


Recurrent acute pancreatitis is not uncommon in our clinical setting

La pancreatitis aguda recurrente no es infrecuente en la práctica clínica habitual

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ABSTRACT

Data on recurrent episodes of acute pancreatitis (RAP) are scarce. The aim of the study was to evaluate our rate of RAP and risks factors. This is a retrospective, single-center, study of consecutive patients admitted for AP and followed-up. Patients with more than one AP attack (RAP) were compared with patients with only a single AP episode (SAP). Clinical, demographic, outcome measures and severity were studied. 561 patients were included and follow-up over a mean 67.63 months' time. Our rate of RAP was 18,9%. Most patients suffered from only one episode of RAP (93%). Etiology of RAP episodes was mainly biliary (67%). On univariate analysis younger age (p 0.004), absence of high blood pressure (p 0.013) and absent of SIRS (p 0.022) were associated with recurrence of AP. On multivariate analysis only younger age was related to RAP (OR 1.015 95%IC 1.00-1.029). There were no statistical differences in outcome measures between both cohorts. RAP had a milder course in terms of severity (SAP 19% moderately severe/severe versus 9% in SAP). Almost 70% of the biliary RAP patients did not have a cholecystectomy performed. In this subset of patients, age OR 0.964 (95%IC 0.946-0.983), cholecystectomy OR 0.075 (95%IC 0.189-0.030) and cholecystectomy plus ERCP OR 0.190 (95%IC 0.219-0.055) were associated with absent of RAP. The rate of RAP in our series was 18,9%. Younger age was the only risk factor associated. Biliary etiology accounts for a large proportion of our RAP which could have been prevented with cholecystectomy or cholecystectomy plus ERCP.

Keywords: Pancreatitis; Recurrence; Cholecystectomy (source: MeSH NLM).

RESUMEN

La Pancreatitis Aguda Recurrente (PAR) es una entidad frecuente de la que hay pocos datos publicados. El objetivo del estudio es hallar la tasa y factores de riesgo asociados a PAR en nuestro medio. Es un estudio retrospectivo, unicéntrico, de pacientes ingresados por Pancreatitis Aguda (PA) y seguidos posteriormente. Se dividen en 2 grupos de pacientes: 1.- pacientes con un solo episodio de PA (PAS) y 2.- pacientes con más de un ingreso por PA (PAR). Se comparan variables clínicas, demográficas y de resultado. **Resultados:** 561 pacientes fueron incluidos y seguidos durante una media de 67,63 meses. 18,9% tuvieron al menos otro ingreso por PA. La mayoría sufrieron un solo episodio de PAR (93%). La etiología más frecuente fue biliar (67%). En el análisis univariado, una menor edad (p 0,004), la ausencia de hipertensión arterial (p 0,013) y de SIRS (p 0,022) se asociaron con PAR. En el análisis multivariado solo una menor edad se relacionó con PAR (OR 1,015, 95%, IC 1,00-1,029). No encontramos diferencias en las variables resultados entre ambos grupos. La PAR cursó de forma más leve (9% de pancreatitis moderada/graves o graves versus 19%). Casi un 70% de los pacientes con PAR biliar no tenían realizada una colecistectomía tras el ingreso índice. En este subgrupo de PAR, la edad OR 0,964 (95% IC 0,946-0,983), la colecistectomía OR 0,075 (95% IC 0,189-0,030) y la colecistectomía más colangiografía retrógrada OR 0,190 (95% IC 0,219-0,055) se asociaban a ausencia de PAR. **Conclusión:** Nuestra tasa de PAR fue 18,9%, con una menor edad como factor de riesgo. La etiología biliar fue la más frecuente que podría haberse evitado de haber realizado colecistectomía o colecistectomía más colangiografía retrógrada tras el primer ingreso.

Palabras clave: Pancreatitis; Recurrencia; Colecistectomía (fuente: DeCS Bireme).

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INTRODUCTION

Acute pancreatitis (AP) is the most common gastrointestinal hospital admission with an incidence of 4.6–100 per 100,000 cases in Europe. ⁽¹⁾ Recurrent episodes of acute pancreatitis (RAP) can occur in patients who survive their first admission. Although numerous studies have investigated AP, little research has been performed on the risk of recurrent episodes of AP and the reasons for readmissions after a first AP attack. ^(2,3,4) Repeated admissions for AP increase hospitalizations and costs; furthermore, RAP is the most important risk factor for progression to chronic pancreatitis with loss of exocrine and endocrine pancreatic functions and, ultimately, pancreatic cancer. ⁽⁵⁾

Moreover, patients who suffer from several bouts of AP have significantly impaired their health-related quality of life ⁽⁶⁾ as it has been assessed in quality of life (QOL) scales for RAP patients. ⁽⁷⁾ Consequently, investigate the course and risk factors for RAP would certainly reduce readmissions, decrease costs, and improve patient's quality of life.

Data available on the incidence of RAP and predictive factors are scarce and heterogeneous due to differences in study design, variability in follow-up, and no clear consensus in the definition of relapsing. ⁽⁸⁻¹¹⁾ In 2018, the American Pancreatic Association published an agreement document for definition and diagnosis of RAP ⁽¹²⁾ which, undoubtedly, will help researchers to contrast their investigations and allow data comparison among centers. The aim of the study is to assess, in our Institution, the rate of RAP and the clinical outcomes in a cohort of RAP patients. We also want to investigate the risk factors of readmissions after a sentinel attack of AP.

PATIENTS AND METHODS

Study subjects

Retrospective single-center study obtained from a prospectively maintained database on AP patients admitted to the Gastroenterology Department of the Hospital Clínico Universitario (Valladolid, Spain). Our hospital is a tertiary, academic center, which serves a population of around 250,000 inhabitants. Patients studied were admitted to hospital between March 2014 and December 2020 and they were followed up until May 2021. For our purpose, patients were assigned into two groups: patients with more than one AP admission (RAP) and patients with a single episode of acute pancreatitis (SAP). Time, reason, number of readmissions, clinical outcomes and severity of the episodes were registered for the patients with RAP.

Definitions

The diagnosis and severity of AP (mild, moderately severe and severe) was carried out according to the revised Atlanta Classification by the International Consensus of 2012. ⁽¹³⁾

RAP was defined following the International State-of-the-Science Conference Guidelines: a syndrome of multiple distinct acute inflammatory responses originating within the pancreas in individuals with genetic, environmental, traumatic, morphologic, metabolic, biologic, and/or other risk factors, who experienced 2 or more episodes of documented AP, separated by at least 3 months. ⁽¹²⁾

Exclusion criteria

The exclusion criteria were the following: 1.- Patients who did not sign the informed consent to be included in our database. 2.- Patient admission more than 5 days after the pain onset or patients referred from another hospital. 3.- Patients who could not be followed up. 4.- Patients who died in their first admission. 5.- Patients who suffered from chronic pancreatitis or pancreatic cancer.

Data collection

Clinical, demographic, analytical and radiologic data were recorded which included age sex, body mass index (BMI), Charlson Comorbidity Index, and smoking and alcoholic status on admission. High blood pressure (HBP), diabetes mellitus (DM), and dyslipidemia were also registered. Local pancreatic or peripancreatic complications (fluid or necrotic collections, pseudocyst and walled-off necrosis) were identified. The presence of single or multiple organ failure (respiratory, cardiovascular and renal) was registered according to the modified Marshall score system ⁽¹⁴⁾ and was defined as a score of 2 or more for one of those three organs. The etiology of the episode of SAP/RAP was attributed to: 1.- Gallstones (cholelithiasis or choledocholithiasis, or both, found by either transabdominal or endoscopic ultrasound, computer tomography CT, endoscope retrograde cholangiopancreatography ERCP, or magnetic resonance cholangiopancreatography MRCP), 2.- Alcohol (alcohol consumption of more than 80 g/d over the previous 5 years) 3.- Post-endoscopic retrograde cholangiopancreatography 4.- Other etiologies (hypertriglyceridemia, pancreatic cancer, chronic pancreatitis, drug-induced...) 5.- Idiopathic (no causative factor was identified).

Statistical analysis

Quantitative variables are presented with mean and standard deviation and qualitative variables according to their frequency distribution. The Kolmogorov-Smirnov test was used to check normality. Pearson's Chi-square test was used to analyze the association of qualitative variables. In cases where the number of cells with expected values less than 5 was greater than 20%, Fisher's exact test or the Likelihood Ratio test were used for variables with more than two categories. Comparisons of quantitative values were performed using Student's t-test for independent samples. Data were analyzed with IBM SPSS Statistics version 24.0 for Windows. Values of $p < 0.05$ were considered statistically significant.

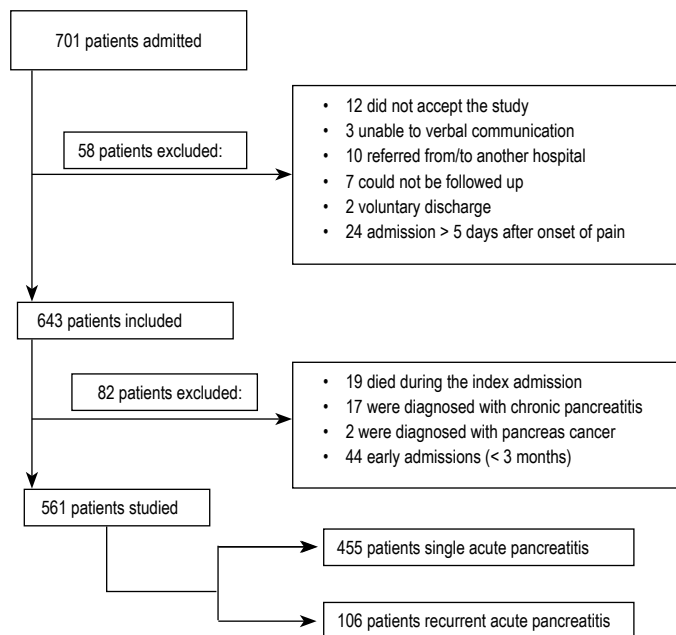


Figure 1. Patients flow-chart.

RESULTS

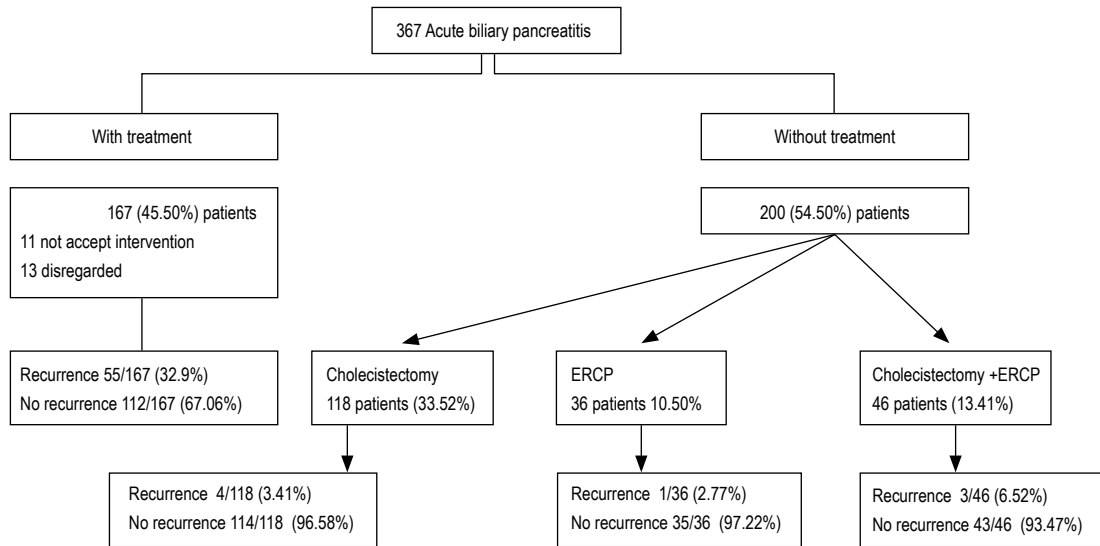
Over the time period considered, 701 admissions for AP were registered in our department. 561 patients were eventually enrolled in the study (Figure 1). 455 of them suffered from a single acute pancreatic event and 106 patients were admitted for two or more episodes of acute pancreatitis (18.9%). Table 1 shows data and outcome parameters of both cohorts.

A total of 154 episodes of RAP were registered. Patients with RAP were 57% females and 43% males, aged 64 ± 20 years. Mean follow-up was 67.63 months (95% IC 65.3-69.95). Most patients suffered from only one episode of RAP (93%); nine patients had 2 relapses, three patients suffered from 3 AP readmissions and four patients experienced 4 bouts of AP. The mean time for the first AP readmission was 10.25 months (95%IC 8.5-11.9), the

Table 1. Clinical data, demographics, etiology and clinical outcomes.

	Single acute pancreatitis	Recurrent acute pancreatitis	p
	N=455	N=106	
Age (m/sd)	70 ± 16	64 ± 20	0.004
Gender (Male/Female)	203/252	45/61	0.686
Alcohol intake (No/Yes /Former > 6 mo)	330/103/22	69/32/5	0.258
Smoking status (No/Yes /Former > 6 mo)	306/28/13	62/23/21	0.130
Etiology (biliar/alcohol/postERCP/others/idiopathic)	306/28/13/22/86	61/10/17/7/27	0.183
Charlson comorbidity index (≤2/ >2)	385/70	94/12	0.286
High blood pressure (no/yes)	200/253	61/45	0.013
Diabetes (no/yes)	381/72	96/10	0.091
Dislipemia (no/yes)	303/150	70/35	0.965
Body mass index (m/sd)	34.73±137.06	26.58±4.87	0.541
Length of hospital stay (m/sd)	8± 11	9 ± 11	0.577
SIRS (no/yes)	314/144	85/21	0.022
OUTCOMES			
ICU admission (no/yes)	449/6	105/1	1
Organ failure (no/yes)	411/44	101/5	0.104
Local complications (no/yes)	398/57	86/20	0.088
Endos/Surgery/Radiological intervention (no/yes)	442/13	100/6	0.356
Atlanta Classification (mild/ moderately severe-severe)	366/89	87/19	0.700

Table 2. Management of acute biliary pancreatitis after the first hospital admission.



shortest duration for recurrency was 3.5 months and the longest was 49 months. The etiology of AP did not differ among both cohorts; it was mainly biliary (67% SAP and 57.5% RAP), followed by unknown etiology (18.9% SAP and 25.5% RAP) (Figure 2). Length of hospital stay was similar in both cohorts. Severity, according to modified Atlanta

classification, was mild in most of patients who developed SAP and RAP (80,4% and 82%) (Table 1). Of the 154 bouts of RAP, only 15 episodes (9%) were classified as moderately severe/severe in comparison to 108 episodes (19%) in the index attack. 19 patients died in their first AP episode, while only 1 RAP patient died.

Table 3. Published studies on RAP.

Author/ Year	N	RAP definition	% RAP	Main etiology	Factors related	Follow-up (months)	Country
Cho 2019 ⁽³⁾	617	>3 months	16.2%	Alcohol 48% Biliary 31%	Local complications Male Aged < 60	40	Korea
Yu 2020 ⁽⁴⁾	522	>3 months	10.7%	HyperTg 44.6% Biliary 28,6%	Local complications Male Alcohol	36	China
Stigliano 2018	266	Early RAP < 30 days Late RAP > 30 days	25%	-	-	42	Italy
Gao 2006 ⁽⁹⁾	1471	-	10.7%	OH 20,4% Biliar 20,4% OH 57 %	-	-	China
Gullo 2002 ⁽⁶⁾	1068	-	27%	Biliar 25% Biliayr 62% Idiopathic 27%	Male Younger age	-	Europe
Zhang 2005 ⁽¹⁶⁾	245	Any time after clinical and analytical normalization	31.43%	-	Local complications	-	China
Vipperla 2014 ⁽¹¹⁾	127	Early RAP < 30 days Late RAP > 30 days	34%	-	Male Alcohol intake Local complications Severe disease	36	USA
Yadav 2014 ⁽⁵⁾	6010	> 30 days	21.9%	Alcohol	Younger age, Alcohol intake	39	USA
Takuma 2012 ⁽¹⁹⁾	381	>3 months	19%	Alcoholic 38% Idiopathic 26%	Younger age, Smokers	-	Japan
Bertilsson 2015 ⁽¹⁰⁾	1457	-	23%	-	Alcohol intake Organ failure Local complications	240	Sweden
Mallick 2018 ⁽²⁰⁾	724	> 2 months	12.7%	Biliary 32.6% Alcohol 30.4%	Younger age Male	192	India
Lee 2015 ⁽²¹⁾	294	< 2 months	-	Idiopathic	-	48	USA

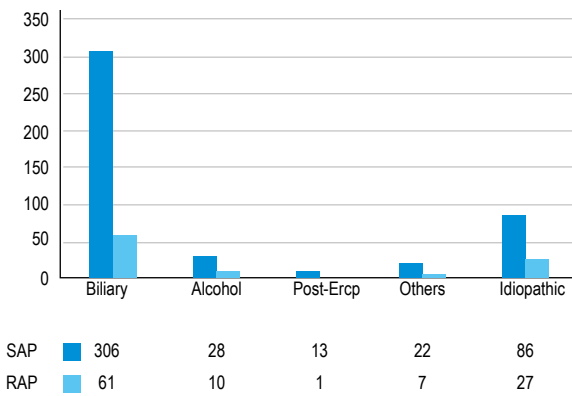


Figure 2. Etiology of pancreatitis in SAP and RAP patients.

Univariate analysis showed that younger age ($p\ 0.004$), absence of HBP ($p\ 0.013$) and no development of SIRS in the first AP attack ($p\ 0.022$) were associated with recurrence of AP. No differences were seen in terms of gender, alcohol and smoking status, BMI, comorbidities, diabetes and dislipemia. There were no statistical differences in relation to outcome measures such as organ failure, ICU admission or drainage of fluid collection and necrosectomy between both cohorts. We found that patients with local complications in their first bout of AP had a tendency to develop RAP ($p\ 0.088$) (Table 1). On multivariate analysis younger age was the only single factor related to recurrent episodes of acute pancreatitis (OR 1.015 95% IC 1.00-1.029)

Focusing on the most frequent etiology of RAP which in our series was gallstones (63/106 patients) we analyzed how these patients were managed after their first hospitalization for AP. Forty-four (69,8%) patients did not have a cholecystectomy performed after their first gallstone AP admission. Eight (12%) patients had received a cholecystectomy, one patient ERCP and three patients had cholecystectomy plus biliary sphincterotomy performed at the end of the follow-up period or before recurrence. Five patients did not accept surgical intervention, and two patients were disregarded for surgery due to comorbidities. Table 2 shows management of acute biliary pancreatitis.

When we performed a comparison between both cohorts (SAP and RAP of biliary etiology) including demographic, clinical, analytical and outcome parameters, univariate analysis showed that older age ($p\ 0.017$), previous cholecystectomy ($p < 0.0001$) or cholecystectomy plus biliary sphincterotomy performed ($p < 0.0001$) were statistically associated with absent of recurrent biliary pancreatitis which were confirmed on multivariate analysis: age OR 0.964 (95%IC 0.946-0.983), cholecystectomy OR 0.075 (95%IC 0.189-0.030) and ERCP+ cholecystectomy OR 0.190 (95%IC 0.219-0.055)

DISCUSSION

In our research, clinical, demographic, etiology and outcome parameters in patients with RAP were studied, and figures were compared with SAP patients.

The term "recurrent acute pancreatitis" was first described in medical literature in 1948,⁽¹⁶⁾ and was accepted during the Marseille symposium in 1963.⁽¹⁷⁾ However, in clinical practice, there has been much ambiguity over the years on the definition of RAP. It was not until 2018, when the International State-of-the-Science Conference established uniform diagnostic, management and definition of RAP by consensus. RAP was therefore considered as 2 or more well-documented separate attacks of AP, with complete resolution for more than 3 months between attacks⁽¹²⁾. It is regarded that abdominal pain or elevation of pancreatic enzymes within three months can be attributed to a complication of the first AP episode, rather than a new bout of AP.

There is a lack of research on RAP in literature; however, it deserves especial dedication. Repeated attacks of AP lead to pancreatic fibrosis, chronic pancreatitis and, in the long run, can derive in the development of pancreatic cancer.⁽⁵⁾ Moreover, the impact of recurrent bouts of AP, even in the absence of overt chronic pancreatitis, reduces physical and mental quality of life.⁽⁷⁾ Change in dietary habits, helplessness, anxiety and fear to suffer another attack, are frequent feelings in these patients.⁽⁶⁾

Figures published on RAP are conflicting, with frequencies ranging from 10% to 30%^(4,11,19,20). In contrast to our research, some of the previous studies do not clearly defined the diagnostic criteria for RAP⁽⁸⁻¹⁰⁾ or do not followed the international consensus guidelines^(5,11,18,20) (Table 3). Our rate of RAP, according to the standard definition was 18,9%, like data from the publications^(3,19) that also follow the American Pancreatic Association recommendations⁽¹²⁾. More than half of our RAP were of biliary etiology (57.5%), resembling data reported from Zhang *et al.*⁽¹⁸⁾ and Mallick *et al.*⁽²⁰⁾

Unlike some other studies^(5, 8), alcohol etiology did not represent a great proportion of RAP in our series (9%); it may be because patients diagnosed with chronic pancreatitis, where alcohol is the main culprit, were excluded from the follow-up. According to several previous research^(5,8,19,20) our data also show that younger age is a risk factor of readmission (OR 1.015 95%IC 1.00-1.029) both in global RAP and in biliary RAP. Vipperla *et al.*⁽¹¹⁾ in USA, and Gullo *et al.*⁽⁸⁾ in a multicenter European study evidenced a male predominance in RAP patients which was not observed in our cohort. In terms of the outcome measures, we found a slight tendency to have RAP when local complications were developed at the first AP episode ($p\ 0,088$); nevertheless, there were no differences in terms of length of hospitalization, UCI admission, organ failure, drainage of collections/necrosectomy, and severity. In contrast, Vipperla *et al.*⁽¹¹⁾ noticed that readmission was

higher in patients who developed local complications and more severe course at index admission; however, their study included patients readmitted less than one month after discharge. In such a short period of time, a new admission could be considered the same attack, rather than a second episode. Bertilsson *et al.* ⁽¹⁰⁾ also mention that an increased first attack severity was associated with an increased frequency of RAP in all etiology groups; however, a clear definition of RAP is not referred in their text.

An issue of great concern is whether RAP episodes have a worse prognosis than the index attack. In the study by Lee *et al.* ⁽²¹⁾ specially designed for this purpose, it was clearly demonstrated that severe outcomes are less frequent in RAP bouts. The researchers claim that a former AP episode is protective against organ failure, intensive care admission, and mortality in the second episode. The authors state that previous acinar necrosis produces a decrease in pancreatic cells with less auto digestion, necrosis and inflammatory response in subsequent attacks. Our results are alike, RAP bouts had milder disease course and less mortality when compared to the index episode of AP. In contrast to some other studies ^(4,10) where alcohol intake and smoking status were related to RAP episodes, in our series, this association was not found. Currently, there are little research on blood pressure in relation to AP and RAP. Yu *et al.* ⁽⁴⁾ did not find association between hypertension and RAP, as could be expected. In our cohort, on univariate analysis hypertension was a protective factor against RAP which could not be found on multivariate analyses.

Special attention must be given to biliary pancreatitis which accounts for more than half of our RAP cases. Gallstones are the leading cause of AP, and cholecystectomy must be performed after the first AP episode. In our series, cholecystectomy alone and/or cholecystectomy plus ERCP were associated with a reduced risk of pancreatitis recurrence (Figure 2). Several societies, including American Gastroenterology Association (AGA) guidelines, strongly recommend cholecystectomy during the index admission ⁽²²⁾ or at least within 2-4 weeks after discharge for mild acute pancreatitis ⁽²³⁾. It is well established that non-adherence to the guidelines results in subsequent AP readmissions ⁽²⁴⁾. Despite the recommendations, in our clinical setting, as in some other reports ⁽²⁾, we observed a low adherence to guidelines in routine clinical practice; almost 70% of our cohort did not had an early cholecystectomy performed.

The strengths of our study are several: Firstly, we defined RAP according to the state-of-art conference recommendations and early readmissions were excluded; secondly, we presented a large cohort of patients followed over a long period of time, and, finally, patients diagnosed with chronic pancreatitis, with different natural course of the disease, were excluded. However, limitations warrant mention: our database is a prospective one. We performed a retrospective design, which could have led to bias in follow-up. RAP patients admitted at another institution or patients attending only at emergency room without hospitalization, were not considered. Finally, we did

not have genetic analysis or performed Oddi sphincter dysfunction tests or microscopic bile crystals detection to better classify idiopathic RAP (25% in our cohort)

In conclusion, our study demonstrates that RAP is a common clinical issue. Younger age was the strongest risk factor for RAP development in our research. Fortunately, repeated episodes of AP have a lower mortality rate and do not follow a more severe course than the index episode. In our series, gallstone accounts for more than half of our RAP. Management of acute biliary pancreatitis in our hospital merits a special mention, as consensus guidelines on early cholecystectomy are not particularly followed. Therefore, we have an important area of improvement in our clinical practice. Adherence to clinical guidelines must be implemented and the results in terms of improving our RAP data should be hence reassessed.

Ethical Considerations: The study was approved by the Research and Ethical Board of our institution (CEIC PI-19-1335). The research is reported following the Strengthening reporting of observational studies epidemiology (STROBE) statement for observational studies ⁽¹⁵⁾. Participants provided signed informed consent to be included in our database. All data were coded.

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Author Contribution:

Ruiz-Rebollo ML: Conception and study design, drafting the article, revising the article critically, final approval of the version to be published.

Muñoz-Moreno MF: Statistical analysis, final approval of the version to be published.

Busta-Nistal R: Acquisition of data, drafting part of the article, final approval of the version to be published.

Rizzo-Rodriguez MA: Acquisition of data, drafting part of the article, final approval of the version to be published.

Izquierdo Santervás S: Acquisition of data, drafting part of the article, final approval of the version to be published.

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