CLINICAL RESEARCH

Does an association exist between chronic pancreatitis and liver cirrhosis in alcoholic subjects?

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Abstract

AIM: To study the possible association between chronic pancreatitis (CP) and liver cirrhosis (LC) of alcoholic etiology, after excluding any other causes.

METHODS: One hundred and forty consecutive alcoholic patients were subdivided into three groups: CP (n = 53), LC (n = 57), and asymptomatic alcoholic (n = 30). Clinical, biochemical and morphological characteristics, Child-Pugh index, indocyanine green test, and fecal pancreatic elastase-1 test were assessed.

RESULTS: In patients with cirrhosis, major clinical manifestations of CP such as pancreatic pain and steatorrhea, as well as imaging alterations of CP such as calcifications, duct dilation and pseudocysts were absent; insulin-dependent diabetes was present in 5.3% of cases, and elastase-1 test was altered in only 7%, and severely altered in none. In patients with CP, clinical characteristics of cirrhosis such as ascites, encephalopathy and gastrointestinal hemorrhage were present in one case, Child-Pugh grade > A in 5.7%, and altered indocyanine green test in 1.9% cases. In asymptomatic alcoholism, there was only a non-coincident alteration of elastase-1 test and indocyanine test in 14.8% and 10%, respectively, but other characteristics of cirrhosis or CP were absent. An inverse correlation (r = -0.746) between elastase-1 test and indocyanine test was found in alcoholic patients.

CONCLUSION: There is a scarce coincidence in clinical and morphological alterations among patients with CP or LC of alcoholic etiology, but an inverse correlation between pancreatic and liver function tests. These findings support that these alcoholic diseases evolve in a different manner and have different etiopathogenesis.

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INTRODUCTION

Chronic alcoholism is a well-known etiologic factor associated with chronic and irreversible pancreatic and liver disorders. Excessive alcohol consumption is the most frequent cause of chronic pancreatitis (CP) in Western countries[1]. There is a correlation between increased ethanol consumption over many years and the risk of developing CP[2,3]. Nevertheless, it has recently been estimated that < 5% of alcoholic subjects develop CP[1,4,5]. This low percentage, together with the absence of adequate experimental models of alcoholic CP, suggest that ethanol is only a cofactor in the development of CP, and therefore other predisposing

factors may be involved[6].

An excessive consumption of alcohol is also associated with liver cirrhosis (LC), again with a correlation between increased ethanol consumption and the risk of LC[7,8]. The development of LC also requires chronic alcoholism over several years[8,9]. For decades, it was considered that around 10%-35% of subjects with chronic alcoholism developed alcoholic LC[10]. However, more recent prospective studies have shown that the prevalence in alcoholics is indeed much lower, around 2%[7,8], once having excluded the confusing cases of hepatitis B or C[11,12]. Experimental models of chronic alcoholism have not provided insights into the pathophysiological mechanisms responsible for the different outcome in CP and LC[13].

There is still controversy about the frequency of coincidence between CP and LC in alcoholic patients. This lack of coincidence may rely on differences in methodology, retrospective *versus* prospective studies[14], and evaluated parameters such as clinical[15], functional[16], imaging[17] or histopathological[18,19]. In addition, there are diagnostic difficulties in the initial stages[20], as well as several confounders hindering this question, such as the presence of hepatitis B or C virus[14,19], and age-related pancreatic alterations[21,22].

It is worth noting that pancreatic function is often increased in patients with alcoholic LC, leading to the hypersecretory status of the pancreas[16,23]. Thus, Hayakawa et al[24] have reported that pancreatic secretion, measured with the pancreozymine-secretine test, increases with severity of liver damage in alcoholic liver disease. It has been suggested that this hypersecretory status diminishes protein and calcium concentration in pancreatic juice, protecting against formation of protein plugs and pancreatic stones[16].

In clinical practice, the coincidence of both diseases, LC and CP, is rare[15,24]. Furthermore, these two diseases do not share risk factors apart from alcohol consumption[15]. In alcoholic CP, the duration of chronic alcoholism is shorter than in LC, and liver disease is found at older ages[14]. Nakamura et al[15] have recently assessed the genotypes of alcohol dehydrogenase (ADH), ductal anatomy by endoscopic retrograde cholangiopancreatography (ERCP) and the Child-Pugh classification in Japanese alcoholics, and reported a lack of association between the risk of LC and CP. In addition, no clear genetic predisposition has been found so far in studies of genetic polymorphisms in alcoholic CP[25] and alcoholic LC[26].

To the best of our knowledge, there are no previous studies comparing clinical, functional, morphological and biochemical parameters in alcoholic subjects with a definitive diagnosis of CP or LC. In this study, we therefore aimed to assess the association of CP and LC, both with definitive diagnosis, in subjects with chronic alcoholism, based on clinical, functional and morphological parameters.

MATERIALS AND METHODS

Case-control study with two groups of consecutive patients who attended the University Clinic Hospital of Valencia, Spain for 3 years included: (1) alcoholic CP (*n* = 53); and (2) alcoholic LC (*n* = 57). Controls were 30 asymptomatic alcoholic (ASA) patients. The diagnosis of CP was based on the Cambridge and Marseille criteria[27,28]. The diagnosis of cirrhosis was histologically proven in 27 patients and based on compatible clinical, laboratory and ultrasonographic finding in the others[29]. Daily ethanol intake was over 40 g for more than 5 years in alcoholic subjects[7,8] and before entering the study a period of 60 d of alcohol abstinence was required. Exclusion criteria for alcoholic LC were the presence of antigens or antibodies against B or C virus, as well as liver diseases not related to chronic alcoholism such as hemochromatosis or any other causes. Exclusion criteria for CP were the presence of toxic-metabolic (other than alcohol), genetic, autoimmune, and obstructive factors considered as confounders[6]. Other exclusion criteria for the study were gastric or liver surgery, pancreatic surgery prior to diagnosis, and gastrointestinal neoplasia. Smoking was considered when more than 10 cigarettes were consumed daily[30,31].

Characteristic manifestations of LC[13] were assessed in all patients, including hemorrhage in the digestive tract secondary to portal hypertension, ascites, hepatic encephalopathy, alterations of the Quick index, and Child-Pugh index (PI)[32]. PI was classified according to the following scoring system: A (5-6 score), B (7-9 score), and C (10-15 score)[32]. The following characteristic manifestations of CP[27,28] were also assessed in all patients: pancreatic pain, non-insulin-dependent diabetes mellitus (NIDDM), insulin-dependent diabetes mellitus (IDDM), and chronic diarrhea/steatorrhea. Liver function was assessed by indocyanine green clearance test (ICG test). Pancreatic function was assessed by determination of fecal pancreatic elastase-1 test (E1 test) and oral glucose tolerance test (OGTT). The presence of esophageal varices, splenomegaly, portal hypertension, pancreatic calcifications, pseudocysts or alterations of the pancreatic duct were assessed by ultrasonography (US), computer tomography (CT), magnetic resonance cholangiopancreatography (MRCP), or ERCP. Splenomegaly was considered when the size of the spleen was $\geqslant$ 135 mm. Portal hypertension was established according to the following criteria: Portal vein diameter > 12 mm and/or presence of esophageal varices and/or splenomegaly. Alterations in the Quick index were established when the international normalized ratio (INR) was higher than 1.2[33].

The ICG test was performed by pulsidensitometry (Limon PC5000, Pusion Medical Systems, Munich RFA). Briefly, ICG was intravenously administered at a dose of 0.5 mg/kg, monitoring the blood concentration of ICG to determine the plasma disappearance rate (PDR, %/min). It was considered that the ICG clearance was altered when PDR was < 15%, and severely altered when PDR was < 10%[34,35].

Pancreatic fecal elastase-E1 activity was determined by ELISA (Pancreatic Elastase stool test, Schebo-Biotech, Giessen RFA). E1 activity was considered altered when it was < 200 μg/g, and severely altered when it was <

Table 1　General characteristic of patients with ACP, ALC or ASA

	ACP (*n* = 53)	ALC (*n* = 57)	ASA (*n* = 30)	*P*
Age at the beginning of the study	51.8 ± 9.7	56.1 ± 9.9	49.9 ± 7.9	CP *vs* LC, CP *vs* ASA, NS; LC *vs* ASA, *P* = 0.010
Men (%)	98	84	70	CP *vs* LC, *P* = 0.011; CP *vs* ASA, *P* = 0.001; LC *vs* ASA, NS
Age at diagnosis	39 ± 9.2	51.5 ± 9.6	-	*P* = 0.001
Alcohol intake (g/d)	120 ± (75-250)	118 (70-255)	121 (70-400)	NS
Years of alcoholism	20 (10-35)	25 (10-52)	18.5 (9-36)	CP *vs* LC, *P* = 0.01; LC *vs* ASA, *P* = 0.006; CP *vs* ASA, NS
Ethanol, kg of total intake	876 (273-2920)	1095 (481-3832)	965 (229-3358)	NS
Smoking	94.3%	80.7%	96.7%	CP *vs* LC, *P* = 0.030; CP *vs* ASA, NS; LC *vs* ASA, *P* = 0.035
BMI	23.4 ± 3.6	26.5 ± 4.4	24.8 ± 4.6	CP *vs* LC, *P* = 0.001

Data are expressed as mean ± SD, percentage or median (minimum-maximum). NS: Not significant.

100 µg/g[36] in at least two consecutive determinations. Fecal fat was determined by the van de Kamer method[37].

The body mass index (BMI) was measured in all subjects as index of nutritional status. BMI values < 20 were considered malnutrition, whereas values > 28 were considered as indicative of being overweight[38].

Statistical analysis
Proportions for qualitative variables and mean ± SD for quantitative variables were calculated. Means were compared by *t* test or ANOVA and post-hoc Scheffe test. According to the Kolmogorov-Smirnov test, when quantitative variables did not fit a normal distribution, medians and ranges and consequently Kruskal-Wallis test were used. Qualitative variables were analyzed by χ^2 test or Fisher's exact test when appropriate. Odds ratios (ORs) with 95% confidence intervals (95% CI) were also calculated. Spearman's rank correlation coefficient between E1 test and indocyanine green test (ICG test) or PI was calculated. *P* < 0.05 was considered statistically significant.

RESULTS

General characteristics of patients: Alcohol consumption, smoking, and nutritional status
Table 1 shows the general characteristics of each group of subjects. Although the age of patients when entering the study was not different between CP and LC, the age at the moment of diagnosis was significantly lower in CP than LC patients. Most patients were men in all groups, especially in the CP group.

Regarding the alcohol consumption, the daily alcohol intake did not differ among groups. The percentages of heavy drinkers (daily consumption > 150 g) were 30.2%, 33.3%, and 45.0% for CP, LC and ASA groups, respectively, without significant differences among the groups. The duration of alcohol consumption was lower in CP than in LC patients. However, there was no significant difference between CP and LC in the percentage of patients with more than 20 years of alcohol consumption (41.6% and 52.6% for CP and LC subjects, respectively). The percentage of patients with more than 20 years of alcohol consumption was significantly higher in LC than in ASA patients (52.6% *vs* 33.7%). The total amount of ethanol consumed before

Table 2　Potential risk factors for CP or LC: Distribution of frequencies and OR in patients with ACP or ALC　*n* (%)

	ACP 53	ALC 57	OR (95% CI)	*P*
Gender (female)	1 (1.9)	9 (15.8)	9.7 (1.1-79.8)	0.017
BMI > 28	4 (7.5)	15 (26.8)	4.5 (1.4-14.5)	0.008
BMI < 20	7 (13.2)	4 (7)	0.49 (0.13-1.8)	0.280
Age > 45 yr at diagnosis	14 (26.4)	41 (71.9)	7.1 (3.1-16.6)	0.001
Smoking	50 (94.3)	46 (80.7)	0.25 (0.06-0.95)	0.044
Alcohol > 150 g/d	16 (30.2)	19 (33.3)	1.12 (0.5-2.5)	0.775
Years alcoholism > 20	22 (41.5)	30 (52.6)	1.56 (0.73-3.32)	0.243

diagnosis did not differ among groups (Table 1).

The percentage of cigarette smokers was slightly higher in CP than in LC patients. The BMI was higher in LC than in CP patients. The percentage of patients with overweight (BMI > 28) was also higher in LC than in CP group, but it was no different when compared to ASA patients (7.5%, 26.8% and 9% for CP, LC and ASA subjects, respectively) (Table 2). The percentage of patients with malnutrition (BMI < 20) was low in all groups, without significant differences among them (13.3%, 7.0% and 13.3% for CP, LC and ASA subjects, respectively).

Features of alcoholic CP in CP, LC and ASA subjects
It is worth noting that there was absence of the two major clinical manifestations of CP, pancreatic pain and diarrhea/steatorrhea in patients with LC (Table 3). IDDM was frequent in CP (35 cases, 68%), but was found only in three LC cases (5.3%) and in none with ASA. Among these three LC patients with IDDM, one exhibited reduced E1 test (164 µg/g) as the unique altered pancreatic parameter. However, the percentage of patients with NIDDM was higher in the LC group (19.3%) than in the CP group. Diarrhea/steatorrhea was present in many patients with CP (54.7%), but absent in the other two groups (Table 3).

The major morphological alterations such as calcification, dilatation of the pancreatic duct, and pseudocysts were found only in CP patients.

Features of alcoholic LC in CP, LC and ASA subjects
Clinical manifestations characteristic of LC such as ascites, encephalopathy, or upper gastrointestinal

Table 3 Clinical manifestations, functional parameters and imaging characteristics of CP in patients with ACP, ALC or ASA

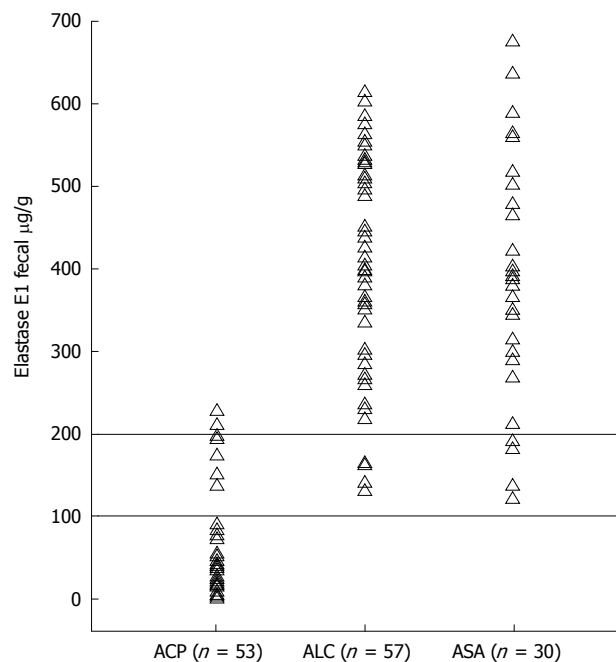|	ACP (n = 53)	ALC (n = 57)	ASA (n = 30)	P
Pancreatic pain	85%	0%	0%	< 0.001
IDDM	68%	5.3%	0%	< 0.001
NIDDM	5.7%	19.3%	10%	CP vs LC, P = 0.03; CP vs ASA, LC vs ASA, NS
Diarrhoea/ steatorrhoea	54.7%	0%	0%	< 0.001
Calcifications	77.4%	0%	0%	< 0.001
Dilatation of pancreatic duct	67.9%	0%	0%	< 0.001
Pancreatic pseudocysts	58.5%	0%	0%	< 0.001

NS: Not significant.

Table 4 Clinical manifestations, functional parameters and imaging characteristics of LC in patients with ACP, ALC or ASA

	ACP (n = 53)	ALC (n = 57)	ASA (n = 30)	P
Ascites	0%	66.7%	0%	
Haemorrhage in upper digestive tract	1.9%	45.6%	0%	< 0.001
Child-Pugh index > 5	5.7%	98.2%	0%	< 0.001
INR > 1.2	0%	73.7%	0%	< 0.001
Esophageal varices	1.9%	77.2%	0%	< 0.001
Splenomegaly	1.9%	77.2%	0%	< 0.001
Portal hypertension	3.8%	96.5%	0%	< 0.001

Figure 1 Fecal E1 test (μg/g feces) in patients with ACP, ALC or ASA. Reference lines for altered E1: < 200 μg/g, and severely altered E1: < 100 μg/g. ACP vs ALC, P < 0.001; ACP vs ASA, P < 0.001; ALC vs ASA, P = 0.747.

hemorrhage were found in most patients with LC, in one case (1/53) with CP and in none with ASA (Table 4). This particular case with CP exhibited gastrointestinal hemorrhage and portal vein thrombosis secondary to pancreopathy, splenomegaly, a PI of 6, with serum albumin level of 2.9 g/dL, severe steatorrhea, severe diabetes mellitus and malnutrition. Nevertheless, his ICG test was normal (23.8%/min).

The PI was > 5 in almost all cases (56/57) with LC, in three (3/53) with CP and in none (0/30) with ASA (Table 4). According to Child-Pugh classification, 35% (20/57) of LC patients were ascribed to class A, 35% (20/57) belonged to class B, and 30% (17/57) belonged to class C. Three cases of CP had a PI of 6. One was the previously described patient with gastrointestinal hemorrhage. In another case, a liver biopsy was available and ruled out the diagnosis of cirrhosis; however, the patient had an elevated Quick index (1.5 INR) at the moment of inclusion which could be attributed to severe steatorrhea because it normalized after parenteral treatment with vitamin K. The third CP case had a CPI of 6, and at the moment of inclusion exhibited cholestasis (total serum bilirubin = 2.6 mg/dL) due to compression of the common bile duct secondary to pancreopathy. This patient had a normal ICG test (28.9% min) and did not exhibit signs of hepatopathy.

Esophageal varices were found in 77% of LC

patients, in one case (1/53) with CP and in none with ASA (Table 4). In this CP patient, there were no manifestations of hepatopathy, and varices were secondary to pancreopathy involving portal vein thrombosis. This patient had a large pseudocyst (50 mm × 50 mm) in the head of the pancreas, which caused obstructive jaundice that required surgical treatment, but the ICG test later at the moment of inclusion was normal (PDR = 28.9%/min).

Splenomegaly was also found in 72.2% of LC patients, in one case with CP and in none with ASA (Table 4). This CP case was the one with upper gastrointestinal hemorrhage, which has been previously described.

Portal hypertension was present in almost all LC patients (96.5%), in two patients with CP and in none with ASA (Table 4). In these two CP cases, portal hypertension was secondary to pancreatic disease, as previously described, with normal ICG test.

Pancreatic fecal elastase E1 in CP, LC and ASA subjects

Fecal E1 test was significantly lower ($P < 0.001$) in CP patients [9 (0.1-228) μg/g feces] than in LC patients [400.0 (130-614) μg /g feces] and ASA subjects [388 (121-675) μg/g feces] (Figure 1). Moreover, 94.3% of CP patients (50/53) exhibited E1 test lower than the normal limit of 200 μg/g feces, whereas 84.9% (45/53) had very low levels (i.e. < 100 μg/g feces), and among them 29, (64.4%) with diarrhea/steatorrhea. All these percentages were markedly higher ($P < 0.001$) than those in the LC and ASA groups.

In the LC group, E1 test was < 200 μg/g only in four of 57 cases (7%), and in none of them was it < 100 μg/g. As mentioned before, none of the LC patients exhibited diarrhea/steatorrhea or pancreatic alterations assessed
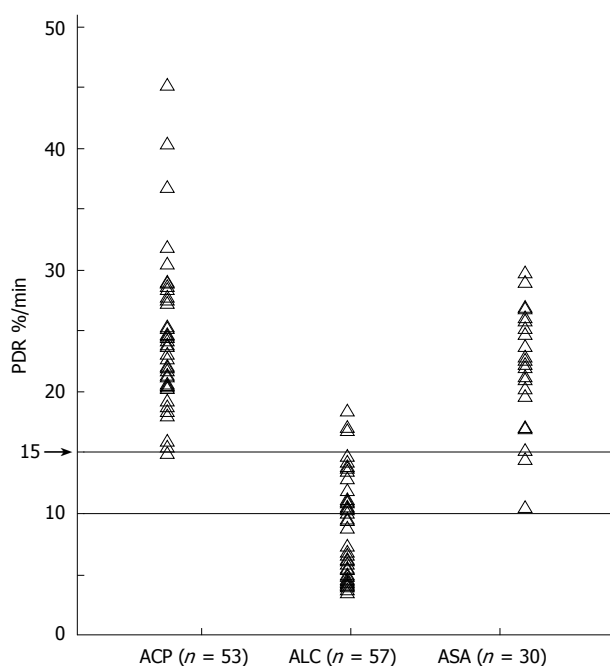
Figure 2 PDR, %/min of ICG in patients with ACP, ALC or ASA. Reference lines for altered PDR: < 15%/min, and severely altered PDR: < 10%/min. ACP *vs* ALC, *P* < 0.001; ACP *vs* ASA, *P* = 0.048; ALC *vs* ASA, *P* < 0.001.

Figure 3 An inverse correlation (*r* = -0.746, *P* < 0.001) between indocyanine clearance (PDR, %/min) and fecal E1 test (μg/g feces) in patients with ACP, ALC or ASA. Reference lines: PDR (%/min) = 15; E1 test = 100. Vertical line for PDR (%/min) = 10, and horizontal line for E1 test = 100 are marked in the figure.

by imaging studies.

Among the 27 ASA subjects, E1 test was reduced only in four (14.8%), but it was never < 100 μg/g. As mentioned, none of the ASA subjects exhibited diarrhea/steatorrhea or pancreatic alterations assessed by imaging studies.

ICG clearance test in CP, LC and ASA subjects

PDR values of the ICG test were markedly more reduced in LC patients [6.1 (3.4-18.2)%/min] than in CP patients [22.6 (14.8-45)%/min] and ASA subjects [22.1 (10.4-30.2)%/min] (Figure 2). Ninety-three percent of LC patients (53/57) had a PDR lower than the normal limit (< 15%/min), and 64% of them exhibited a severe PDR reduction (< 10%/min). However, only one patient with CP (1.9%) showed PDR < 15%/min and none had PDR < 10%/min.

In the ASA group, three of 29 subjects (10%) had reduced PDR (< 15%/min) and none had PDR < 10%/min. These ASA subjects had a normal E1 test, and had no pancreatic or hepatic alterations assessed by imaging studies compatible with CP or LC; all had PI of 5.

It is worth noting that a significant inverse correlation (*r* = - 0.746; *P* < 0.001) was found between E1 test levels and PDR values in patients with CP or LC (Figure 3). A significant correlation was also found between E1 test levels and PI (*r* = 0.759; *P* < 0.001). Therefore, in general, the reduction of functional hepatic reserve was associated with normal pancreatic function, and vice versa.

The analysis of potential risks of developing CP or LC showed significantly different values for gender, overweight (BMI > 28), age > 45 years at the time of diagnosis, and smoking (Table 2). Nevertheless,
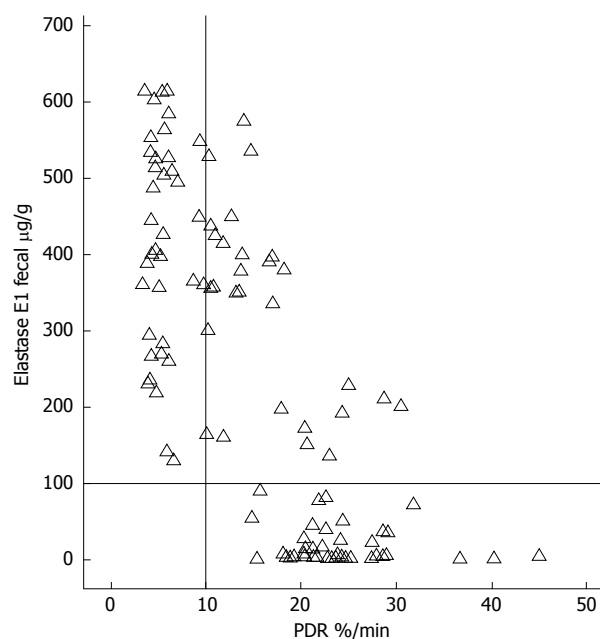
these differences were too low to explain the different evolution towards CP or LC. No significant differences were found regarding malnutrition (BMI < 20), elevated alcohol consumption (> 150 g/d) or long-term chronic alcohol consumption (> 20 years).

DISCUSSION

Chronic ethanol consumption is a common and frequent etiological factor in both CP and LC, and their risk correlates very well with the amount of ethanol daily consumed[2,7]. However, only a minority of alcoholics develop these diseases[1,4,5,7,8]; this together with the requirement of several years of ethanol intake, racial factors[39], and the difficulty of developing adequate experimental models have led to the consideration of other associated etiological factors[26].

The presence of a common etiological factor, i.e. alcoholism, for CP and LC could lead to the assumption that both diseases may coincide in some patients. The study of the presence and coincidence of these two diseases and their risk factors may provide new insights into their etiopathogenesis. Nevertheless, there is controversy about the frequencies of the coincidence between CP and LC in the studies published so far[15-19]. Differences in methodology, and particularly, the presence of hepatitis B or C virus are important confounders which hinder an accurate and reliable interpretation of the data. In fact, more than one-third of patients with alcoholic LC exhibit antibodies against hepatitis C virus[11,12].

In the present study, the frequency of the association between alcoholic CP and LC has been assessed after exclusion of main confounders (hepatitis B or C virus,

non-alcoholic liver or pancreatic diseases, or surgery) and taken into account the major clinical manifestations, the morphological alterations detected by imaging studies, and the alterations of pancreatic and hepatic functions assessed by specific tests.

Our results clearly showed no overlapping between patients with alcoholic CP and alcoholic LC, not only regarding clinical manifestations, but also in imaging studies and functional tests. Furthermore, an inverse relationship was found between pancreatic and liver function in patients with CP or LC.

In our clinical study, the median age of patients at the moment of diagnosis was around a decade higher in LC than in CP (Table 1), due to the different natural history of these diseases[1,2,6,40]. Nevertheless, the age of patients at the time of inclusion in the study was not significantly different. As previously reported in other studies, the percentage of men was higher than that of women in all groups of alcoholics[21,41].

Regarding ethanol consumption, only the duration of ethanol intake was different among groups (20, 25 and 18.5 years for CP, LC and ASA, respectively) (Table 1). However, the mean daily ethanol intake and the total amount of ethanol consumed before diagnosis were not significantly different among groups, which is in agreement with those reported by other authors[2,8,19,42]. Moreover, the percentage of patients with ethanol intake > 150 g/d and the percentage of drinkers for more than 20 years were not significantly different. Therefore, the populations of the three groups in this study were homogeneous regarding ethanol intake.

The percentage of smokers was higher in CP (94.3%) and ASA (96.7%) than in LC (80.7%) (Table 1). Previous studies have reported that smoking is a risk factor for CP in alcoholics, which promotes the progression of the disease[31,43-45]. In addition, smoking has also been considered a risk factor in LC induced by hepatitis C virus[46]. The present study demonstrates that smoking is a risk factor not only for alcoholic CP but also for LC.

The BMI was slightly but significantly lower in CP than in LC, but not when compared with ASA. This slight difference may be ascribed to the presence of steatorrhea and diabetes mellitus in CP. In addition, the percentage of patients with BMI > 28 was significantly higher in LC than in CP and ASA, and these differences may by ascribed to retention of liquids in advanced LC.

The diagnosis of alcoholic CP is hindered in the initial stages of the disease due to the lack of specificity of clinical manifestations. Because of the difficulty in obtaining pancreatic biopsy, the diagnosis is established by combination of clinical manifestations, morphological alterations and impairment of the pancreatic exocrine and endocrine function[27,28].

In our study, 94.3% CP patients showed low E1 levels together with a high percentage of steatorrhea and IDDM, indicating that most patients were at an advanced stage of the disease. However, only four LC patients (7%) had E1 levels between 100 and 200 μg/g (Figure 1), and they neither exhibited steatorrhea nor any clinical or morphological manifestations of CP. In a similar fashion, only three LC patients (5.3%) exhibited IDDM, without the other clinical and morphological manifestations of CP. Only one of these patients exhibited 164 μg/g E-1 level; hence, the presence of CP in this patient could not be ruled out. Eleven LC patients exhibited NIDDM, which is common in LC[47] with normal E-1 level, but not a characteristic manifestation of CP[48]. In the ASA group, three subjects exhibited NIDDM, without symptoms of pancreopathy and normal E-1 and ICG tests.

The former studies that assessed the frequency of pancreatic alterations in patients with LC showed contradictory results. The frequency of pancreatic fibrosis compatible with CP in autopsies of LC patients was between 2% and 20% when the presence or absence of hepatitis B or C was not taken into account[14,16,18,19]. In addition, the age-related changes in morphofunctional parameters of the pancreas may be another confounder when the diagnosis of CP is based only on these parameters[49-53]. In a study using endoscopic ultrasonography and ERCP, Hastier et al[17] reported only moderate pancreatic alterations in 5.5% patients with alcoholic LC, without evolution to CP.

Some previous studies[51,54,55] on necropsies of patients with alcoholic LC showed very low frequency of the fibrotic pancreatic alteration characteristic of CP, which is predominantly perilobular fibrosis with heterogeneous distribution. In contrast, these patients exhibited diffuse and intralobular pancreatic fibrosis without calcifications or pseudocysts. Accordingly, these authors suggested that pancreatic morphological lesions in alcoholic LC correspond to a pathological process different from that of alcoholic CP.

It is worth noting that many studies on the association of CP and LC involve patients older than 50 years. It is well known that normal subjects at this age exhibit some morphofunctional pancreatic alterations[21,22,49-51,53] that could be taken for those characteristic of CP, but without evolution towards this disease. Consequently, morphofunctional pancreatic alterations with age may be another confounding factor. These findings might explain some of the discrepancies reported by different authors.

On the other hand, regarding the hepatic alterations, most LC patients in our study were at an advanced stage of the disease and showed ascites, encephalopathy and/or gastrointestinal hemorrhage as well as Child-Pugh B or C and markedly reduced PDR in the ICG test. However, only a few CP patients exhibited these manifestations, which were not ascribed to any hepatic disorder (Table 4).

There is also controversy concerning the frequency of LC in CP patients. Previous studies have reported that the presence of LC in patients with CP was variable, ranging between 5% and 30%[56]. Later, Angelini et al[19] found 12.5% of LC cases in CP patients. Although, in this study, cases with hepatitis C virus were not excluded, the authors did not find any relationship between the grade of hepatic histological alteration and the degree of pancreatic functional severity. Recently, Nakamura

et al[15] found no association between liver and pancreatic disease in a population of alcoholics with abdominal pain, after exclusion of patients with viral hepatitis[15]. Accordingly, only 5% of patients who had altered ERCP also exhibited Child-Pugh class B or C[15].

It should be taken into account that many hepatic alterations in patients with alcoholic CP are ascribed to cholestasis secondary to pancreatitis[57,58], and indeed, they are not characteristic of advanced alcoholic liver disease[19,55]. Moreover, most of these cases exhibit regression of liver fibrosis after biliary drainage[59].

In our study, there was no coincidence at all between severe alterations of the pancreatic function assessed by fecal E-1 test and severe alterations of the liver function assessed by ICG test. Furthermore, we found a strong inverse correlation ($r = -0.752$; $P < 0.001$) between these functions (Figure 3). Similarly, we found a significant correlation between PI and fecal E-1 test ($r = 0.759$; $P < 0.001$). These findings support the hypothesis of a different and independent etiopathogenesis of CP and LC associated with alcoholism[25]. Hayakawa *et al*[24] reported a negative correlation between pancreatic and liver functions, but only in patients with alcoholic liver disease. In this regard, a general increase in exocrine pancreatic secretion in LC patients has been reported[19,60]. Thus, Dreiling *et al*[23] have suggested a hypersecretory state of the pancreas in alcoholic LC, with increased volume output[16] and maintaining either normal or elevated bicarbonate and enzyme outputs[16,19,23,24]. This has been considered a washout phenomenon, resulting in a decreased tendency of ductal protein and calcium precipitation in these patients[16].

Hayakawa *et al*[24] have reported that pancreatic secretion increases in patients with different degrees of alcoholic liver disease, assessed by the cholcystokinin-secretin test, ICG test and liver histopathology. Moreover, these authors have found a significant inverse correlation between bicarbonate secretion and ICG clearance[24].

The hypersecretory state of the pancreas in alcoholics with LC has been ascribed to a reduced inactivation of secretin[60] or even to the increased portal pressure[24]. Recently, it has been confirmed by an experimental result that chronic alcoholism impairs the neurohormonal control of the pancreas, both at the central nervous system and acinar levels, promoting the secretory response to feeding or other stimuli[61]. All these findings regarding the inverse correlation between the alterations of liver and pancreatic function tests may be a reflection of some correlation in the etiology of both diseases.

In summary, the present study demonstrates the scarce coincidence in clinical manifestations, morphological alterations and organ function between CP and LC in alcoholic subjects. This finding, together with the inverse correlation between indexes of pancreatic and liver functions in these patients, supports the hypothesis that alcoholic CP and LC evolve in a different manner and have different etiopathogenesis. Accordingly, chronic alcoholism, although a necessary factor, is not a sufficient cause in their etiopathogenesis. Further studies should provide new insights into the different risk factors-other than alcoholism-involved in the etiopathogenesis of alcoholic CP and LC.

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COMMENTS

Background
Despite sharing similar risk factors, medical literature regarding the simultaneous occurrence of chronic pancreatitis (CP) and liver cirrhosis (LC) in patients with chronic alcoholism is scarce and the results are uncertain. This lack of coincidence may rely on differences in methodology such as retrospective *versus* prospective studies, and the evaluated parameters such as clinical, functional, imaging or histopathological. However, it may also reflect the hypothesis that alcoholism is not a sufficient cause, but a cofactor, for the development of such diseases.

Research frontiers
This study has been carefully designed to investigate the coincidence in clinical manifestations, morphological alterations and organ function between CP and LC in alcoholic subjects. The results support the hypothesis that alcoholic CP and alcoholic LC evolve in a different manner and have different etiopathogenesis, despite sharing a common risk factor.

Innovations and breakthroughs
There is a lack of coincidence between CP and LC in alcoholic subjects. There is an inverse correlation between indexes of pancreatic and liver functions in these patients, supporting the hypothesis that chronic alcoholism, although a necessary factor, is not a sufficient cause in their etiopathogenesis.

Applications
This paper suggests the necessity for researching other factors together with chronic alcoholism involved in the development of CP or LC.

Peer review
Authors studied the possible association between CP and LC of alcoholic etiology, after excluding any other causes. This is an interesting study. It was undertaken according to a carefully designed plan and with adequate statistical considerations. The authors successfully provided the evidence, suggesting that CP and LC evolve in a different manner, which will be useful for clinical researchers of these diseases.

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