

ORIGINAL PAPERS

Influence of delayed cholecystectomy after acute gallstone pancreatitis on recurrence. Consequences of lack of resources

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ABSTRACT

Introduction: Acute pancreatitis is often a relapsing condition, particularly when its triggering factor persists. Our goal is to determine the recurrence rate of acute biliary pancreatitis after an initial episode, and the time to relapse, as well as to identify the risk factors for recurrence.

Material and method: We included all patients admitted for a first acute gallstone pancreatitis event during four years. Primary endpoints included readmission for recurrence and time to relapse.

Results: We included 296 patients admitted on a total of 386 occasions. The incidence of acute biliary pancreatitis in our setting is 17.5/100,000 population/year. In all, 19.6% of pancreatitis were severe (22.6% of severe acute pancreatitis for first episodes versus 3.6% for recurring pancreatitis), with an overall mortality of 4.4%. Overall recurrence rate was 15.5%, with a median time to relapse of 82 days. In total, 14.2% of patients relapsed after an acute pancreatitis event without cholecystectomy or endoscopic retrograde cholangio-pancreatography. Severe acute pancreatitis recur in 7.2% of patients, whereas mild cases do so in 16.3%, this being the only risk factor for recurrence thus far identified.

Conclusions: Patients admitted for pancreatitis should undergo cholecystectomy as soon as possible or be guaranteed priority on the waiting list. Otherwise, endoscopic retrograde cholangio-pancreatography with sphincterotomy may be an alternative to surgery for selected patients.

Key words: Acute gallstone pancreatitis. Recurrence. Cholecystectomy. Waiting list.

INTRODUCTION

The incidence of acute pancreatitis (AP) is increasing, with significant differences in etiology. Gallstone-related AP (AGP) is most common in women, alcoholic AP is most common among mid-aged men, and idiopathic AP involves both sexes alike (1). In our setting, AP incidence is 13-45 cases/100,000 inhabitants/year (2), and as in most western countries biliary lithiasis is the single most common cause (24-71%) (3).

AP is a usually recurring condition, particularly when its trigger persists (4,5). Cholecystectomy and endoscopic retrograde cholangio-pancreatography (ERCP) are presently recommended to prevent recurrence for patients with AP originating in the biliary system (6). Studies assessing the presence of risk factors have attained conflicting results. There are studies that identify no risk factors for recurrence, and then studies that relate AP recurrence to gallstone size (7), episode severity (8), early reintroduction of food, biochemical changes in liver function, age, or race (9). However, the incidence of AGP recurrence and the time to recurrence are highly variable in reported series (10-13).

The goal of the present study is to determine AGP recurrence rate and time to recurrence after an index pancreatitis event, and the identification of risk factors in our setting.

MATERIAL AND METHOD

This is a prospective, longitudinal, descriptive study performed in our hospital, which serves a population of 430,000 inhabitants. The course of our study did not alter the management of included patients in any way whatsoever. It was approved by the hospital's Ethics Committee, and always complied with the ethical standards for human research as specified in the Declaration of Helsinki (14). The study started with the inclusion of its first subject in January 2007, and ended in December 2010.

All patients admitted for a first AGP episode were consecutively included. We used for AP the internationally endorsed diagnostic criteria (15), and established the biliary origin of pancreatitis when gallstones or bile sludge were present in the gallbladder as demonstrated by imaging techniques (sonography, computerized tomography, or magnetic resonance cholangiography [MRC]). Endoscopic ultrasounds (EUS) were not used for diagnosis as this test was unavailable in our institution during the study period. Patients having undergone cholecystectomy or ERCP prior to inclusion were excluded from the study.

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Main variables included readmission for recurrence and time to relapse. Recurrence was defined using the same set of criteria used for the index AP event (15), and we classified patients into three groups: patients with recurrence in the absence of cholecystectomy or ERCP, patients with relapsing AP after cholecystectomy and patients with relapsing AP after ERCP for suspected residual choledochal lithiasis. Time to recurrence is the interval of time between the index AP event and relapse.

Other variables recorded included age, sex, liver chemistry (aspartate transaminase [AST U/L], conjugated bilirubin [mg/dL], alkaline phosphatase [U/L]), bile duct dilation (diameter > 7 mm), AP severity, surgery for AP, hospital stay, cholecystectomy, maximum gallstone size (in cholecystecmy specimen), time to cholecystectomy, reason for non-cholecystectomy, ERCP, presence of choledocolithiasis, time to ERCP, other non-AP biliopancreatic causes of readmission (acute cholangitis, acute cholecystitis, prior AP-related complications, nonspecific abdominal pain), follow-up duration, and patient demise. ERCP was indicated as urgent for patients with AP-associated cholangitis, and was scheduled following the AP event in cases with a high suspicion of associated choledocolithiasis after positive imaging test.

We defined AP episode severity according to the criteria by Ranson et al. (16), and the index of severity (IS) (17), with AP being considered as mild when fewer than 3 Ranson criteria are met, or IS is lower than 3.

Data were recorded from January 2007 until two months after last patient inclusion in order to provide a minimum follow-up of two months. Data were recorded by a single person. Data were always managed in compliance with the Spanish “Ley Orgánica 15/1999, de 13 de diciembre, sobre Protección de Datos de Carácter Personal” (LOPD) (18).

We used the statistical package SPSS-19, IBM SPSS Statistics (SPSS Inc., an IBM Company) for the analysis of variables.

In the descriptive analysis, data are presented as mean plus standard deviation values for normally distributed continuous variables, median plus p₂₅ and p₇₅ percentile values for non-normally distributed

continuous variables, and percentages for categorical variables.

In the inferential analysis, single comparisons between groups are provided by Student’s t-test for normally distributed continuous variables, the Mann-Whitney U-test for non-normally distributed continuous variables, Fisher’s exact test for categorical variables, and the Mantel-Haenszel linear test for ordered categorical variables.

RESULTS

We included 296 patients in the study, who were admitted a total of 386 times. In all, 351 admissions were for AGP (first episode or recurrence), and 35 took place for other biliopancreatic conditions (Fig. 1). Follow-up lasted for a median of 309 days (p₂₅ 127 days, p₇₅ 569 days).

AGP incidence in our setting is 17.2/100,000 population per year.

In our sample, 58% of subjects were females (173 patients) and 42% were males (123 patients), with a mean age of 67 years (range 18 -92). Hospital stay was a median of 7 days (p₂₅ 5 days, p₇₅ 11 days). Of all (351) AP episodes, 69 were classified as severe (i.e., 19.6%), with 11 undergoing urgent surgery for severe AP (3%). Of these 11 patients, 10 were operated upon during their first episode, and 9 of them underwent cholecystectomy during the same procedure. Furthermore, we saw that recurrent AP events were less severe (22.6% of severe index AP cases vs. 3.6% of recurring AP events). Mortality was 4.4% with 13 deaths, 12 of these during the first episode. The characteristics of first and recurring episodes are summarized in table I.

Following AP, 209 (70.6%) patients underwent cholecystectomy, with a median wait time of 97 days (p₂₅ 60 days, p₇₅ 173 days), and no statistically significant differ-

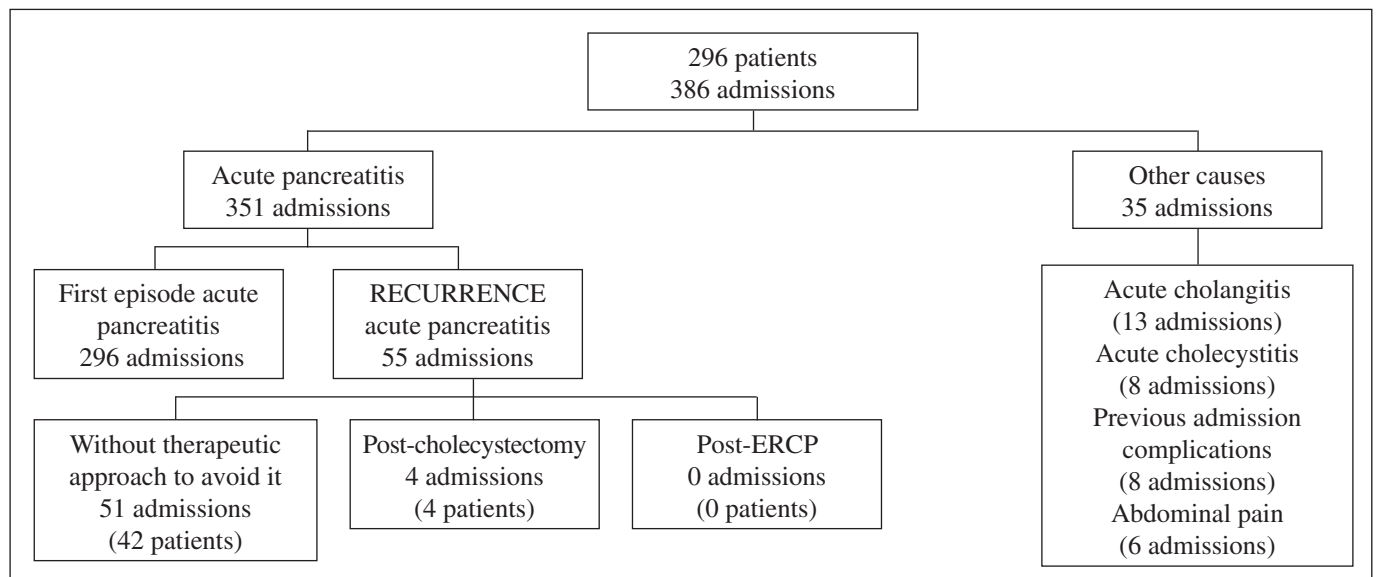


Fig. 1. Summary patient inclusion.

Table I. First AP episode vs. recurrent AP characteristics

	First AP episode (n = 296)	Recurrent AP (n = 55)
Gender		
Male	123 (42%)	22 (40%)
Female	173 (58%)	33 (60%)
Age (years)	70	73
Hospital stay (days)	7	7
Surgery for severe AP (patients)	10	1
Severe cases (patients)	67 (22.6%)	2 (3.6%)*
Mortality (patients)	12 (4%)	1 (1.8%)**

AP: Acute pancreatitis. *Both severe recurrent cases were also severe in the first episode. **Patient with end-stage amyotrophic lateral sclerosis.

ences were found between mild AP (96 days) and severe AP (105 days) cases ($p = 0.992$). Patients not subjected to cholecystectomy for whatever cause represented 20.4% (87 subjects).

ERCP was performed for 64 (22%) patients, with a 10 days median from admission to the procedure (p_{25} 4 days, p_{75} 65 days), choledochal lithiasis being identified in 56 (19%) patients. Of all 87 patients not undergoing cholecystectomy, 21 received ERCP as single therapeutic procedure.

During follow-up, overall recurrence rate was 15.5% (46 of 296 patients); 14.2% of patients recurred after their index AGP event in the absence of cholecystectomy or ERCP (42 of 296 patients). Of these, 35 recurred once, 5 recurred twice, and 2 had recurrence on three occasions, for a total of 51 relapsing events (Fig. 1). These recurrences developed after a median of 82 days (p_{25} 22 days, p_{75} 126 days, range 6-767 days).

Four patients had a recurrence event after cholecystectomy (at 24 hours, at 12 days, and 2 at 6 months after cholecystectomy). Only in one patient with recurrence at 6 months was choledochal lithiasis identified. No relapses occurred in patients after ERCP (with or without cholecystectomy) (Fig. 1).

Furthermore, 35 patients were readmitted for other reasons in association with their biliopancreatic disease. On 13 occasions for cholangitis (5 patients after ERCP and 6 after cholecystectomy), 8 for cholecystitis, 8 for complications of prior pancreatitis events, and 6 for abdominal pain or malaise not attributable to any of their previous diagnoses (Fig. 1).

Having analyzed the study-defined variables potentially associated with recurrence, we may safely claim that age, sex, liver chemistry changes (AST, alkaline phosphatase, bilirubin), gallstone size, and bile duct dilation bear no statistically significant relationship to recurrent AP. Only the fact that severe AP is less recurrent could be established. Severe AP recurs in 7.2% of cases whereas mild AP does so in 16.3% of cases ($p = 0.036$) (Table II).

Table II. Relationship between variables and recurrence AP

		No recurrence	Recurrence	p
Average age (years)		68.3	65.7	0.628
Gender	Male	84.8%	15.2%	0.774
	Female	85.9%	14.1%	
Liver biochemical abnormalities*	AST	5.2	5.3	0.771
	Alkaline phosphatase	4.8	4.8	0.996
	Bilirubin	0.01	0.07	0.720
Bile duct dilatation	No	82.6%	17.4%	0.527
	Yes	77.3%	22.7%	
Severity AP	Mild	83.7%	16.3%	0.036
	Severe	92.8%	7.2%	

AST: Aspartate transaminase; AP: Acute pancreatitis. *These variables with non-normal distribution have become regular taking their neperian logarithms.

DISCUSSION

An ideal study to analyze AGP recurrence would include patients undergoing no therapy apt to influence recurrence (cholecystectomy or ERCP) following the AP event. However, current AGP-related clinical guidelines recommend cholecystectomy or ERCP to prevent such recurrence (6,19-22), hence it would be unethical to hold back these therapies in order to assess recurrence rate.

We report the results from the first study to assess AGP recurrence in our setting, as well as the potentially associated risk factors. The present status of our public health care system, with long waiting periods, specifically for cholecystectomy, allows the scheduling of observational studies such as ours.

AGP incidence as observed in our study is 17.5/100,000 inhabitants per year. This is the highest incidence reported in Europe during the past few years (1). This may be due to increased life expectancy, as the incidence of both cholelithiasis and AGP increase with age. Our patients have a median age of 70 years, and 25% are above 79 years of age, which supports the fact that patients presenting with AP are increasingly older (1). Females predominate, a fact that we attribute to the inclusion of only patients with biliary AP, with gallstones being more common in women.

Upon reviewing the studies that have assessed recurrence, we came across conflicting figures oscillating between 3% (23) and 61% (24). Obviously, the reasons recorded for cholecystectomy also vary. Our results show that 14% of patients with a first AGP event have at least one recurrence, this being the actual proportion of AGP recurrence in the absence of any management or therapy to prevent it. With this percentage we deem cholecystectomy as appropriate to influence AGP recurrence and readmissions for gallstones, including acute cholecystitis episodes (Fig. 1).

Another significant aspect is the interval of time between first AGP event and AGP recurrence. Time to recurrence provides a key factor when considering the most appropriate timing of cholecystectomy or otherwise, only in selected cases, ERCP. Reported times oscillate between 0 days (9) and 129 days (13). Our results, with a median of 82 days, are near the longest times seen in the studies reviewed.

In our study, recurrence usually occurs as mild AP, with only 3.6% of severe forms and a mortality rate of 1.8%. The two patients who had severe recurring AP had suffered from severe AP in the past, and one of them died during the second episode from his underlying disease (end-stage amyotrophic lateral sclerosis). These results match those of the reviewed literature (25,26). During the study period, as described in Material and method, the criteria by Ranson et al. (16) and the IS (17) were used to define severity. We presently believe the international consensus Acute Pancreatitis Classification Working Group (27), a revision of the Atlanta system, to be more appropriate.

International clinical guidelines recommend cholecystectomy after an AGP event with an etiologic diagnosis standard higher than 80% and mortality below 10%. However, no mention is made of the percentage of patients that should undergo cholecystectomy (6,20-22). Few reported series discuss the percentage of cholecystectomized patients after AGP. In these few series cholecystectomy rates vary from 23% to 88% (28-32). In our site, 209 (70.6%) patients underwent cholecystectomy, which places our practice high amongst reported series. As for waiting time to cholecystectomy, our results are far removed from international clinical guidelines (6,20,22). The latter recommend that the procedure be performed during admission or within two weeks after admission in order to prevent recurrence. A randomized, multicenter study has been recently reported, which shows reduced AP recurrence-associated complications in patients undergoing cholecystectomy during their admission for AGP (33). We performed the procedure after a median of 97 days, and most patients were operated on after 60 to 173 days. Because of this, our recurrence rate was 14.2%.

Moreau et al. (34) claimed that the risk for recurrent AP after cholecystectomy resembled the risk of AP among the general population. Other authors describe recurrence rates of 13% (35) to 17% (36). Such relapses have been attributed to residual choledochal lithiasis (35). However, our recurrence rate is higher by only 2% (4 patients), and only one residual choledocholithiasis case was seen.

Another factor to be considered when surgery is indicated is readmission for other gallstone-related conditions. Seven of the 13 patients readmitted for cholangitis had not undergone cholecystectomy yet. Despite the fact that our readmission rate for cholecystitis was lower than elsewhere reported (2.3% vs. 5-9.1%) (37,40), this is another reason to make cholecystectomy a priority.

ERCP plus sphincterotomy may be a valid therapeutic alternative for patients not eligible for cholecystectomy, as none of our patients undergoing this technique relapsed within the follow-up period. However, this procedure is not exempt from complications, including AP. Hence, we think that the absence of EUS prior to ERCP is a limitation of our study. Such test allows to identify choledochal lithiasis with greater sensitivity than MRC and a high negative predictive value. This might have prevented some of our 8 "blank" ERCP procedures from taking place (38,39).

In an attempt to improve patient prioritization in the cholecystectomy waiting list, we endeavored to identify potential recurrence risk factors by analyzing etiopathogenic, epidemiologic and severity variables. We found no relationship whatever with gender or age, our results being consistent with those reported elsewhere (9). Hence, based on these results, we do not consider the trend to subject older people to fewer procedures as warranted. We also found no relationship between recurrence and bile duct dilation, liver chemistry changes, or gallstone size. Authors do take issue with this. While Lee (49) and Zhang et al. (9) also failed to identify these variables as recurrence risk factors, Monkhouse et al. (8) described an association between liver chemistry changes and readmission, but do not specify any reasons regarding the latter. Furthermore, Diehl et al. (7) report that gallstone size is a risk factor for AP.

The sole risk factor for relapsing AGP that we found is AP severity. We may safely state that patients with mild AGP are more likely to develop recurrence as compared to severe AP. This relationship has been revealed by no other study. We believe that several factors may play a role in this. On the one hand, patients with severe AGP undergo surgery and cholecystectomy more often during their first admission, and die also more often. On the other hand, this may result from greater fibrosis secondary to inflammation in patients with severe AP. In this regard, we believe the fact that patients who die from severe AP cannot relapse to be a bias of the present study.

In summary, despite our low rate of recurrence we deem it as necessary to perform early cholecystectomy for patients with AGP, hence our endeavors should focus on prioritizing these patients in waiting lists. This refers most particularly to patients who suffered from mild pancreatitis, as this is the only risk factor for recurrence found in our study. An alternative form of recurrence prevention may be ERCP for those who are not eligible for surgery because of advanced age or comorbidity.

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