

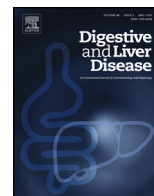


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Liver, Pancreas and Biliary Tract

# 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.

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## 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 conjugated bilirubin, alkaline phosphatase,  $\gamma$ -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 PO<sub>2</sub> <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 through 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.

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