

Etiology, Severity and Recurrence of Acute Pancreatitis in Southern Taiwan

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Background/Purpose: Changes in lifestyle have led to variation in the etiologies of acute pancreatitis in different areas of Taiwan. This study investigated the etiologies and factors associated with severity and recurrence of acute pancreatitis in southern Taiwan.

Methods: Eighty acute pancreatitis patients (M/F: 64/16), including 53 (66.2%) with alcohol abuse, 16 (20%) with biliary disease, five (6.3%) with hyperlipidemia, and six (7.5%) with other risk factors, etiologies or idiopathic disease, were included. The mean follow-up period was 20 months. Contrast-enhanced computed tomography (CT) was used to assess the severity of acute pancreatitis.

Results: Biliary pancreatitis was significantly associated with females while alcoholic pancreatitis occurred predominantly in males. Univariate analysis showed that male gender, alcoholic pancreatitis, and elevated serum triglyceride (> 170 mg/dL) were significantly associated with severe acute pancreatitis. Multivariate logistic regression analysis revealed that male gender and abnormal serum triglyceride were independent risk factors for severity. Alcohol abuse was an independent risk factor for recurrent pancreatitis.

Conclusion: Alcoholic pancreatitis was the major etiology of acute pancreatitis in southern Taiwan, exhibiting a strong male predominance and higher risk of severe CT grading. Abnormal serum triglyceride was independently associated with the severity of acute pancreatitis. Alcoholic pancreatitis had a higher risk of recurrence than other etiologies. [*J Formos Med Assoc* 2006;105(7):550–555]

Key Words: alcoholism, etiology, gallstone, hypertriglyceridemia, pancreatitis, Taiwan

The major etiologies of acute pancreatitis are alcohol and biliary lithiasis. Some studies have reported differences in the clinical course and outcome of acute pancreatitis due to etiologic factors,¹ while others did not find any such differences.^{2,3} The etiologic factors, associated with severity and recurrence of acute pancreatitis, are not well established. Bile duct stones and alcohol misuse together account for more than 80% of cases.^{4,5} However, wide variations exist regarding the incidence of etiologies of various acute pancreatitis worldwide.^{3–6} These differences may reflect an

environmental diversity in the incidence of alcohol consumption, cholelithiasis, and other factors.⁵ Therefore, local data on the etiology of acute pancreatitis are required among different areas and population.

Only two studies of the etiology of acute pancreatitis have been reported from Taiwan. In 1987, Tsai⁷ reported that the most common etiologic factor of acute pancreatitis in Taiwan was biliary disease (41.9%). Alcohol abuse was present in 14.9% and unknown factors in 27%.⁷ With the westernization of lifestyles and increased

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consumption of alcohol in Taiwan, Chang et al found that alcohol (35.4%) has become the predominant cause of acute pancreatitis in 2003.⁸ They showed that 40.9% of cases in southern Taiwan had an alcohol-related etiology. The associations among etiology, severity and recurrence have not been reported in southern Taiwan. The aim of this study was to evaluate the factors associated with the severity and recurrence of acute pancreatitis and the etiology of this disease in southern Taiwan.

Methods

This study was approved by the hospital ethics committee. One hundred and six consecutive patients (85 males, 21 females) admitted due to acute pancreatitis to Kaohsiung Municipal Hsiao-Kang Hospital between June 1999 and May 2001 were included. The patients were all residents of the suburban area of southern Taiwan. Only those patients suffering from a first attack of acute pancreatitis were included. Acute pancreatitis was defined as an episode of acute characteristic abdominal pain associated with at least twofold increase in serum amylase and lipase, further confirmed by imaging techniques such as ultrasonography (US) and/or contrast-enhanced computed tomography (CECT). All patients were treated with currently accepted concepts of medical and surgical therapies.^{9,10} Patients with chronic pancreatitis and pancreatic cancer were excluded.

Patients were divided into four primary etiologic groups (alcoholic, biliary, hyperlipidemic, and other/idiopathic). The etiology was considered to be of biliary origin when biliary tract stones were diagnosed based on imaging study, such as US, CT, endoscopic retrograde cholangiopancreatography, or operative findings, without evidence of recent alcohol consumption. The etiology was considered to be of alcoholic origin when the patient had consumed more than 40 g ethanol per day for at least 5 years and the possibility of a biliary origin had been excluded.⁶ Hyperlipidemic pancreatitis was considered to be

the associated origin when serum triglyceride was greater than 500 mg/dL without evidence of biliary and alcoholic factors.¹¹ The other causes of acute pancreatitis and idiopathic origin were classified as the other/idiopathic group.

Clinical features including gender, age, amylase, lipase, diabetic history, abnormal serum triglyceride level (> 153 mg/dL), severity, and recurrence were compared between these four etiologic groups. At this hospital, the normal range of serum amylase was 33–96 U/L, and of serum lipase was 23–300 U/L, and of serum triglyceride was 35–153 mg/dL. Recurrent pancreatitis was defined as at least two episodes of acute pancreatitis during a follow-up period of 5–36 months (mean, 20 months) without evidence of chronic pancreatitis or pancreatic cancer.

The severity of the disease was assessed using the CT severity index.^{9,12,13} According to CECT appearance, index 1 or 2 was classified as mild acute pancreatitis and indices 3–10 as severe acute pancreatitis. In addition, abnormal serum triglyceride, regardless of etiology, was considered as a risk factor for severe acute pancreatitis. The area under the curve was compared with receiver-operating characteristics (ROC) analysis and in an attempt to derive a suitable clinical cut-off for serum triglyceride to predict the severity of acute pancreatitis.

The mean values and standard deviations of age, amylase and lipase levels in patients with these four etiologies were analyzed by the Kruskal–Wallis test. Gender, diabetic history, abnormal serum triglyceride, recurrence and severity were compared among these four etiologies by means of Pearson χ^2 test and Fisher's exact test. Univariate and stepwise multivariate logistic regression analyses were performed to identify the risk factors associated with the severity and recurrence of acute pancreatitis. Two-tailed *p* values less than 0.05 were considered statistically significant.

Results

Eighty (64 males, 16 females; mean age, 43.5 ± 12.9 years; age range, 20–79 years) of 106 reviewed

Table 1. Clinical features of patients with acute pancreatitis of various etiologies

	Etiology				p
	Alcoholic	Biliary	Hyperlipidemia*	Other/idiopathic	
Patients, n (%)	53 (66.2)	16 (20)	5 (6.3)	6 (7.5)	–
Gender (male/female)	52/1 ^{††}	7/9 [†]	4/1	1/5 [‡]	<0.001
Age, yr (mean ± SD)	40.8 ± 9.3 [§]	54.1 ± 15.5 [§]	37.4 ± 13.5	44.7 ± 19.4	0.025
Amylase, U/L (mean ± SD)	185.3 ± 251.8	349.1 ± 362.6	227.2 ± 167.4	167.8 ± 155.8	0.264
Lipase, U/L (mean ± SD)	1305.5 ± 1909.4	1302.2 ± 1122.2	1319.4 ± 1427.3	670.8 ± 274.4	0.448
Diabetes history, n (%)	11/53 (20.8)	4/16 (25)	4/5 (80)	0/6 (6)	0.012
Triglyceride > 153 mg/dL, n (%)	36/47 (76.6)	3/14 (21.4)	5/5 (100)	1/3 (33.3)	<0.001

*The etiology of hyperlipidemia was defined as acute pancreatitis associated with serum triglyceride >500 mg/dL in a patient without an alcohol- or biliary-related etiology; [†]p < 0.001; [‡]p < 0.001; [§]p = 0.004.

Table 2. Univariate analysis of risk factors for severe acute pancreatitis

	Severe acute pancreatitis*	p
Gender, n (%)		0.002
Male	46/61 (75.4)	
Female	5/15 (33.3)	
Etiology, n (%)		0.010
Alcoholic	39/52 (75) [‡]	
Biliary	7/15 (46.7)	
Hyperlipidemia [†]	4/4 (100) [§]	
Other/idiopathic	1/5 (20) ^{‡§}	
Diabetic history, n (%)		0.270
Diabetic	14/18 (77.8)	
Nondiabetic	37/58 (63.8)	
Triglyceride > 170 mg/dL, n (%)		0.005
Abnormal	32/38 (84.2)	
Normal	14/27 (51.8)	

*Severity was classified by CT grading of acute pancreatitis: mild was defined as grades A or B, and severe as grades C, D or E;⁹ [†]etiology of hyperlipidemia was defined as acute pancreatitis in a patient with serum triglyceride >500 mg/dL without alcohol misuse and biliary disease; [‡]p = 0.024; [§]p = 0.048.

patients met the criteria for study inclusion. The clinical features of patients with acute pancreatitis are shown in Table 1. The etiology of acute pancreatitis was associated with alcohol abuse in 53 patients (66.2%), biliary disease in 16 (20%), hyperlipidemia in five (6.3%), and other factors or idiopathic in six (7.5%). Age was significantly higher in patients with biliary pancreatitis (54.1 ± 15.5 years) than in the other three etiologic

groups. The age of females was significantly higher than that of males (50.9 ± 14.4 vs. 41.6 ± 11.9 years, p = 0.011). The most frequent etiology of male patients was alcoholic pancreatitis (81.3%). In contrast, biliary pancreatitis was the most frequent etiology in female patients (56.3%). Amylase and lipase levels of the four etiologic groups were not significantly different. There were 26 patients with at least two episodes of acute pancreatitis during an average of 20 months' follow-up. Patients with alcohol abuse tended to suffer recurrent pancreatitis (35.9%). The recurrence rate of biliary pancreatitis was 12.5%, and that of hyperlipidemia was 60%. No recurrent pancreatitis was found in five patients in the etiologic group of other/idiopathic pancreatitis (p = 0.033). The frequency of severe acute pancreatitis was significantly associated with the etiology, being significantly higher in patients with alcohol abuse (75%) and hyperlipidemia (100%) than in patients with biliary (46.7%) and other/idiopathic etiologies (20%) (p = 0.01) (Table 1).

Seventy-six patients (61 males, 15 females) with complete CECT study were included in the analysis of severity. The results of univariate analysis of risk factors for severe acute pancreatitis are shown in Table 2. Male gender was associated with severe acute pancreatitis (p = 0.002). Alcohol misuse and hyperlipidemia were also associated with severe acute pancreatitis (p = 0.01). Regardless of etiology, the frequency of severe acute pancreatitis was significantly

higher in patients with elevated serum triglyceride (> 153 mg/dL). When serum triglyceride was greater than 170 mg/dL, the sensitivity and specificity were the best for predicting severe acute pancreatitis (sensitivity, 69.57%; specificity, 68.42%) ($p=0.005$). In addition, there was no significant difference in the frequency of severe acute pancreatitis between diabetic and nondiabetic patients (77.8% [14/18] vs. 63.8% [37/58], $p=0.43$).

The results of univariate analysis of risk factors for recurrent pancreatitis are shown in Table 3. There was no significant difference in risk of recurrence associated with gender ($p=0.056$), diabetic history ($p=0.644$), or abnormal serum triglyceride ($p=0.97$). Alcoholic pancreatitis was significantly more likely to recur than biliary pancreatitis (39.6% vs. 12.5%, $p=0.044$). Although the recurrence rate of hyperlipidemic pancreatitis was 60%, it was not significantly different than in the other three etiologic groups (hyperlipidemic vs. alcoholic, $p=0.37$; vs. biliary, $p=0.063$; vs. other/idiopathic, $p=0.061$).

In order to avoid confounding, a stepwise multivariate logistic regression analysis of risk factors for severity and recurrence of acute pancreatitis was performed. The results are summarized in Table 4. Gender and abnormal serum triglyceride were the only independent factors associated with severity. Male patients had a higher risk (odds ratio, OR = 7.68, $p=0.01$) of severe acute pancreatitis. When serum triglyceride was greater than 170 mg/dL, the OR of severe acute pancreatitis was 3.66 ($p=0.04$). Moreover, the results of multivariate analysis for recurrence were consistent with the univariate analysis, with

alcoholic pancreatitis being the only independent risk factor for recurrence (OR = 3.50, $p=0.04$).

One 34-year-old male patient with Ranson's score of 8 died 19 days after admission. He had a history of alcohol abuse and hyperlipidemia. Although the CECT results were grade D with mild necrosis during the initial admission, follow-up exam results 2 weeks later were grade E, with severe necrosis of the pancreas and neighboring organs.

Table 3. Univariate analysis of risk factors for recurrent acute pancreatitis

	Recurrence*	<i>p</i>
Gender, <i>n</i> (%)		0.056
Male	22/64 (34.4)	
Female	2/16 (12.5)	
Etiology, <i>n</i> (%)		0.033
Alcoholic	19/53 (35.9) [†]	
Biliary	2/16 (12.5) [†]	
Hyperlipidemia [†]	3/5 (60.0)	
Other/idiopathic	0/6 (0)	
Diabetic history, <i>n</i> (%)		0.644
Diabetic	7/19 (36.8)	
Nondiabetic	17/61 (27.9)	
Triglyceride > 170 mg/dL, <i>n</i> (%)		0.970
Abnormal	13/41 (31.7)	
Normal	9/28 (32.1)	
Severity, <i>n</i> (%)		0.32
Mild	6/25 (24.0)	
Severe	18/51 (35.3)	

*Recurrent pancreatitis was defined as at least two episodes of acute pancreatitis during an average of 20 months' follow-up without evidence of chronic pancreatitis or pancreatic cancer; [†]etiology of hyperlipidemia was defined as acute pancreatitis associated with serum triglyceride > 500 mg/dL in a patient without alcohol misuse or biliary disease; [‡] $p=0.044$.

Table 4. Multiple logistic regression analysis of risk factors associated with severity and recurrence of acute pancreatitis

	Dependent variable	Odds ratio	95% CI
Severity*	Gender (male = 1, female = 0)	7.68	1.64–36.08
	Serum triglyceride (> 170 mg/dL = 1, ≤ 170 mg/dL = 0)	3.66	1.06–12.64
Recurrence [†]	Alcoholic pancreatitis (alcoholic = 1, non-alcoholic = 0)	3.50	1.06–11.59

*Severity was classified by CT grading of acute pancreatitis: mild was defined as grades A or B, and severe as grades C, D or E; [†]recurrent pancreatitis was defined as at least two episodes of acute pancreatitis during an average of 20 months' follow-up without evidence of chronic pancreatitis or pancreatic cancer.

Discussion

In Western countries, biliary stone and alcohol are the most frequent causes of acute pancreatitis and account for about 80% of all causes of the disease.⁴ Biliary pancreatitis and alcoholic pancreatitis are triggered by different pathophysiologic mechanisms and this accounts for the differences in the severity of the disease.¹⁴ In this study, we found that alcohol abuse was the most common etiology of acute pancreatitis (66.2%) whereas acute biliary pancreatitis accounted for only 20%. The percentage of acute pancreatitis with alcoholic etiology in this study is much higher than in previous studies from Taiwan^{7,8} and in some western countries.^{1,2,6,7,12,14} This finding could indicate a change in the etiology of acute pancreatitis in southern Taiwan. Some studies suggested that alcoholic pancreatitis is correlated with societal increases in alcohol consumption.^{8,15} It is thought that alcohol consumption has increased in suburban areas of southern Taiwan in the last 15 years,⁸ but whether this is correlated with increased rates of acute pancreatitis with an alcohol etiology requires further investigation.

Our data agree with the results of previous studies that alcoholic pancreatitis is more frequent in young people, whereas the frequency of biliary pancreatitis is higher in patients of advanced age.^{1,3,6,8,16} Regarding the influence of gender, alcoholic pancreatitis occurred predominantly in males, whereas half of females had pancreatitis of biliary origin. These data are supported by the fact that the prevalence and incidence of gallstone disease increase markedly with age, especially in women.¹⁴ The gender differences in disease prevalence may also explain the finding of the older age of female patients with acute pancreatitis.

There are many methods that can be used to assess the severity of acute pancreatitis. CT is a rapid and definitive examination for this assessment. Recent studies suggest that the likelihood of prolonged pancreatitis or a serious complication is negligible when the CT severity index is 1 or 2.^{9,13} Therefore, in this study, grades A and B were

considered to be mild forms and C–E as severe forms of acute pancreatitis. Because contrast CT cannot be performed in a subset of patients, including those with renal failure or contrast allergy, the assessment of pancreatic necrosis must be made by other methods. In this study, alcoholic pancreatitis and hyperlipidemic pancreatitis tended to have a severe CT grading. These findings are in partial agreement with previous studies, which showed that patients with idiopathic pancreatitis and those with alcoholic pancreatitis had a higher risk of developing severe pancreatitis than patients with biliary pancreatitis or other disease etiologies. Although these studies used different methods of assessment (Atlanta criteria, organ failure, or Balthazar score) to evaluate severity, it was also concluded that alcoholic pancreatitis was associated with severe acute pancreatitis.

This study found that abnormal triglyceride (>170 mg/dL) was a risk factor for severe CT grading. The significant association of alcoholic pancreatitis with severe acute pancreatitis in the univariate analysis may be explained by the effect of abnormal serum triglyceride, which was an independent risk factor for severity in stepwise multivariate logistic regression. This may be a useful finding to further investigate the cause and mechanism. A relationship between hypertriglyceridemia and the early stage of alcoholic pancreatic injury has been reported,¹⁷ and a poor outcome of pancreatitis associated with hypertriglyceridemia was also demonstrated.¹⁸ These findings may support the hypothesis that hypertriglyceridemia contributes to the severity of acute pancreatitis. Therefore, it may be important to consider aggressive treatment of hypertriglyceridemia in patients with acute pancreatitis to limit its role in the development of severe acute pancreatitis.

The duration of follow-up in this study ranged from 5 to 36 months. Only two patients had a follow-up period of less than 10 months (5.4 and 7.2 months). The mean duration from initial event to recurrence was 6.5 months. No difference was found between the duration of follow-up and

recurrence rate ($p=0.935$), suggesting that the duration of the follow-up period might not have influenced the recurrence rate. Further study with longer follow-up duration is required to elucidate the risk factors for recurrence.

Acute pancreatitis associated with alcohol misuse was more likely to recur in this study, although the pathogenesis of alcoholic pancreatitis is multifactorial. The association of recurrence with hyperlipidemic pancreatitis was of borderline significance in this study ($p=0.061$). The small number of patients with hypertriglyceridemia (only five patients), however, may explain why hypertriglyceridemia was not an independent risk factor for recurrence. A recent study showed that adequate diet and drug treatment, including dose titration, are very effective in preventing relapse in patients with hypertriglyceridemic acute pancreatitis.¹⁹ Plasmapheresis may be useful to prevent recurrent acute pancreatitis in patients with primary severe hypertriglyceridemia.²⁰

In conclusion, acute pancreatitis is most often associated with alcoholism in southern Taiwan and this etiology predominates in male patients. In females, biliary stones predominate, and the age of female patients is significantly higher than the males. Patients with alcoholic and hyperlipidemic pancreatitis are at higher risk of severe CT grading than other etiologic groups. Regardless of other etiologic factors, hypertriglyceridemia (>170 mg/dL) may contribute to the severity of acute pancreatitis. In addition, acute pancreatitis associated with alcohol misuse tends to recur more frequently.

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