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# Recurrent biliary acute pancreatitis is frequent in a real-world setting

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ABSTRACT

*Background:* Data about recurrent acute pancreatitis (RAP) are limited.
*Aims:* To evaluate the rate of RAP and associated factors.
*Methods:* Single-centre prospective study of consecutive patients at first episode of acute pancreatitis (AP) being followed-up.
*Results:* Of 266 consecutive AP patients, (47% biliary, 15.4% alcoholic, 14.3% idiopathic) 66 (24.8%) had RAP in a mean follow-up of 42 months; 17.9% of recurrences occurred within 30 days from discharge. Age, gender, smoking and severity of first AP were not associated with RAP risk. The rate of biliary RAP was 31.3% in patients who did not receive any treatment, 18% in those treated with ERCP only, 16% in those who received cholecystectomy only, and 0% in those treated both with surgery and ERCP. Patients with biliary AP who received cholecystectomy had a significantly longer time of recurrence-free survival and reduced recurrence risk (HR = 0.45). In patients with alcoholic AP, the rate of recurrence was lower in those who quit drinking (5.8% vs 33%; p = 0.05). The alcoholic aetiology was associated with a higher risk of having >2 RAP episodes.
*Conclusion:* RAP occurs in about 25% of cases, and failure to treat biliary aetiology or quitting drinking is associated with increased recurrence risk.


## 1. Introduction

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas that frequently involves also *peri*-pancreatic tissues and remote organ systems. It is one of the most common gastrointestinal disorders requiring urgent hospitalization worldwide, with a reported annual incidence of 13/45 cases per 100,000 persons [1,2].

The severity of the disease varies widely from the most frequent mild forms to severe disease with multi-systemic organ failure, occurring in about 10–20% of cases, that can eventually lead to death [3].

The most common causes of AP are gallstones (40–70%) and alcohol consumption (25–35%). The aetiology is not evident in 20–25% of patients after standard initial evaluation and it is defined as idiopathic AP [1,4].

Recurrent acute pancreatitis (RAP) is a clinical condition characterized by repeated and separate episodes of acute pancreatitis without clinical, biochemical or radiological findings of chronic pancreatitis. It is therefore diagnosed retrospectively by clinical definition after at least the second episode of AP [5].

There are few published data on the risk of RAP, and its exact incidence is difficult to estimate because of the heterogeneity in geographical location, distribution of aetiology of the first attack, and study design among published studies.

The prevalence of RAP in previous retrospective studies varied from 10% to 30%. In these studies, most cases of RAP were males (63–79%), possibly due to the more common alcoholic aetiology of acute pancreatitis (AAP) that seems to have a higher propensity to recur [6,7].

Indeed, patients who have had an attack of AP are at risk of having a recurrence of pancreatitis if the offending cause/agent is not removed [8]

Vipperla et al. also showed that the risk of readmission for a new AP episode was higher in patients with local complication or a first severe episode [9].

As the commonest causes of AP, gallstones and alcohol are both likely to cause recurrent pancreatitis, the risk of recurrence is often predictable and there is the possibility to treat the cause in order to reduce it [10,11].

In particular, early cholecystectomy significantly lowers the incidence of recurrent pancreatobiliary complications when com-

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pared with delayed cholecystectomy in patients with biliary AP (BAP) [12,13].

However, many of the above mentioned studies enrolled a limited number of patients, and did not evaluate specifically whether treatment of BAP with endoscopic retrograde cholangiopancreatography (ERCP) only lowers the risk of recurrence [14–16]. Finally, whether a more severe initial AP with necrosis and fluid collections is associated with an increased risk of recurrence or to further hospitalization due to complications of the very first episode could be difficult to distinguish in previous studies that were often retrospective and based on hospital records.

The aim of this study is therefore to evaluate the rate of RAP, particularly in patients with initial BAP, and to investigate factors associated with RAP in a prospective cohort of AP patients followed-up in a dedicated outpatients clinic after the first episode.

## 2. Methods

This is a prospective single-centre study of consecutive patients with a first AP episode admitted to the Gastroenterology Department of Sant'Andrea Hospital in Rome, Italy, between March 2007 and March 2015, and followed-up until March 2017. Enrolled patients provided written informed consent. The study received local IRB approval. Methods were performed in accordance with the relevant guidelines and regulations.

The diagnosis of AP was obtained according with the modified Atlanta criteria [17] by the presence of two of the three following parameters: clinical symptoms (right upper quadrant of the abdomen pain with posterior irradiation), biochemical analysis (amylase or lipase value 3-fold greater than the upper limit of normal) and with radiological examinations (ultrasound (US) or CT).

Patients with previous biliary disease, previous cholecystectomy, with chronic pancreatitis, or pancreatic cancer were excluded. Patients who died during the first hospitalization or did not receive at last one follow-up visit were also excluded.

The aetiology of AP at hospital admission was assessed by family and clinical history (drugs, alcohol consumption), biochemical parameters (total and coniugated bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, transaminases, calcium, triglycerides) and typical findings at one or more abdominal imaging techniques (ultrasonography, CT scan, magnetic resonance imaging (MRI) with or without cholangio-pancreatography (CPRM) or endoscopic ultrasound (EUS)). Cases for whom there was no convincing aetiology were deemed as idiopathic.

As far as regards imaging procedures, all patients received an abdominal ultrasound and/or a CT scan at the moment of the access in the emergency room or within 72 h; CT scans were repeated to exclude complications when clinically indicated. When a biliary aetiology was suspected, to rule out the presence of common bile duct stones, MRI with CPRM or EUS were performed.

The severity of the disease was defined according to the revised Atlanta classification [17] on the presence of local complications or multi-organ failure. Mild AP is characterized by the absence of organ failure and the absence of local or systemic complications. Moderately severe AP instead is defined by the presence of transient organ failure (<48 h) and/or local or systemic complications without persistent organ failure. Severe AP is characterized by persistent organ failure (>48 h).

Organ failure was defined by the presence of shock (systolic blood pressure <90 mmHg), pulmonary insufficiency (arterial PO2 <60 mmHg at room air or the need for mechanical ventilation), or renal failure (serum creatinine level >2 mg/dL after rehydration or haemodialysis).

Demographic information and clinical and biochemical data regarding the first episode of each patient were collected.

**Table 1**
Demographics and clinical features of the enrolled patients with a first episode of acute pancreatitis.

| General features (266) | N | % |
|---|---|---|
| Sex (male) | 158/266 | 59% |
| Mean age | 58.6 ± 17 | |
| Mild AP | 172/266 | 64.7% |
| Moderate AP | 39/266 | 14.7% |
| Severe AP | 55/266 | 20.7% |
| Pancreatic necrosis | 31/266 | 11.7% |
| Alcoholic aetiology | 41/266 | 15.4% |
| Idiopathic aetiology | 38/266 | 14.3% |
| Biliary aetiology | 125/266 | 47% |
| Hypertriglyceridemia | 8/266 | 3% |

AP = acute pancreatitis.

All patients were followed-up in a dedicated outpatients clinic with regular visits, the first one being within three months after the first episode and subsequently annually. During the visits possible new episodes of symptoms requiring hospitalization were analysed in order to define whether they were due to recurrence of AP, and their aetiology were recorded. RAP episodes were classified as "early" or "late" if the readmission was either before or after 30 days from the first discharge.

The possible evolution in chronic pancreatitis during the follow-up was also recorded according to the Mannheim classification, considering morphological changes of the organ or by the presence of exocrine or endocrine insufficiency.

### 2.1. Statistical analysis

The rate of patients with RAP in subgroups according with demographics, aetiology, severity of the disease and treatment of the cause of AP, were evaluated trough Fisher's exact test for categorical variables and *t*-test for continuous variables.

In addition, the time of recurrence-free survival was analysed with a Kaplan–Meier curves and Logrank test. A $p < 0.05$ was considered statistically significant. A dedicated software (MedCalc, Version 12.1, Mariakerke, Belgium) was used throughout the study.

## 3. Results

### 3.1. Patients characteristics

In the study period, 337 patients with a diagnosis of AP were admitted to the Gastroenterology department. Of these, 71 were excluded as 21 had a previous episode of AP or showed signs of chronic pancreatitis, 9 had a diagnosis of pancreatic cancer and 4 of other pancreatic neoplasms, 11 had previous cholecystectomy, 23 were not seen at follow-up visits, and 3 because of death during the hospitalization.

Therefore, 266 patients were enrolled, 158/266 (59%) being male, with a mean age of 58 ±17 years.

The most frequent aetiologies were biliary (125/266, 47%), alcoholic (41/266, 15.4%), drug-related (12/266, 4.5%) and hypertriglyceridemia (8/266, 3%). Of the 266 included patients, 38 (14.2%) were deemed to have an idiopathic AP without an identified cause during hospitalization.

The vast majority of cases were classified as mild, according with the modified Atlanta Classification (172, 64.7%), 39 (14.7%) as moderate and 55 (20%) as severe. Pancreatic necrosis was diagnosed in 31/266 (11.7%) patients. The mean length of hospital stay was 15 ± 11 days. Details regarding this population are provided in Table 1.

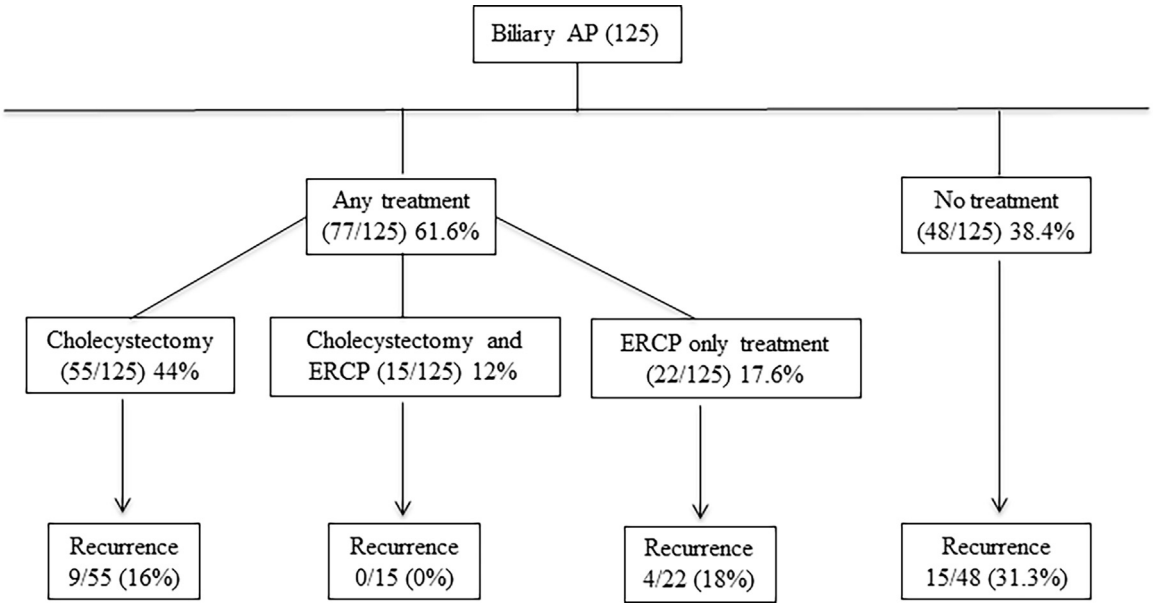


**Fig. 1.** Schematic representation of the managment of biliary acute pancreatitis. The rate of recurrence for patients receiving no treatment, cholecystectomy, cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP) or ERCP only is summarized.

**Table 2**
Factors associated with recurrent acute pancreatitis.

| | Recurrent (N = 66) % | Not recurrent (N = 200) % | p |
|---|---|---|---|
| Mean age | 56 ± 18 | 59 ± 17 | 0.24 |
| Sex (male) | 42/66 (63.6) | 116/200 (58) | 0.47 |
| Length of first hospital stay (days) | 12 ± 9 | 15 ± 11 | 0.11 |
| Mild AP | 46/66 (69.6) | 126/200 (63) | 0.37 |
| Moderate AP | 10/66 (15.2) | 29/200 (14.5) | 1 |
| Severe AP | 10/66 (15.2) | 45/200 (22.5) | 0.22 |
| Pancreatic necrosis | 3/66 (4.5) | 28/200 (14) | 0.04 |
| Alcoholic aetiology | 9/66 (13.6) | 32/200 (16) | 0.7 |
| Biliary aetiology | 28/66 (42.4) | 97/200 (48.5) | 0.39 |
| Hypertriglyceridemia | 4/66 (6) | 4/200 (2) | 0.11 |
| Drugs aetiology | 1/66 (1.5) | 11/200 (5.5) | 0.3 |
| Idiopathic aetiology | 8/66 (12) | 30/200 (15) | 0.68 |

### 3.2. Recurrent acute pancreatitis

During a mean follow-up time of 42 ± 33 months, 66/266 (24.8%) patients had a hospital readmission for recurrent acute pancreatitis. Eleven of 266 patients (4.1%) had early recurrence (within 30 days from discharge). The mean time of recurrence was 18 ± 26 months.

The most common aetiologies of RAP were biliary (28/66, 42.4%), idiopathic (8/66, 12.1%), alcoholic (9/66, 13.6%) and hypertriglyceridemia (4/66, 6%).

No differences were found between the 66 patients who had RAP and the 200 who did not in terms of age, gender, and features of the first AP such as its severity, aetiology and the length of first hospital stay (Table 2). The rate of smokers was not different in patients with RAP (25/66, 38%) to that observed in patients who did not experience recurrence (71/200, 36%) (p = 0.76). None of these patients quit smoking after the first AP episode.

### 3.3. Risk of recurrence in biliary acute pancreatitis

Of the 125 patients with a first episode of ABP, cholecystectomy was performed before the end of the follow-up or before recurrence in 55 (44%). In 15 of them, endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy was also performed before surgery, during the first hospitalization because of common bile duct stones. In other 22 patients ERCP with biliary sphincterotomy was performed during the first hospitalization and remained the only treatment. In the majority of these 37 patients receiving ERCP (28/37, 76%) stones were confirmed and removed during the endoscopic procedure. Therefore, the remaining 48 patients (38.4%) did not receive any active treatment for their biliary aetiology. This was due to comorbidities or advanced age, patients' refusal or failure to provide a timely second hospitalization in the surgery Unit (Fig. 1).

The mean age of patients who received cholecystectomy was, indeed, lower compared to that of patients who did not (57 ± 14 vs 71 ± 15; p < 0.001).

Of the 28 patients with biliary RAP only 9 (32%) had received cholecystectomy after the first episode of AP, compared to 46 (47.4%) of the 97 who did not have recurrence, however this difference was not statistically significant (p = 0.19). The rate of recurrence in patients who received at least one type of treatment for their biliary aetiology (surgery or ERCP or both) was 13/77 (17%), being lower compared to the 15/48 (31%) observed in patients not receiving any active treatment, with borderline significance (p 0.07).

Among the different subgroups of patients with biliary AP, no patients who received cholecystectomy combined with ERCP (0/15, 0%) had a recurrence compared to 31% of patients who did not receive any treatment (15/48) (p = 0.01). The differences between the other subgroups are shown in Fig. 1.

Of the 125 patients with biliary AP, cholecystectomy was performed within 30 days from occurrence of AP in 21 cases (16.8%); interestingly, however, the rate of early (within 30 days) cholecystectomy was not different among patients with biliary AP who had a recurrence (5/28; 17.8%) and those who did not have recurrence (16/97; 16.4%; p = 1).

Considering the risk of recurrence during the time of follow-up, patients with biliary AP who did not receive cholecystectomy had a significantly shorter time of recurrence-free survival compared to patients who had cholecystectomy (mean of 75 months compared to not reached; p = 0.0383) (Fig. 2) with an hazard ratio of 0.45 (95% CI 0.21–0.95) confirming the protective effect of cholecystectomy.

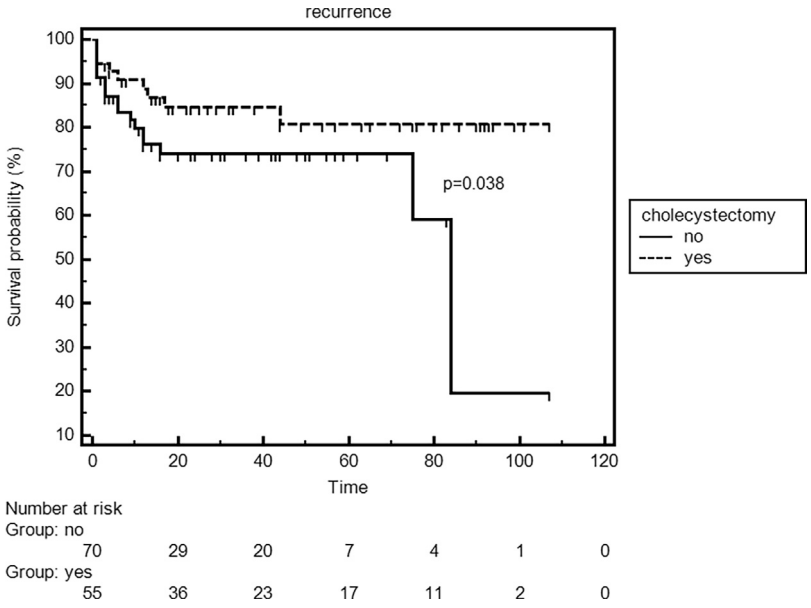


**Fig. 2.** Kaplan–Meier curve of recurrence-free survival in patients with biliary AP with and without cholecystectomy. Time is expressed in months. Patients with biliary AP who did not receive cholecystectomy had a significantly shorter time of recurrence-free survival compared to patients who had cholecystectomy (mean of 75 months compared to not reached; p = 0.0383) with an hazard ratio of 0.45 (95% CI 0.21–0.95) at Logrank test supporting a protective effect of cholecystectomy.

### *3.4. Risk of recurrence in acute pancreatitis due to other aetiologies*

Of the 41 patients with initial alcoholic AP, 17 (41%) quit drinking after the first episode. Of these patients only 1 had a RAP while the remaining 16 did not; the other 8 patients who had alcoholic RAP did not quit drinking (p = 0.05).

Five of the 9 patients with alcoholic RAP (55%) had more than two recurrent AP attacks. The alcoholic aetiology was associated with a borderline significant higher risk of having more than two RAP episodes compared to other aetiologies (OR 3.5; 95% CI 0.8–16; p 0.08).

On the other hand, patients with hypertriglyceridemic AP had a higher mean number of AP episodes compared to patients with all other aetiologies (3.6 ±3 vs 1.5 ± 1; p 0.008).

### *3.5. Occurrence of chronic pancreatitis*

During the follow-up, 22 of the 266 (8.3%) patients developed morphological and/or biochemical changes suggestive of definite chronic pancreatitis according to the M-ANNEHIM classification. The rate of chronic pancreatitis was not different among patients with RAP (6/66; 9%) and those without RAP (16/200; 8%).

## 4. Discussion

Recurrent acute pancreatitis (RAP) is a clinical condition characterized by repeated and separate episodes of acute pancreatitis without clinical, biochemical or radiological findings of chronic pancreatitis. Data investigating the rate and the factors associated with RAP after the first AP episode are limited to relatively small and retrospective studies.

Of an initial population of 337 consecutive patients with a diagnosis of AP, we report data on 266 patients with a first episode of AP and no sign of malignancy or of CP who were investigated in a mean follow-up of 42 months; 66 patients (25%) had RAP and the most frequent aetiology of recurrence was biliary. RAP was not associated with sex, age or severity of the first episode of AP. The rate of smokers did not differ between patients with or without RAP.

The observed rate of RAP is similar to the 20.4% reported by Cavestro et al. in a consecutive population of 196 Italian patients [15] and slightly higher than the 17% in a study conducted in the US [9]. Regarding the aetiology of the recurrent acute episodes, alcoholic aetiology was associated with a higher risk of having more than two episodes of acute pancreatitis compared with the other causes, while the mean number of acute episodes was higher in patients with hypertriglyceridemia. The 8% rate of CP diagnosed during the follow-up is also similar to that previously reported by others [15,18].

Intuitively, the rate of recurrence is associated with the lack of removal of the initial cause of the first AP episode.

As most cases of AP and RAP in the present study had a biliary aetiology, we focused our analysis on the treatment of BAP. Current guidelines recommend cholecystectomy as definitive treatment for BAP, that should be performed during the same hospitalization [1] or within 30 days from the first hospitalization [4].

A systematic review about the timing of cholecystectomy after an episode of mild biliary acute pancreatitis found a high rate of readmission (18%) in patients that had delayed cholecystectomy (after 40 days) [19]. However, in the present study, the rate of early (within 30 days) cholecystectomy was not different among patients with biliary AP who had a recurrence and those who did not (17.8% vs 16.4%; p = 1).

Another recent study confirmed that the risk of hospitalization for a new episode of biliary acute pancreatitis was higher when there was failure to adhere to the guideline recommendations, in particular when patients did not receive cholecystectomy [20].

In the present study, only 44% of patients received cholecystectomy after the first episode of biliary AP and 38% received no treatment (see Fig. 1). In our recurrence-free survival analysis, patients with biliary AP who did not receive cholecystectomy had a significantly shorter time of recurrence-free survival compared to patients who received cholecystectomy (see Fig. 2). The treatment of the biliary aetiology with cholecystectomy was associated with a reduced risk of recurrence with an hazard ratio of 0.45 (95% CI 0.21–0.95).

The observed low adherence to guidelines suggesting early cholecystectomy after BAP was somehow surprising, but is related to the real-world setting of the study, analysing consecutive

patients. In previous studies, the rate of the lack of treatment in biliary acute pancreatitis for whatever cause ranged between 20% and 31% [20,8,23]. In the present series, patients who did not receive cholecystectomy were older (mean age 71) and often had concurrent cardiovascular or respiratory comorbidities.

There are limited data investigating whether a combined endoscopic (ERCP and biliary sphinterectomy) and surgical treatment reduces the risk of biliary RAP. In a recent study by Lee et al., there was no significant difference in the rate of RAP between patients receiving cholecystectomy with or without combined endoscopic treatment [24].

In the present study, the subgroup of patients receiving a combined treatment both with surgery and ERCP had the lowest rate of recurrence (0% compared to 31% of patients who did not receive any treatment). Notably, the presently reported RAP rate of 16% after cholecystectomy is very similar to the 14% reported by Vipperla et al. [9]. The lack of significant risk reduction observed in patients receiving cholecystectomy only might be due to persistence or recurrence of stones in the common bile duct. As more accurate methods for detecting CBD stones, such as endoscopic ultrasound [25,26], become widely available, it is possible that more endoscopic treatments will be performed thus reducing the risk of biliary RAP.

The most recent EASL guidelines for the prevention, diagnosis and treatment of gallstones recommend cholecystectomy also in elderly patients and in those with high anaesthetic risk, although this recommendation is weak and with very low quality evidence [27]. However, postponing cholecystectomy after ERCP with sphincterotomy is considered a possibility in patients with biliary pancreatitis based on findings of a small RCT reported that ERCP with sphincterotomy was superior to conservative therapy in patients with high surgical risk [28]. Further studies examining the role of ERCP in reducing the risk of recurrent BAP are therefore needed. Overall, our results support the indication to perform at least ERCP as an active treatment for biliary AP if cholecystectomy is delayed. A conservative treatment seems to be not only associated with a higher risk of recurrence, but also with additional costs due to the new hospitalization. Previous studies have shown how the same-admission cholecystectomy is safe and can reduce the cost for managing biliary AP [21,22].

Some 15% of our patients had an alcoholic aetiology for their AP. Patients with an alcoholic aetiology had a low risk of recurrence if quitting drinking, but more often experienced multiple AP attacks if continuing alcohol consumption. Abstinence from alcohol after the first AP episode protects against RAP even in long-term follow-up, but is infrequently achieved. In a randomized controlled trial, Nordback et al. concluded that scheduled visits at 6-month intervals to a gastrointestinal outpatient clinic, including a repeated intervention against alcohol consumption, resulted in a lower recurrence rate of AP during a 2-year follow-up period than an initial intervention only during the hospitalization for the first alcohol-associated AP [29]. Similar results were obtained in another recent study with special focus on young patients that are at high risk for developing RAP and eventually CP and should be included in a more intense follow-up program [30].

For this reason, it is important to have a tight follow-up with supporting program in patients with an episode of alcoholic acute pancreatitis.

Finally, in the present study, patients with hypertriglyceridemia-induced AP had a higher number of recurrent episodes. Besides of secondary hypertriglyceridemia, a large amount of these patients are likely to be affected by hereditary lipid metabolism disorders. Previous studies have shown that patients with hypertriglyceridemia-induced AP had significantly more prior episodes of pancreatitis and more complications [31,32] compared to other aetiologies.

The present study has some strengths, such as the prospective design, the possibility to have follow-up data for a mean of 42 months, as the patients had access to a dedicated outpatients facility, and the relatively high number of evaluated patients compared to previous publications on this issue. However, there are limitations, such as the low compliance with recommendations in terms of early cholecystectomy in BAP patients. Moreover, although the rate of patients who were excluded because they did not adhere to the follow programme was relatively low as compared with previous studies, there is the possibility of a bias as these subjects might have had recurrence or treatments in other clinical Centres.

In conclusion, the present results underline the importance of an appropriate treatment of the initial aetiology in patients with AP and of careful discharge planning. Patients with BAP should receive early cholecystectomy, and possibly additional ERCP with biliary sphincterotomy might further reduce their risk of recurrence. An active approach to support alcohol withdrawal is mandatory in patients with alcoholic aetiology. More prospective studies and possibly randomized controlled trials are necessary to confirm these findings.

## Conflict of interest

None declared.

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