Risk factors for the concomitant occurrence of alcoholic chronic pancreatitis and alcoholic liver cirrhosis: a 10-years cohort study at a tertiary hospital in China

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Objective Concomitant occurrence of alcoholic chronic pancreatitis (ACP) and alcoholic liver cirrhosis (ALC) is rare with few reported cases. The present study aimed to identify the potential risk factors of chronic pancreatitis (CP) and liver cirrhosis (LC) in ALC patients and ACP patients, respectively.
Methods A retrospective analysis was performed on 536 patients with CP and 647 ALC patients without CP (Group A). Among the 536 CP patients, 213 ACP cases were divided into two groups: ACP with LC (Group B, n = 52) and ACP without LC (Group C, n = 161). A comparison between Group A and B was carried out to identify the potential risk factors of CP in ALC patients, while Group B and C were compared to determine the independent risk factors of LC in ACP patients.
Results Concomitant occurrence of ACP and ALC accounted for 24.4% (52/213) in this cohort. Significant risk factors for CP in ALC patients included smoking [odds ratio (OR), 2.557; 95% confidence interval (CI): 1.531–5.489; $P = 0.003$] and multiple bouts of acute pancreatitis (OR, 4.813; 95% CI: 3.625–12.971; $P < 0.001$). Hepatitis B virus (HBV) infection (OR, 4.237; 95% CI: 1.742–7.629; $P = 0.012$) was the only independent risk factor associated with LC in ACP patients.
Conclusion HBV infection exacerbated liver damage in ACP patients. Alcoholic patients who smoked and suffered from ongoing bouts of acute pancreatitis are prone to develop CP. Eur J Gastroenterol Hepatol 32: 1229–1234

Introduction

Alcohol abuse may contribute to global health problems. In 2001, it is estimated that 101 million (49%) of 205 million American adults consumed alcohol. More than 60% of adult male drinkers aged 18–25 years reported binge drinking. Compared to nonbingers, binge drinkers are 14 times more likely to drive while impaired by alcohol [1]. The harmful use of alcohol causes more than 3 million deaths and 5% of the global disease burden in 2016 around the world [2].

In China, alcohol consumption has increased rapidly compared to other countries. The expansion of alcohol production and consumption in China has been followed by a predictable increase in both acute and chronic illness resulting from alcohol abuse [3]. These trends are expected to continue and accelerate in the future.

The liver and pancreas are considered the most sensitive organs resulted from alcoholic etiology. Being the most common causes of end-stage liver and pancreatic disease, alcoholic liver cirrhosis (ALC) and alcoholic chronic pancreatitis (ACP) constitute the major share (31.5%) of alcohol-related morbidity and mortality [4]. In addition, ACP and ALC have both been identified as the risk factors for tumorigenesis.

The concomitant occurrence of ACP and ALC is considered rare in routine clinical practice. In recent years, research on the correlation between the two diseases has gained increasing attention [5–7]. It appears that chronic liver cirrhosis (LC) in alcohol-related chronic pancreatitis (CP) is not rare [8–10]. Hence, the identification of risk factors for accurate prediction of ALC and ACP is crucial to prevent the disease progression and improve the disease outcomes.

To the best of our knowledge, no study has yet been done to elucidate the risk factors for concomitant occurrence of ALC and ACP. Considering the increased incidence of alcoholism and the high morbidity of ALC and ACP, more research is urgently needed to identify the underlying risk factors of these diseases. Therefore, this study aimed to investigate the potential risk factors of CP and LC in ALC patients and ACP patients, respectively.

Patients and methods

Patient selection

CP is a pathological fibro-inflammatory syndrome of the pancreas in patients with genetic, environmental and/or other risk factors who develop persistent pathological

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responses to parenchymal injury or stress [11]. It was diagnosed in accordance with the guidelines for the management of CP (2014) published by the Group of Pancreas Surgery, Chinese Society of Surgery, Chinese Medical Association. However, there were no universally accepted criteria exist to assign alcohol consumption as an etiology of CP. Several studies have used definitions ranging from 40 to 80 g of alcohol consumption per day with or without a minimum drinking period as the major cause of ACP [12–14]. Therefore, in this study, alcohol consumption over 50 g/day with a minimum duration of 5 years was defined as the inclusion criterion of ACP.

LC is a diffuse pathophysiological state of the liver representing the final stage of various liver injuries, characterized by fibrosis and structurally abnormal nodules [15]. ALC was diagnosed in accordance with the guidelines of prevention and treatment for alcoholic liver disease: a 2018 update published by National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association and Fatty Liver Expert Committee, Chinese Medical Doctor Association. In this study, ALC patients with hepatitis B virus (HBV) positive were included, due to the high incidence of HBV infection in Chinese population, and we proposed that HBV infection is a potential risk factor for ALC. Besides, we did exclude the patients with active liver diseases, including viral active hepatitis, in order to avoid any bias that could impact the results.

Patient grouping

Data collected from 716 ALC patients without CP and 573 CP patients between February 2008 and August 2018 were retrospectively analyzed. A total of 647 ALC patients without CP (Group A) and 536 CP patients were included according to the selection criteria (Fig. 1). Among the CP patients, 213 ACP cases were divided into two groups: ACP cases with LC (Group B, n = 52) and ACP cases without LC (Group C, n = 161). Group B was compared with Group A to identify the potential risk factors for CP in ALC patients, and with Group C to identify the potential risk factors for LC in ACP patients. All patients were hospitalized in NanFang Hospital, Southern Medical University, and were diagnosed based on their clinical history and laboratory examination.

Furthermore, the education levels of patients were categorized into three groups: low (9 years of basic education), medium (10–12 years of upper secondary, vocational education), and high (>13 years of higher education).

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 for Windows (SPSS, Chicago, Illinois, USA). Two-tailed *t*-tests and χ^2 tests were used to compare the demographic and clinical characteristics between groups. Data were expressed as n (%) or mean ± SD. Univariate and multivariate logistic regression analyses were performed to identify the potential risk factors for CP and LC in ALC and ACP patients, respectively. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of each association. *P* values of less than 0.05 were considered statistically significant.

Results

Clinical characteristics of the 536 CP patients are summarized in Table 1. The mean age at diagnosis was 48.4 ± 16.2 years, and 71.8% (385/536) of them were male. These patients accounted for 39.7% (213/536) of ACP cases, and the incidence of LC was 14.2% (76/536). Among the 213 ACP patients, ACP with LC (Group B) accounted for 24.4% (52/213), while the remaining were ACP without LC (Group C; n = 161/213).

Clinical characteristics of the 647 ALC patients without CP (Group A) are summarized in Table 2. The mean age at diagnosis was 53.4 ± 10.3 years and 97.8% (633/647) of them were male. The comorbidity rates of HBV and HCV infections were 15.0% (97/647) and 1.9% (12/647), respectively. The complications of ALC included

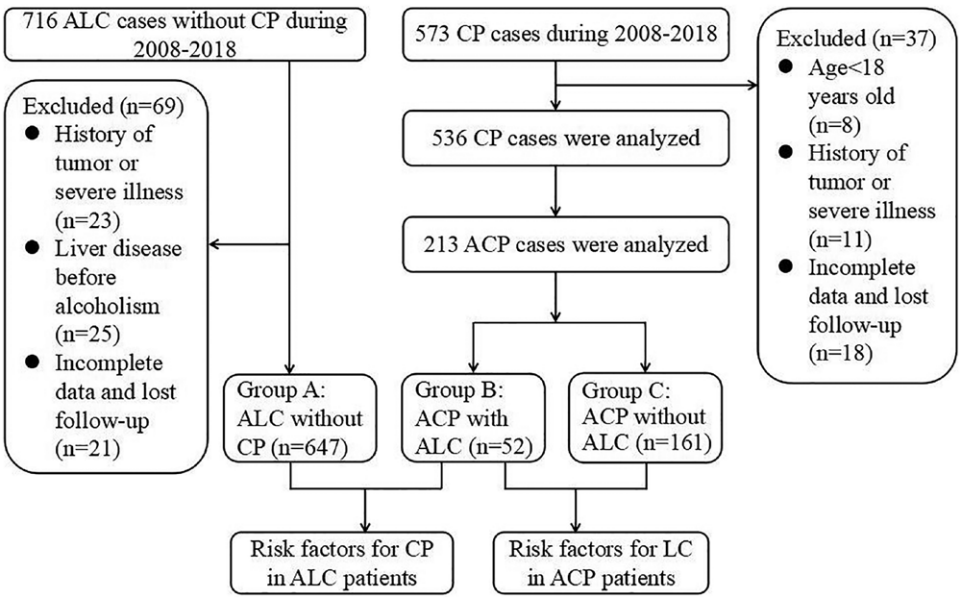

Fig. 1. Flow chart of patient selection process.

Table 1. Demographics of 536 chronic pancreatitis patients

Factors	Number (%) or mean ± SD
Gender	
Male	385 (71.8%)
Female	151 (28.2%)
Age at onset (years)	44.6 ± 14.2
Age at diagnosis (years)	48.4± 16.2
Duration of symptoms (months)	52.5 ± 21.9
BMI	22.8 ± 2.7
Etiology	
ACP	213 (39.7%)
Non-ACP	323 (60.3%)
Smoking	307 (57.3%)
Pancreatic stones	226 (42.2%)
Pancreatic pseudocyst	133 (24.8%)
Cholelithiasis	87 (16.2%)
Bouts of acute pancreatitis	349 (65.1%)
Symptoms	
Abdominal pain	381 (71.1%)
Steatorrhea	109 (20.3%)
Jaundice	145 (27.1%)
Complications	
Diabetes mellitus	226 (42.2%)
Liver cirrhosis	76 (14.2%)
Ascites	53 (9.9%)
Portal hypertension	59 (11.0%)
Treatment	
Surgery	83 (15.5%)
ERCP	34 (6.3%)
Surgery + ERCP	17 (3.2%)
pharmacotherapy	402 (75.0%)

ACP, alcoholic chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography.

Table 2. Demographics of 647 alcoholic liver cirrhosis patients (group A)

Factors	Number (%) or mean ± SD
Gender	
Male	633 (97.8%)
Female	14 (2.2%)
Age at diagnosis (years)	53.4 ± 10.3
Duration of symptoms (months)	49.2 ± 18.5
BMI	21.8 ± 2.3
Duration of drinking (years)	22.6 ± 7.1
Daily alcohol consumption (g)	189.2 ± 85.9
HBV infection	97 (15.0%)
HCV infection	12 (1.9%)
Smoking	284 (43.9%)
Comorbidity	
Hypertension	87 (16.2%)
Respiratory diseases	72 (11.1%)
Cholelithiasis	142 (21.9%)
Diabetes mellitus	134 (20.7%)
Symptoms	
Weakness	349 (53.9%)
Poor appetite	464 (71.7%)
Ventosity	287 (44.4%)
Jaundice	311 (48.1%)
Complications	
Gastrointestinal bleeding	128 (19.8%)
Ascites	474 (73.3%)
Hepatic encephalopathy	113 (17.5%)
Hepatorenal syndrome	39 (6.0%)
Lab examination	
AST (U/L)	78.1 ± 59.3
ALT (U/L)	63.5 ± 43.2
TBIL (μmol/L)	37.6 ± 28.4
ALB (g/L)	27.8 ± 6.3

ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; TBIL, total bilirubin.

gastrointestinal bleeding (19.8%), ascites (73.3%), hepatic encephalopathy (17.5%) and hepatorenal syndrome (6.0%). As shown in Fig. 2, upper gastrointestinal bleeding was observed in an ACP patient with LC. The CT scans revealed portal hypertension, splenomegaly and pseudocyst in the tail of the pancreas. Another ACP patient with LC developed ascites, as indicated by portal hypertension, ascites and multiple pancreatic duct stones throughout the whole pancreas (Fig. 3).

Potential risk factors for the concomitant occurrence of ACP and ALC were compared between the three groups by using univariate and multivariate analyses (Table 3). HBV infection was found to be a significant risk factor for LC in ACP patients (OR, 4.237; 95% CI: 1.742–7.629; $P = 0.012$). On the contrary, the independent risk factors for CP in ALC patients were smoking (OR, 2.557; 95% CI: 1.531–5.489; $P = 0.003$) and multiple bouts of acute pancreatitis (OR, 4.813; 95% CI: 3.625–12.971; $P < 0.001$) (Table 4).

Discussion

In 2004, about 3.8% of all global deaths are attributable to alcohol consumption, which is higher in males than in females (6.3% vs. 1.1%) [16]. According to WHO, alcohol is responsible for 3.3 million deaths or 5.9% of all global deaths, in 2012 alone. As the end-stage liver and pancreatic diseases, ALC and ACP are the most frequent organ manifestations. In addition, alcohol-related cancer, LC and injury account for most of the burden of alcohol-attributable mortality.

In this single-institutional retrospective analysis, smoking and bouts of acute pancreatitis were identified as significant risk factors for CP in ALC patients, while HBV infection appeared to be the only risk factor for LC in ACP patients. A review of literature was conducted by searching ‘chronic pancreatitis’ or ‘alcohol’, or ‘liver cirrhosis’ in PubMed, which restricted to English-language publications. To the best of our knowledge, this is the first systematic, retrospective analysis of risk factors for CP in ALC patients and LC in ACP patients.

In China, HBV infection is the leading cause of liver-related morbidity and mortality. The prevalence of HBV infection has fallen by 3% between 1992 and 2006, as a result of the national HBV vaccination program [17]. However, due to an increase in alcohol production and consumption in China, the prevalence of alcohol-related diseases, such as alcoholic liver disease, has increased dramatically over the past two decades, with a median of 4.5% among Chinese population [18]. Alcohol abuse has a significantly greater impact on the mortality of LC compared to morbidity. Moreover, excess alcohol intake is associated with more severe liver damage in patients with HBV infection. In this study, HBV infection was proved to be a risk factor for the exacerbation of LC in ACP patients (OR, 4.237; 95% CI: 1.742–7.629; $P = 0.012$). However, there is no evidence for the association of HBV genotype with LC in ACP patients [19]. Iida-Ueno *et al*. reported a significant association between alcohol consumption and the severity of clinical outcomes in patients with chronic HBV infection. Excessive alcohol consumption can accelerate the progression of liver disease to cirrhosis and hepatocellular carcinoma with a 1.3- to 8.4-fold increased risk, which is obviously higher than light-to-moderate alcohol consumption [20]. Nevertheless, another study showed that alcohol abuse combined with hepatitis C virus infection may accelerate

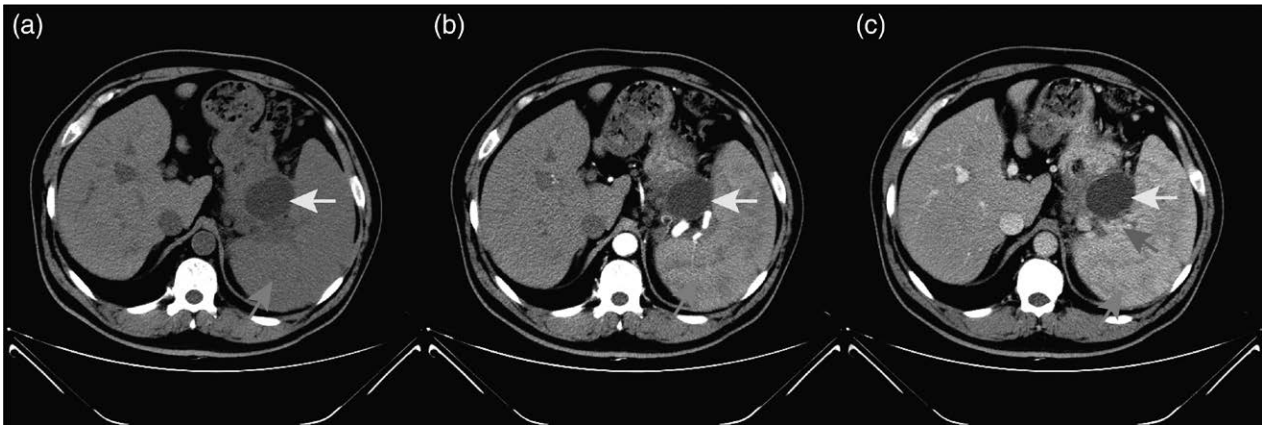

Fig. 2. A case with concomitant ACP and ALC developed upper gastrointestinal bleeding. Representative CT images showing that (a) the main trunk of the portal vein dilated (about 1.8 cm), and the splenic vein also showed obvious varices; multiple gastroesophageal varices could be seen at the splenic hilus; (b) the spleen was significantly enlarged, with a length of about 7 ribbed units, which indicated obvious portal hypertension; (c) a well-bordered elliptic cystic density shadow, which was considered as pancreatic pseudocyst, was seen at the tail of the pancreas. Red arrows (↑): splenic vein; blue arrows (↑): spleen; yellow arrows (↑): pancreatic pseudocyst. ACP, alcoholic chronic pancreatitis; ALC, alcoholic liver cirrhosis.

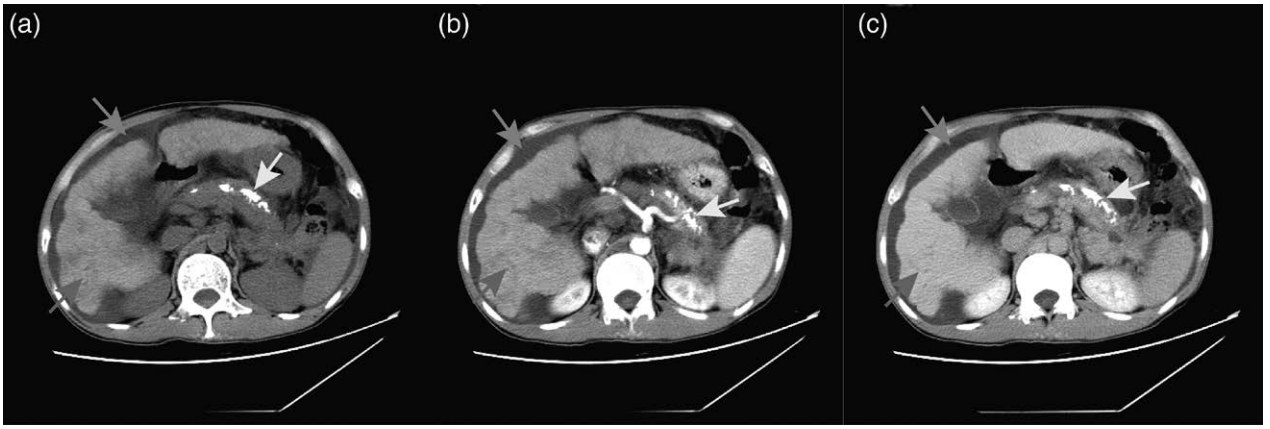

Fig. 3. A case with concomitant ACP and ALC developed ascites and liver dysfunction. Representative CT images showing that (a) reduced volume of liver, wavy liver margin and widened liver fissure; (b) large amount of ascites in abdominal cavity surrounded the liver and spleen; (c) multiple pancreatic duct stones formatted throughout the whole pancreas. Red arrows (↑): liver; blue arrows (↑): ascites; yellow arrows (↑): pancreatic duct stones. ACP, alcoholic chronic pancreatitis; ALC, alcoholic liver cirrhosis.

the development of hepatocellular carcinoma, but not with HBV infection [21].

Alcohol abuse has long been regarded as the leading cause of CP worldwide [22,23]. In China, the morbidity rate of CP has been increased recently, and the main etiologic factor has changed from biliary diseases in the 1990s (decreased from 36.8 to 28.1%) to alcohol abuse after the year 2000 (increased from 26.5 to 36.8%) [24]. In addition, the presence of nonalcoholic fatty liver diseases (NAFLD) at admission is a risk factor for severe acute pancreatitis [25]. Smoking can influence the progression of NAFLD through its effect on insulin resistance. Moreover, diabetes mellitus was independently associated with advanced fibrosis in NAFLD patients [26]. In this study, smoking was significantly associated with the development of CP (OR, 2.557; 95% CI: 1.531–5.489; $P = 0.003$) in ALC patients, but not with LC in ACP patients. These results are consistent with an earlier study showing that smoking is significantly associated with the risk of ACP but not ALC, and the age at onset of pancreatitis is lower among smokers [27]. Spicak *et al*. also found that ACP patients have higher smoking rate and earlier smoking age than ALC patients [10].

Recurrent attacks of acute pancreatitis had a severe influence on alcoholism patients. In this study, we found that multiple bouts of pancreatitis were associated with CP (OR, 4.813; 95% CI: 3.625–12.971; $P < 0.001$) in ALC patients. Based on the results from the Dutch Pancreatitis Study Group, the first episode of acute pancreatitis can lead to recurrent pancreatitis in 17% of patients, and 8% of patients progressed to CP within 5 years. Smoking has been regarded as the most important factor for recurrent pancreatitis, and its combination with alcohol abuse is most deleterious to the progression of CP [28]. Additionally, alcohol abuse, current smoking and history of acute pancreatitis have appeared as the independent risk factors in a cross-sectional study [29].

Alcoholism has been recognized as the most common etiology for both CP and LC. The preferred type of alcoholic beverage and the pattern of alcohol intake are the significant lifestyle factors for concomitant occurrence of CP and LC. Excessive alcohol consumption has been associated with LC, with a positive correlation between increased ethanol consumption and the risk of CP [9]. Constant alcohol abuse not only causes LC and CP, but also leads to severe outcomes such as portal hypertension, upper gastrointestinal bleeding, splenomegaly, ascites,

Table 3. Univariate and multivariate regression analyses of risk factors associated with liver cirrhosis occurrence in alcoholic chronic pancreatitis patients

	Univariate analysis			Multivariate analysis	
Variable	Group B (n = 52)	Group C (n = 161)	*P* value	OR (95% CI)	*P* value
Age at onset (years)	46.1 ± 15.5	44.2 ± 13.1	0.302		
Age at diagnosis (years)	47.8 ± 17.1	48.1 ± 16.2	0.471		
Sex (male/female)	50/2	156/5	0.795		
BMI	22.6 ± 2.5	22.4 ± 2.5	0.235		
Smoking (±)	35/17	92/69	0.194		
Education level			0.108		
High	7	39			
Medium	12	58			
Low	33	86			
Duration of drinking (years)	23.2 ± 6.6	24.5 ± 7.8	0.336		
Daily alcohol consumption (g)	171.3 ± 92.6	168.2 ± 88.7	0.279		
Duration of symptoms (months)	53.7 ± 34.4	51.9 ± 32.6	0.349		
Bouts of acute pancreatitis (±)	38/14	108/53	0.418		
Cholelithiasis	7/45	27/137	0.605		
HBV infection (±)	13/39	18/143	0.014[a]	4.237 (1.742–7.629)	0.012[a]
HCV infection (±)	3/49	5/156	0.380		
Comorbidity					
Hypertension	12	28	0.270		
Respiratory diseases	4	11	0.833		
Symptoms					
Abdominal pain	37	132	0.093		
Steatorrhea	14	31	0.239		
Jaundice	16	46	0.762		
Diabetes mellitus	31	92	0.754		
Lab examination					
Amylase (U/L)	123.6 ± 36.7	115.3 ± 46.4	0.277		
WBC (10^9/L)	6.4 ± 2.3	6.5 ± 2.7	0.539		
TBIL (μmol/L)	28.7 ± 14.3	31.6 ± 16.3	0.156		
Main pancreatic pain narrowing (±)	25/27	77/84	0.975		

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; TBIL, total bilirubin.
[a]Statistically significant results ($P < 0.05$).

Table 4. Univariate and multivariate regression analyses of risk factors associated with chronic pancreatitis occurrence in alcoholic liver cirrhosis patients

	Univariate analysis			Multivariate analysis	
Variable	Group B (n = 52)	Group A (n = 647)	*P* value	OR (95% CI)	*P* value
Age at diagnosis (years)	47.8 ± 17.1	53.4 ± 10.3	0.061		
Sex (male/female)	50/2	633/14	0.326		
BMI	22.6 ± 2.5	21.8 ± 2.3	0.618		
Smoking (±)	35/17	284/363	0.001[a]	2.557 (1.531–5.489)	0.003[a]
Education level			0.927		
High	7	89			
Medium	12	170			
Low	33	481			
Duration of drinking (years)	23.2 ± 6.6	22.6 ± 7.1	0.698		
Daily alcohol consumption (g)	171.3 ± 92.6	189.2 ± 85.9	0.235		
Bouts of acute pancreatitis (±)	38/14	158/489	0.000[a]	4.813 (3.625–12.971)	0.000[a]
Cholelithiasis	7/45	142/505	0.151		
HBV infection (±)	13/39	97/550	0.057		
HCV infection (±)	3/49	12/635	0.061		
Comorbidity					
Hypertension	12	87	0.055		
Respiratory diseases	4	72	0.444		

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio.
[a]Statistically significant results ($P < 0.05$).

pancreatic pseudocyst and pancreatic duct stones (Figs. 2 and 3). In a Japanese cohort study, the drinking of spirits and a high daily consumption of alcohol are independent risk factors for ACP, while never-married status is the only risk factor identified in male Japanese patients with ALC [30]. Different risk factors may confer susceptibility to ACP and ALC, which may explain the nonparallel relationship between the severities of the two diseases in Japanese alcoholics [30]. In the present study, differences between the risk factors of CP and LC were observed in ALC and ACP patients, respectively. Therefore, prevention strategies for alcoholic-related CP and LC diseases should consider these risk factors.

Conclusion

In overall, alcohol is the main reason for concomitant occurrence of CP and LC. Different risk factors were found

to be associated with CP in LC patients and LC in CP patients due to alcohol abuse. Hence, alcohol withdrawal and smoking cessation may be the most effective ways to prevent the diseases from developing. Furthermore, limitations undoubtedly existed in single-institutional retrospective cohort study, and thus a multi-institutional prospective study is currently being planned.

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Conflicts of interest

There are no conflicts of interest.

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