mortality. All the information on the clinical course during the index admission was collected prospectively.

Validation Cohort

To validate the association of alcoholic etiology and smoking with severe disease, we utilized an independent cohort of AP patients from Alicante, Spain. Demographic, clinical, laboratory and radiographic data for 366 consecutive patients with sentinel attack of AP admitted between 11/2008 and 11/2013 were collected prospectively.²³ Definition of AP, etiologies, and outcomes were similar to the training cohort as described above. Data on alcoholic etiology and cigarette smoking were collected prospectively. Alcoholic etiology was assigned by study physician based on active moderate to severe alcohol consumption in the absence of other etiologies.

Statistical Analysis

Descriptive data was represented as mean (standard deviation) or median (interquartile range; IQR) for continuous variables. Categorical variables were described using frequency (proportion). We used the chi-square or Fisher exact test for categorical data. Student's t-test or Wilcoxon rank-sum test was used for continuous variables as appropriate. The categorical outcomes for which odds ratios were calculated included any OF (transient or persistent) and PNec as assessed by contrast-enhanced imaging. Predictor variables included age (>60 years), sex, race, BMI ≥ 30 , alcoholic etiology and current smoking. Multivariable logistic regression was used to calculate adjusted odds ratios. We assessed for interactions and multicollinearity. The Hosmer-Lemeshow goodness of fit test was used to assess whether there is evidence for lack of fit in the final logistic regression model. All statistical analysis was conducted using STATA (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

Results

Training Cohort Characteristics

Of 344 patients prospectively enrolled in the SAPS trial, 222 patients were identified as having a sentinel (first attack) episode of AP. Their median age was 56 years (IQR 41-70), 50% were female, and 90% were Caucasian. 62% were transfers from referring institutions. The most common etiologies were biliary (48%), idiopathic (14%), and alcoholic (12%). Contrast enhanced imaging was performed in 158 patients. OF developed in 35% (78/222); PNec was identified in 35% (56/158), and death in 7% of patients (16/222; Table 1).

Forty eight % of patients were active drinkers; 30% of them reporting heavy consumption. Twenty two % of patients were active smokers, 60% of which were smoking over 1 PPD. Overall, 9% of patients reported combined, active heavy drinking and smoking. Patients reporting never having consumed alcohol and cigarettes comprised 34% and 49% of our cohort, respectively.

Among patients with alcoholic etiology (n=26, 12%), 85% classified as heavy alcohol drinkers and the remaining patients as moderate drinkers at the time of admission. Sixty-five

% of these patients were also smokers. Conversely, among patients without alcoholic etiology, only 5% reported heavy alcohol use. In all these patients, there was clear evidence supporting a different etiology of AP, i.e. presence of common bile duct stones on abdominal ultrasound.

Association of Alcoholic Etiology and Smoking with SAP

Alcoholic etiology was significantly associated with the development of OF (54% vs. 33%, $p=0.03$). Greater proportion of patients with alcoholic etiology required ICU admission (58% vs. 36%, $p=0.03$) and had a longer median hospitalization (20 vs. 8 days, $p=0.007$) when compared to patients with non-alcoholic etiologies (Table 1). Alcoholic etiology was also significantly associated with the development of PNec (62% vs. 31%, $p=0.006$). Mortality was similar between the two groups (7% vs. 7%, $p=0.92$). Active smoking was neither associated with OF (42% vs. 33%, $p=0.3$) nor with PNec (42% vs. 33%, $p=0.3$).

Age (>60 years), gender, race (Caucasians vs. non-Caucasians), obesity (BMI 30 vs. BMI<30), etiology (alcohol vs. non-alcohol), and current smoking were then assessed as potential risk factors for severe disease. On univariate analysis, BMI 30 [odds ratio (OR) 2.3, confidence interval (CI) 1.3-4.1; $p=0.003$], male gender (OR 2.7, CI 1.5-4.8; $p<0.001$), and alcoholic etiology (OR 2.4, CI 1.1-5.5; $p=0.03$) were significantly associated with OF. For PNec, analyzing only patients who underwent contrast enhanced imaging ($n=158$), male gender (OR 2.0, CI 1.0-4.0; $p=0.03$), and alcoholic etiology (OR 3.6, CI 1.4-9.2; $p=0.009$) were found to be significant risk factors (Table 2).

Multivariate regression analysis including age > 60 years, sex, BMI 30, and alcoholic etiology as predictors demonstrated BMI 30 (OR 2.5, CI 1.4-4.5; $p=0.003$), male sex (OR 2.6, CI 1.4-4.7; $p=0.002$), and alcoholic etiology (OR 2.6, CI 1.0-6.3; $p=0.04$) to be independently associated with OF. Only alcoholic etiology (OR 4.1, CI 1.5-11.3; $p=0.007$) was independently associated with PNec.

Spanish Cohort Characteristics and Findings

The median age of the 366 consecutive patients with sentinel AP in the validation cohort was 62 years (IQR 45-75) and 51% were female. The most common etiologies included biliary (69%), alcoholic (11%), and idiopathic (9%). Contrast enhanced imaging was available in 265 (72%) patients. OF was identified in 10% (36/366), PNec in 17% (46/265), and death in 3% (11/366; Table 3). Twenty-eight % of the patients were cigarette smokers at the time of presentation.

Alcoholic etiology ($n=41$, 11%) was significantly associated with the development of OF (24% vs. 8%, $p=0.001$). Greater proportion of patients with alcoholic etiology required ICU admission (20% vs. 3%, $p<0.001$) and had a longer median hospitalization (17 vs. 11 days, $p=0.04$) when compared to patients with non-alcoholic etiologies (Table 3). Alcoholic etiology was also significantly associated with the development of PNec (38% vs. 14%, $p<0.001$). Mortality did not reach statistical significance between the two groups (8% vs. 2%, $p=0.08$). Cigarette smoking was not associated with OF (14% vs. 7%, $p=0.0643$), but was associated with PNec (29% vs. 13%, $p=0.004$).

Univariate analysis was performed including age (>60 years), gender, BMI 30, alcoholic etiology, and current smoking as predictors and OF and PNec as outcomes. BMI 30 (OR 2.1, CI 1.1-4.3; p=0.03) and alcoholic etiology (OR 3.7, CI 1.6-8.4; p=0.002) were significantly associated with OF. For PNec, male sex (OR 2.8, CI 1.4-5.7; p=0.004), alcoholic etiology (OR 3.9, CI 1.8-8.2 p<0.001), and cigarette smoking (OR 2.7, CI 1.4-5.4; P=0.005) were found to be significant risks (Table 4).

Multivariate regression analysis using age (>60 years), sex, BMI 30, alcoholic etiology and cigarette smoking as predictors demonstrated BMI 30 (OR 2.6; CI 1.1-5.9; p=0.03) and alcoholic etiology (OR 5.6, CI 1.7-18.3; p=0.005) to have an independent association with OF. Male sex (OR 2.5, CI 1.1-5.8; p=0.03) and alcoholic etiology (OR 3.0, CI 1.1-7.6; p=0.03) were independently associated with PNec.

Discussion

In this study, we describe prospectively recorded patterns of alcohol consumption and cigarette smoking in a large cohort of patients from the U.S. with their first attack of AP. Around 50% of patients were active drinkers, with one third of them being heavy drinkers.⁶ In respect to smoking, around one quarter of patients were active smokers with the majority smoking more than 1 PPD. Furthermore, we explored possible associations between alcoholic etiology and smoking with severe disease as defined by the current revised classifications, specifically by OF and PNec.^{5,24} We demonstrated that the odds of developing OF and PNec are significantly higher for patients with alcoholic etiology, independently of other clinical risk factors such as BMI and gender. This is a novel and important finding in disease severity stratification.

Our early, previously published work described an association of chronic alcohol use with development of PNec.⁸ However, this previous study was of smaller sample size and was heterogeneous from the standpoint of including patients with prior pancreatic disease. There is recent data reporting that severity of AP diminishes with subsequent episodes of AP.^{25,26} Therefore, by excluding patients with recurrent attacks in the current study, we identified a sentinel cohort with minimal parenchymal fibrosis, which we believe was early in the natural history of pancreatic disease. Hence by focusing on sentinel attacks, we aimed to eliminate bias and/or confounding of outcomes by preexisting pancreatic disease.

The mechanism of pancreatic injury by alcohol remains an area of scientific debate. Theories implicating alcohol in AP include direct mitochondrial injury by metabolic end products of fatty acid ethanol esters, intracellular activation of pancreatic enzymes, pancreatic duct obstruction by alterations in the lithogenicity and viscosity of pancreatic secretions, sensitization of the exocrine pancreas to secretagogues, oxidative stress within pancreatic tissue and destabilization of zymogen membranes.^{9,27,28} Emerging evidence indicates that genetic polymorphisms play a role in susceptibility to alcoholic AP.²⁸⁻³⁰ Of note, this research focuses on mechanisms of direct acinar toxicity.

The strength of association between alcoholic etiology and OF suggests the role of alcohol in SAP is beyond direct pancreatic toxicity. A consequent, severe systemic inflammatory

response in the setting of alcoholic etiology appears to influence outcomes in AP. This is supported in the critical care literature with alcohol identified as an independent risk factor for the acquisition of ICU associated bacterial infections and ICU mortality.^{31,32} There is evidence that alcohol abuse may translate to increased systemic exposure to endotoxins and lipopolysaccharides by elevating gut permeability.^{9,33} The extent to which alcohol withdrawal, poor nutritional status, and concomitant end-organ damage (i.e. liver, or heart) also play a role are unclear. What is evident is that sentinel AP secondary to alcoholic etiology is associated with severity, and is likely due to a robust systemic insult. This translates to higher rates of hospitalization, greater ICU need, and a prolonged length of stay. Based on our results, we believe that these patients should be singled out as an at risk group at the time of presentation for worse outcomes within the context of AP. Future basic research studies are needed to further identify pathogenic mechanisms of OF in alcoholic AP.

We also found that alcoholic etiology in AP is independently associated with development of PNec. This finding is consistent with our previous clinical study, as described above ⁸. Recent experimental studies provide mechanistic insight into alcohol induced necrotizing pancreatitis. Oxidative metabolites of alcohol sensitizes the pancreatic mitochondria, increasing mitochondrial permeability, and ultimately leading to mitochondrial failure and acinar cell necrosis.³⁴ Necrotic cell death appears to activate the local immune response resulting in further pancreatic injury.

We did not find any association of alcoholic etiology with mortality in AP. This finding should, however, be interpreted with caution, owing to the small number of patients that died.

While patients with alcohol abuse tend to be heavy smokers, cigarette smoking was not found to be an independent predictor of severity. It is likely that smoking plays a larger role in mediating chronic inflammation, parenchymal fibrosis, and is synergistic with alcohol to progression to recurrent and chronic pancreatitis rather than influencing the severity of the sentinel attack.^{6,17,18}

Limitations of this study include the fact that our training cohort was captured at a tertiary care center. As a referral center, a significant proportion of enrolled patients were transfers from other institutions. Transferred patients differ in their elevated complexity and acuity. This is reflected by the prevalence of OF and PNec (35% for both), which is higher than expected in the community setting, raising a concern for ascertainment bias. To investigate this potential limitation, we utilized a second, independent, prospective group of patients with sentinel AP as a validating cohort. It included patients from a community hospital, which serves a large geographic area in Spain, Europe. This is reflected in the lower prevalence of OF (10%) and PNec (17%). We were able to reproduce the significant findings between alcoholic etiology and OF and PNec in the validating cohort, which diminishes the concern for ascertainment bias. Furthermore, the large sample size of almost 600 patients with sentinel AP between the two cohorts is a major, unique strength of our study.

Another limitation was the absence of detailed information on the amount of alcohol consumption of patients in the Spanish cohort. However, both centers used the exact same definition for alcoholic etiology. The fact that similar percentages of alcoholic pancreatitis were found in both cohorts increases the internal validity of the study and minimized any potential cultural differences. Finally, as we report our findings within context of patients with sentinel attack of pancreatitis, we advise caution in generalizing our findings to patients with recurrent acute and/or chronic pancreatitis.

In summary, this is the first study to identify alcoholic etiology as a significant risk for severe disease. These findings were generated in a cohort derived from a tertiary care center in the U.S. and subsequently validated in an independent cohort from a community hospital in Spain, Europe. Early recognition of subjects at high risk for severe disease remains a challenging task for clinicians as they strive to realize optimal management of patients with AP. Herein, we demonstrate that alcoholic etiology represents another, if not one of the more important, considerations when evaluating these patients. Within the context of a first episode of AP, alcoholic etiology should be immediately explored for accurate early risk stratification of such patients. Consequently, this group of patients would benefit from early, aggressive medical management at presentation (adequate volume resuscitation), close clinical surveillance once admitted with a low threshold for managing these patients at a higher level of care or transfer to a tertiary center.

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References

1. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012; 143:1179–1187. e1171–1173. [PubMed: 22885331]
2. Petrov MS, Shanbhag S, Chakraborty M, et al. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology*. 2010; 139:813–820. [PubMed: 20540942]
3. Garg PK, Madan K, Pande GK, et al. Association of extent and infection of pancreatic necrosis with organ failure and death in acute necrotizing pancreatitis. *Clin Gastroenterol Hepatol*. 2005; 3:159–166. [PubMed: 15704050]
4. Dellinger EP, Forsmark CE, Layer P, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. *Ann Surg*. 2012; 256:875–880. [PubMed: 22735715]
5. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013; 62:102–111. [PubMed: 23100216]
6. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med*. 2009; 169:1035–1045. [PubMed: 19506173]
7. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. *Am J Gastroenterol*. 2012; 107:1096–1103. [PubMed: 22613906]
8. Papachristou GI, Papachristou DJ, Morinville VD, et al. Chronic alcohol consumption is a major risk factor for pancreatic necrosis in acute pancreatitis. *Am J Gastroenterol*. 2006; 101:2605–2610. [PubMed: 17029614]

9. Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. *Nat Rev Gastroenterol Hepatol*. 2010; 7:131–145. [PubMed: 20125091]
10. Lindkvist B, Appelros S, Manjer J, et al. A prospective cohort study of smoking in acute pancreatitis. *Pancreatol*. 2008; 8:63–70. [PubMed: 18235217]
11. Tolstrup JS, Kristiansen L, Becker U, et al. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. *Arch Intern Med*. 2009; 169:603–609. [PubMed: 19307524]
12. Alsamarrai A, Das SL, Windsor JA, et al. Factors That Affect Risk for Pancreatic Disease in the General Population: A Systematic Review and Meta-analysis of Prospective Cohort Studies. *Clin Gastroenterol Hepatol*. 2014; 12:1635–44. e5. quiz e103. [PubMed: 24509242]
13. Wittel UA, Pandey KK, Andrianifahanana M, et al. Chronic pancreatic inflammation induced by environmental tobacco smoke inhalation in rats. *Am J Gastroenterol*. 2006; 101:148–159. [PubMed: 16405548]
14. Alexandre M, Pandol SJ, Gorelick FS, et al. The emerging role of smoking in the development of pancreatitis. *Pancreatol*. 2011; 11:469–474. [PubMed: 21986098]
15. Sliwiska-Mosson M, Milnerowicz H, Jablonowska M, et al. The effect of smoking on expression of IL-6 and antioxidants in pancreatic fluids and tissues in patients with chronic pancreatitis. *Pancreatol*. 2012; 12:295–304. [PubMed: 22898629]
16. Luaces-Regueira M, Iglesias-Garcia J, Lindkvist B, et al. Smoking as a risk factor for complications in chronic pancreatitis. *Pancreas*. 2014; 43:275–280. [PubMed: 24518508]
17. Nojgaard C, Becker U, Matzen P. Progression from acute to chronic pancreatitis: prognostic factors, mortality, and natural course. *Pancreas*. 2011; 40:1195–1200. [PubMed: 21926938]
18. Lin Y, Tamakoshi A, Hayakawa T, et al. Cigarette smoking as a risk factor for chronic pancreatitis: a case-control study in Japan. *Research Committee on Intractable Pancreatic Diseases. Pancreas*. 2000; 21:109–114. [PubMed: 10975702]
19. Papachristou GI, Papachristou DJ, Avula H, et al. Obesity increases the severity of acute pancreatitis: performance of APACHE-O score and correlation with the inflammatory response. *Pancreatol*. 2006; 6:279–285. [PubMed: 16636600]
20. Mounzer R, Langmead CJ, Wu BU, et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology*. 2012; 142:1476–1482. quiz e1415-1476. [PubMed: 22425589]
21. A Clinician's Guide. Vol. 07. National Institute of Alcohol Abuse and Alcoholism; 2005. Helping Patients Who Drink Too Much.; p. 3769<http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf>. [January 2012]
22. Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. *Am J Gastroenterol*. 1994; 89:1863–1866. [PubMed: 7942684]
23. de-Madaria E, Soler-Sala G, Sanchez-Paya J, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. *Am J Gastroenterol*. 2011; 106:1843–1850. [PubMed: 21876561]
24. Nawaz H, Mounzer R, Yadav D, et al. Revised atlanta and determinant-based classification: application in a prospective cohort of acute pancreatitis patients. *Am J Gastroenterol*. 2013; 108:1911–1917. [PubMed: 24126632]
25. Lee PJ, Bhatt A, Holmes J, et al. Decreased Severity in Recurrent Versus Initial Episodes of Acute Pancreatitis. *Pancreas*. 2015; 44:896–900. [PubMed: 25906451]
26. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas*. 2006; 33:323–330. [PubMed: 17079934]
27. Apte MV, Pirola RC, Wilson JS. Mechanisms of alcoholic pancreatitis. *J Gastroenterol Hepatol*. 2010; 25:1816–1826. [PubMed: 21091991]
28. Pandol SJ, Gorelick FS, Gerloff A, et al. Alcohol abuse, endoplasmic reticulum stress and pancreatitis. *Dig Dis*. 2010; 28:776–782. [PubMed: 21525762]
29. Whitcomb DC, LaRusch J, Krasinskas AM, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. *Nat Genet*. 2012; 44:1349–1354. [PubMed: 23143602]

30. Mounzer R, Whitcomb DC. Genetics of acute and chronic pancreatitis. *Curr Opin Gastroenterol*. 2013; 29:544–551. [PubMed: 23872486]
31. Gacouin A, Tadie JM, Uhel F, et al. At-Risk Drinking Is Independently Associated With ICU and 1-Year Mortality in Critically Ill Nontrauma Patients. *Crit Care Med*. 2014; 42:860–867. [PubMed: 24201172]
32. Gacouin A, Legay F, Camus C, et al. At-risk drinkers are at higher risk to acquire a bacterial infection during an intensive care unit stay than abstinent or moderate drinkers. *Crit Care Med*. 2008; 36:1735–1741. [PubMed: 18520640]
33. Vonlaufen A, Xu Z, Daniel B, et al. Bacterial endotoxin: a trigger factor for alcoholic pancreatitis? Evidence from a novel, physiologically relevant animal model. *Gastroenterology*. 2007; 133:1293–1303. [PubMed: 17919500]
34. Lerch MM, Halangk W, Mayerle J. Preventing pancreatitis by protecting the mitochondrial permeability transition pore. *Gastroenterology*. 2013; 144:265–269. [PubMed: 23260493]

Table 1

Demographics, patterns of alcohol use, cigarette smoking and clinical outcomes for sentinel episode of AP by alcoholic etiology (UPMC Cohort)

Variables		Etiology		P
		Alcoholic	Non-alcoholic	
All Patients, N (%)	222 (100)	26 (12)	196 (88)	
Median Age, (IQR)	56 (41-70)	42 (29-47)	59 (44-72)	<0.001
Males, N (%)	110 (50)	18 (69)	92 (47)	0.03
Caucasians, N (%)	196 (90)	22 (88)	174 (90)	0.5
BMI 30, N (%)	107 (48)	12 (46)	95 (48)	0.82
Transfers, N(%)	138 (62)	17 (65)	121 (62)	0.72
Alcohol Consumption, N (%)				
<i>Ever</i>	146 (66)	26 (100)	120 (61)	<0.001
Current, N (%)	107 (48)	26 (100)	81 (41)	<0.001
<i>Light</i>	38 (17)	0	37 (19)	
<i>Moderate</i>	37 (17)	4 (15)	34 (17)	
<i>Heavy</i>	32 (14)	22 (85)	10 (5)	
Last Drink, N (%)	76 (34) ¹			
<i>< 48 hrs</i>	36 (16)	16 (62)	20 (10)	0.005
<i>> 48 hrs</i>	40 (18)	6 (23)	34 (17)	
Tobacco, N %				
<i>Ever</i>	113 (51)	21 (81)	92 (47)	<0.001
Active Smoking, N (%)	48 (22)	17 (65)	31 (16)	<0.001
<i>< 1PPD</i>	19 (9)	6 (23)	13 (7)	
<i>> 1PPD</i>	29 (13)	11 (42)	18 (9)	
Clinical Outcomes				
<i>Any Organ Failure, N(%)</i>	78 (35)	14 (54)	64 (33)	0.033
<i>Persistent Organ Failure, N (%)</i>	70 (32)	14 (54)	56 (29)	0.009
<i>Pancreas Necrosis, N (%)</i> ²	56 (35)	13 (62)	43 (31)	0.006
<i>ICU Need</i>	85 (39)	15 (58)	70 (36)	0.03
<i>Median hospitalization (IQR)</i>	9 (5-19)	20 (8-28)	8 (5-17)	0.007
<i>Mortality, N (%)</i>	16 (7)	2 (7)	14 (7)	0.92

¹Data available for 76 patients

²Contrast enhanced CT was obtained in 158 patients so determination of pancreatic necrosis could only be made in these patients

Table 2

Univariate analysis: Clinical and demographic risk factors for organ failure and pancreas necrosis in patients with sentinel episode of AP (UPMC Cohort)

Variables	Organ Failure	P	Pancreas Necrosis	P
	N=222		N=158 ^I	
Age > 60 years (OR, 95% CI)	1.1 (0.6-1.9)	0.4	0.9 (0.51.8)	0.8
Males (OR, 95% CI)	2.7 (1.5-4.8)	<0.001	2.0 (1.0-4.0)	0.03
Caucasians (OR, 95% CI)	2.3 (0.7-7.0)	0.2	2.3 (0.7-7.1)	0.2
BMI 30 (OR, 95% CI)	2.3 (1.3-4.1)	0.003	1.5 (0.7-2.9)	0.2
Etiology (OR, 95% CI) Alcoholic	2.4 (1.1-5.5)	0.03	3.6 (1.4-9.2)	0.009
Cigarette Smoking (OR, 95% CI)	1.6 (0.7-2.7)	0.2	1.5 (0.7-3.1)	0.3

^I Contrast enhanced CT was obtained in 158 patients so determination of pancreatic necrosis could only be made in these patients

Table 3

Demographics, patterns of alcohol use, cigarette smoking and clinical outcomes for sentinel episode of AP by alcoholic etiology (Alicante Cohort)

Variables		Etiology		P
		Alcoholic	Non-alcoholic	
All Patients, N (%)	366 (100)	41 (11.2)	325 (88.8)	
Median Age, (IQR)	62 (45-75)	42 (38-48)	65 (49-75)	<0.001
Males, N (%)	178 (49)	35 (85)	143 (44)	<0.001
BMI 30, N (%)	94 (26)	5 (12)	89 (27)	0.03
Alcohol Consumption, N (%)				
Ever	109 (34)	41 (100)	68 (24)	<0.001
Active Smoking, N (%)	90 (28)	31 (79)	59 (21)	<0.001
Clinical Outcomes				
Any Organ Failure, N(%)	36 (10)	10 (24)	26 (8)	0.001
Persistent Organ Failure, N (%)	17 (5)	4 (10)	13 (4)	0.09
Pancreas Necrosis, N (%) ^I	46 (17)	15 (38)	31 (14)	<0.001
ICU Need	18 (5)	8 (20)	10 (3)	<0.001
Median hospitalization (IQR)	11 (7-19)	17 (8-28)	11 (8-18)	0.04
Mortality, N (%)	11 (3)	3 (8)	8 (2)	0.08

^I Contrast enhanced CT was obtained in 265 patients so determination of pancreatic necrosis could only be made in these patients

Table 4

Univariate analysis: Clinical and demographic risk factors for organ failure and pancreas necrosis in patients with sentinel episode of AP (Alicante Cohort)

Variables	Organ Failure	P	Pancreas Necrosis	P
	N=371		N=265 ^I	
Age > 60 Years (OR, 95% CI)	1.5 (0.7-3.0)	0.3	0.6 (0.3-1.1)	0.08
Males (OR, 95% CI)	1.3 (0.6-2.5)	0.5	2.8 (1.4-5.7)	0.004
BMI 30 (OR, 95% CI)	2.1 (1.1-4.3)	0.03	1.1 (0.5-2.2)	0.8
Etiology (OR, 95% CI)				
Alcoholic	3.7 (1.6-8.4)	0.002	3.9 (1.8-8.2)	<0.001
Cigarette Smoking (OR, 95% CI)	2.0 (0.9-4.3)	0.06	2.7 (1.4-5.4)	0.005

^I Contrast enhanced CT was obtained in 265 patients so determination of pancreatic necrosis could only be made in these patients