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Endoscopic ultrasound as a diagnostic and predictive tool in idiopathic acute pancreatitis

Francisco Valverde-López[a], Eva Julissa Ortega-Suazo[a], Charles Mel Wilcox[b], Maria Carmen Fernandez- Cano[a], Juan Gabriel Martínez-Cara[a], Eduardo Redondo-Cerezo[a]

"Virgen de las Nieves" University Hospital, Complejo Hospitalario Universitario de Granada, Granada, Spain; University of Alabama at Birmingham, USA

Abstract

Background Endoscopic ultrasound (EUS) is useful in the diagnostic workup of idiopathic acute pancreatitis but its role as a predictor of recurrence has not been thoroughly assessed. Our aim was to study the performance of EUS in idiopathic acute pancreatitis, its impact on the natural history of the disease, and the factors related to recurrence.

Methods Patients with idiopathic acute pancreatitis referred to our endoscopy unit were enrolled and followed, with assessment of the performance of endoscopic retrograde cholangiopancreatography (ERCP), cholecystectomy, and the incidence of recurrence. EUS findings and recurrence rates were compared between patients with a first episode or recurrent attacks and in patients with previous cholecystectomy versus those with gallbladder *in situ*.

Results One hundred six patients were included (mean follow up: 53.59±27.79 months). Biliary disease related to stones was the most common finding on EUS (49.1%), and patients referred for recurrent attacks showed the highest recurrence rate during follow up (57.1%). ERCP or cholecystectomy reduced recurrences to 14.3% in patients with biliary disease. Age under 65 (odds ratio [OR] 3.56, 95% confidence interval [CI] 1.21-10.44; P=0.02), previous cholecystectomy (OR 3.19, 95%CI 1.11-9.17; P=0.03), and no lithiasis on EUS (OR 2.87, 95%CI 1.04-7.87; P=0.04) were independent risks factors for recurrence.

Conclusions EUS-directed ERCP/cholecystectomy was associated with lower relapse rates in idiopathic acute pancreatitis. Along with age and gallbladder status, it provides predictive information about recurrence likelihood.

Keywords Endosonography, pancreatitis, recurrence

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[a]Department of Gastroenterology and Hepatology, "Virgen de las Nieves" University Hospital, Complejo Hospitalario Universitario de Granada, Granada, Spain (Francisco Valverde-López, Eva Julissa Ortega-Suazo, Maria Carmen Fernandez-Cano, Juan Gabriel Martínez-Cara, Eduardo Redondo-Cerezo); [b]Division of Gastroenterology and Hepatology and Pancreaticobiliary Center, University of Alabama at Birmingham, USA (Charles Mel Wilcox)

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Correspondence to: Francisco Valverde-López, MD, Endoscopy Unit, Gastroenterology and Hepatology Department, Virgen de las Nieves University Hospital, Avenida de las Fuerzas Armadas 2, 18014-Granada, Spain, e-mail: fcovalverde89@gmail.com

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Introduction

Acute pancreatitis (AP) is nowadays the most common cause of hospitalization in the United States [1] and has an incidence between 4.6 and 100 per 100,000 population in European countries [2]. Although it can be caused by many different conditions, it is well known that alcohol and gallstone disease are the primary causes, accounting for more than two thirds of the cases of AP worldwide [3,4]. After a basic clinical workup, an etiology can be established after an acute episode in the majority of patients, but in up to 10-30% of cases, the cause is not found despite a clinical history, laboratory tests (triglyceride and calcium concentrations) and conventional cross-sectional imaging, such as transabdominal ultrasound and computed tomography (CT) [5,6]. While idiopathic AP

(IAP) is usually diagnosed in these cases, a cause may be found after endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP). When a thorough study is done and an etiology is not found, we are facing a true IAP [5]. However, establishing an etiology is essential in AP management, since further therapies such as cholecystectomy or social support can avoid new episodes of AP, with their associated morbidity and mortality [7,8].

Regarding biliary AP, it has been suggested than microlithiasis (defined as stones of less than 3 mm) [9] could explain up to 75% of patients with IAP and an intact gallbladder, and can be undetected by transabdominal ultrasound [10]. In this setting, EUS has shown a high diagnostic accuracy for biliary disease such as cholelithiasis, biliary sludge (defined as a suspension of crystals, mucin, glycoproteins, cellular debris, and proteinaceous material within bile [11]) and choledocholithiasis, and it is more accurate than MRCP in detecting microlithiasis with stones of less than 5 mm [12]. Indeed, EUS has become an important tool in patients with IAP and an intact gallbladder, but its yield is lower in patients with prior cholecystectomy [13], while findings in patients with a single episode are different to those in patients with multiple attacks, a condition also known as recurrent IAP (RIAP) [13]. In the most cited studies in this field, data about further interventions depending on EUS findings, or long-term follow ups for relapse detection, are lacking [14,15]. Furthermore, echoendoscope image quality has significantly improved and, in more recent studies, it has shown better results than in earlier series [16]. Moreover, new criteria for chronic pancreatitis have been developed [17], so that the current diagnostic yield of EUS in the evaluation of IAP may have improved.

The aims of our study were, first, to describe the diagnostic yield of EUS in patients with an initial episode of IAP in comparison with those with RIAP, as well as in patients with previous cholecystectomy compared to those with an intact gallbladder. A second aim was to determine whether there is a relationship between some clinical factors, EUS findings and the rates of recurrence, especially when the procedure is followed by endoscopic retrograde cholangiopancreatography (ERCP), cholecystectomy, or both.

Patients and methods

Data collection

This retrospective study was performed in Virgen de las Nieves University Hospital, a tertiary referral hospital. Patients with a first episode of IAP or RIAP referred to the endoscopy unit for EUS were included. Data including sex, age, history of smoking and alcohol consumption, and liver enzyme abnormalities during admission in the index episode were collected. Triglyceride levels were assessed after discharge. Results regarding cholecystectomy, MRCP or ERCP performance were collected. ERCP and sphincterotomy was performed if biliary sludge or biliary duct stones were found in a previous EUS, whereas patients underwent a cholecystectomy if microlithiasis or biliary sludge was identified in the gallbladder. Chart review was used to determine long-term outcomes.

Definitions

Diagnosis of AP was made when 2 of 3 of the following criteria were met [6]: abdominal pain consistent with pancreatitis; increased serum amylase or lipase levels, by at least 3 times the upper normal limit; and characteristic findings on abdominal imaging (ultrasonography and/or computed tomographic scan). IAP was defined as the development of an episode of AP with normal clinical, laboratory and conventional imaging studies reported by radiologists specifically focused on abdominal disease (transabdominal ultrasound or CT scan) [6]. Alcohol consumption of more than 50g for more than 5 years and hypertriglyceridemia of more than 1000 mg/dL and hypercalcemia were ruled out to establish the diagnosis of IAP, following the recommendation of the American College of Gastroenterology (ACG) guideline [6]. RIAP was defined as at least 2 well documented episodes of IAP, with clinical normality between each episode and no signs of chronic pancreatitis [18]. When assessing EUS findings, a biliary etiology was considered if microlithiasis, gallbladder stones, bile duct stones or biliary sludge was observed (since it has been proven that biliary sludge can contain microlithiasis [19]). For assessment of chronic pancreatitis (CP), the Rosemont criteria were routinely followed [20]. Recurrence was defined as one or more new episodes of AP during follow up.

EUS results were considered diagnostic if they found a biliary etiology related to stones, leading to ERCP or cholecystectomy, or when they found criteria for CP, as well as other potentially causative conditions such as *pancreas divisum*, cystic pancreatic neoplasms, or periampullary masses.

EUS

As a general rule, EUS was performed one month after the patient's discharge following the index episode of AP. Every EUS procedure was performed by 2 experienced ultrasonographers (ERC, JGMC), who perform more than 300 procedures per year. Linear and radial echoendoscopes were used (UCT-GF180-AL5; UCT-GF160-AL5, Olympus, Japan). Every patient received propofol sedation guided by the endoscopist and by a trained nurse. A systematic EUS evaluation was performed in each patient. Biliary tract, pancreas and gallbladder, when present, were thoroughly examined. Biliary sludge was sonographically defined as mobile, low-amplitude echoes in the lumen that layered in the dependent portion of the gallbladder or bile duct, not associated with shadowing [11].

Ethics

The ethical committee for clinical research of Virgen de las Nieves University Hospital approved the protocol and the

database of our study on January 26, 2011. Every patient gave signed informed consent to each procedure and to inclusion in the database. The whole protocol was in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Statistical analysis

Statistical analysis was carried out using the software PAWS Statistics 17.0 (SPSS Inc., Chicago, IL, USA). Comparisons of baseline characteristics such as age, sex, smoking status, recurrence, EUS findings, MRCP and ERCP when performed, were made first between patients with a first episode of AP and RIAP and then between patients with and without a previous cholecystectomy. Fisher's exact test, chi-square test or Student's *t*-test were performed as appropriate and differences were considered statistically significant if P<0.05. Finally, binary logistic regression was used to assess predictive factors of recurrence, with the results being expressed as odds ratio (OR) and 95% confidence interval (CI).

Results

Data from all the patients included (EUS referrals with IAP as the main indication) from January 2010 until January 2017 were collected. Patients were followed up until May 2018. After the exclusion criteria were applied, 106 patients with IAP were included. A first episode of IAP was the leading indication for EUS in 78 patients (73.5%), whereas RIAP was the reason for study in 28 patients (26.5%). When classified by gallbladder status at the time of EUS, 28 patients (26.5%) had previous cholecystectomy, whereas 78 (73.5%) had an intact gallbladder. Results of EUS and recurrences were compared first according to the main indication (first episode of IAP vs. RIAP), and then according to gallbladder status.

First episode IAP vs. RIAP

Characteristics of patients based on the indication for EUS (first episode or RIAP) are shown in Table 1. Patients with a first attack of IAP had an intact gallbladder more often than patients with RIAP, but there were no differences in cholecystectomy rates between the 2 groups (56.3% vs. 50%). ERCP was performed more often in patients with RIAP than in those with a first episode of IAP (42.9% vs. 9.1%; P<0.001). Regarding EUS, biliary findings were the most common finding in patients with a first episode of IAP (51.1%), whereas in patients with RIAP biliary disease and CP were jointly the most common (each 32.1%). Biliary disease (Fig. 1) was more prevalent in patients with a first episode of IAP than in patients with RIAP (51.1% vs. 32.1%; P=0.04) whereas findings suggestive of CP were more common in RIAP (32.1% vs. 6.4%; P=0.01). However, the diagnostic yield of EUS did not differ between the groups. Sixteen patients with RIAP had a recurrence after the index episode, compared with 13 patients with a first episode of IAP (57.1% vs. 16.7%; P<0.0001).

Intact gallbladder vs. previous cholecystectomy

A description of our population based on the presence or absence of prior cholecystectomy is depicted in Table 2. When EUS findings were assessed, biliary disease was more prevalent in the group of patients with a gallbladder than in those who had undergone cholecystectomy (59% vs. 21.4%; P=0.01), whereas findings suggestive of CP (Fig. 2) were more prevalent in patients with a previous cholecystectomy (28.6% vs. 7.7%; P=0.01). Diagnostic yield was better in patients with a gallbladder, although this difference was not statistically significant (71.8% vs. 53.7%; P=0.07). We observed higher ERCP performance in the cholecystectomy group (35.7% vs. 11.7%; P=0.05), but biliary sludge or cholelithiasis were more prevalent in patients without a previous cholecystectomy.

Figure 1 Endoscopic ultrasound showing gallbladder microlithiasis

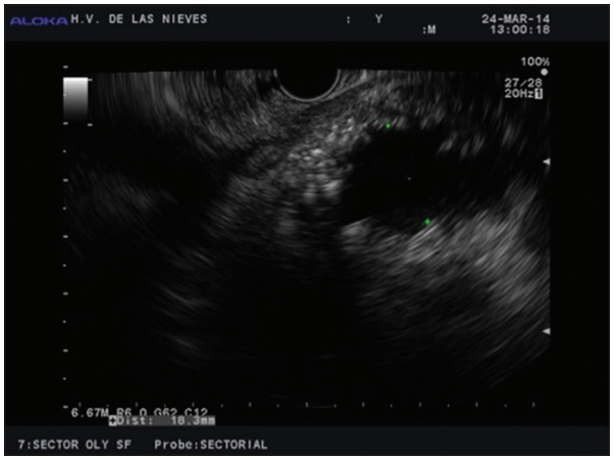

Figure 2 Endoscopic ultrasound showing chronic pancreatitis with a dilated pancreatic duct

Table 1 EUS findings and patients' characteristics (first episode of AP vs. RIAP)

Characteristics	Total	First attack of AP	RIAP	P
N, (%)	106	78 (73.5)	28 (26.5)	
Age, (mean±SD)	56.4±17-66	57.09±17.23	54.46±19	n.s.
Male, n (%)	52 (50)	40 (51.3)	12 (42.9)	n.s.
ASA I-II, n (%)	86 (84.4)	63 (80.8)	23 (82.2)	n.s.
Smoker/previous smoker, n (%)	37 (34.9)	27 (34.6)	10 (35.7)	n.s.
Gallbladder *in situ*, n (%)	78 (73.6)	66 (84.6)	12 (42.9)	<0.001
EUS Findings				
Normal or incomplete	24 (22.6)	20 (25.6)	4 (14.3)	n.s.
Biliary	52 (49.1)	43 (51.1)	9 (32.1)	0.04
Suggestive of CP (Rosemont), n (%)	14 (13.2)	5 (6.4)	9 (32.1)	0.01
Pancreatic mass, n (%)	2 (1.9)	1 (1.3)	1 (3.6)	-
Suggestive of CPN, n (%)	3 (2.8)	1 (1.3)	2 (7.1)	-
Congenital anomalies, n(%)	2 (1.9)	0 (0)	2 (7.1)	-
Other	9 (8.5)	8 (10.2)	1 (3.6)	-
EUS diagnostic yield	71 (67)	51 (65.4)	20 (71.4)	n.s.
MRCP, n (%)	38 (35.8)	21 (26.9)	17 (63)	0.01
MRCP findings				
Normal	22 (56.4)	15 (68.2)	7 (41.2)	n.s.
Congenital anomalies	7 (19.9)	3 (13.6)	4 (23.5)	-
Suggestive of CPN, n (%)	6 (15.4)	3 (13.6)	3 (17.6)	-
Suggestive of CP, n (%)	2 (5.1)	0 (0)	2 (11.8)	-
Other	2 (5.1)	1 (4.5)	1 (5.6)	-
ERCP	19 (18.1)	7 (9.1)	12 (42.9)	<0.001
ERCP Findings				
Normal, n (%)	5 (26.3)	3 (42.9)	2 (16.7)	-
Biliary Sludge /Choledocholithiasis, n (%)	7 (36.8)	2 (28.6)	5 (41.7)	-
Suggestive of CP, n (%)	1 (5.3)	0 (0)	1 (8.3)	-
Other, n (%)	6 (31.6)	2 (28.6)	4 (33.3)	-
Cholecystectomy, n (%)	43 (55.1)	36 (56.3)	7 (50)	n.s.
Elevated ALT/ALP, n (%)	49 (46.2)	39 (50)	10 (37)	n.s.
Recurrence during follow up	29 (27.4)	13 (16.7)	16 (57.1)	<0.001
Follow up in months (mean±SD)	53.59±27.79	54.23±22.11	51.82±24.9	n.s.

AP, acute pancreatitis; RIAP, recurrent idiopathic acute pancreatitis; ASA, American Society of Anesthesiologists (physical status); EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; CP, chronic pancreatitis; CPN, cyst pancreatic neoplasm; ERCP, endoscopic retrograde cholangiopancreatography; ALT, alanine transaminase; ALP, alkaline phosphatase

Recurrence rates were also higher in patients with a previous cholecystectomy (46.4% vs. 20.5%; P=0.08).

Recurrence rate based on EUS findings and further interventions

ERCP or cholecystectomy was performed in 42 patients after biliary stones or sludge were found on EUS, with an overall recurrence rate of 14.3%. This was a lower rate than in the individuals with non-biliary findings on EUS in which follow up was performed (32.5%); these differences were statistically significant (P=0.05). Results depending on the indication for EUS are detailed in Table 3.

Factors associated with recurrence

The relation of patients' characteristics and EUS findings to recurrence was assessed. We found that normal alanine

Table 2 EUS findings and patients' characteristics (gallbladder *in situ* vs. previous cholecystectomy)

Characteristics	Total	Gallbladder *in situ*	Cholecystectomy	P
N, (%)	106	78 (73.5)	28 (26.5)	
Age, (mean±SD)	56.4±17.66	55.18±17.33	59.79±18.47	n.s.
Male, n (%)	52 (50)	38 (48.7)	14 (51.9)	n.s.
ASA I-II, n (%)	86 (84.4)	62 (83.8)	24 (85.7)	n.s.
Smoker/previous smoker, n (%)	37 (34.9)	30 (39)	7 (25)	n.s.
EUS Findings				
Normal or incomplete	24 (22.6)	17 (21.8)	7 (25)	n.s.
Biliary tract disease	52 (49.1)	46 (59)	6 (21.4)	0.01
Suggestive of CP (Rosemont), n (%)	14 (13.2)	6 (7.7)	8 (28.6)	0.01
Pancreatic mass, n (%)	2 (1.9)	0 (0)	2 (7.1)	-
Suggestive of CPN, n (%)	3 (2.8)	3 (3.8)	0 (0)	-
Congenital anomalies, n (%)	2 (1.9)	1 (1.3)	1 (3.6)	-
Other	9 (8.5)	5 (6.4)	4 (14.3)	-
EUS Diagnostic yield	71 (67)	56 (71.8)	15 (53.7)	0.07
MRCP, n (%)	38 (35.8)	24 (31.2)	14 (50)	0.07
MRCP Findings				
Normal	22 (56.4)	16 (64)	6 (42.9)	n.s.
Congenital anomalies	7 (19.9)	4 (16)	3 (21.4)	-
Suggestive of CPN, n (%)	6 (15.4)	4 (16)	2 (14.3)	-
Suggestive of CP, n (%)	2 (5.1)	1 (4)	1 (7.1)	-
Other	2 (5.1)	0 (0)	2 (14.3)	-
ERCP	19 (18.1)	9 (11.7)	10 (35.7)	0.05
ERCP Findings				
Normal, n (%)	5 (26.3)	2 (22.2)	3 (30)	-
Biliary sludge/Choledocholithiasis, n (%)	7 (36.8)	5 (55.6)	2 (20)	-
Suggestive of CP, n (%)	1 (5.3)	1 (11.1)	0 (0)	-
Other, n (%)	6 (31.6)	1 (11.1)	5 (50)	-
Elevated ALT/ALP, n (%)	49 (46.2)	34 (43.6)	15 (55.6)	n.s.
Recurrence during follow up	29 (27.4)	16 (20.5)	13 (46.4)	0.08
Follow up in months (mean±SD)	53.59± 27.79	54.54±21.86	50.96±25.44	n.s.

ASA, American Society of Anesthesiologists (physical status); EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; CP, chronic pancreatitis; CPN, cyst pancreatic neoplasm; ERCP, endoscopic retrograde cholangiopancreatography; ALT, alanine transaminase; ALP, alkaline phosphatase

transaminase (ALT) or alkaline phosphatase (ALP) at the time of admission, previous cholecystectomy and findings other than lithiasis on EUS increased the probability of having a new episode of AP (P=0.04, P<0.01 and P<0.01, respectively). In addition, patients aged below 65 years showed higher recurrence rates than older patients, with differences that almost reached significance (P=0.06). Results are shown in Table 4.

When logistic regression was performed, we found that age under 65 years old (OR 3.56, 95%CI 1.21-10.44; P=0.02), previous cholecystectomy (OR 3.19, 95%CI 1.11- 9.17; P=0.03) and findings other than lithiasis, in either the gallbladder or the common bile duct, on EUS (OR 2.87, 95%CI 1.04-7.87; P=0.04) were all independent risk factors for recurrence.

Discussion

Our study evaluated the diagnostic yield of EUS, describing the most common findings and comparing patients with either a first episode of AP or RIAP, but also patients with an intact gallbladder or a previous cholecystectomy, assessing further interventions during follow up and the recurrence rates of these different patient profiles. Furthermore, it demonstrated the ability of EUS to detect potential causes of AP that can be managed by means of ERCP or cholecystectomy, changing the patient's natural history by minimizing recurrences. We also looked for both endosonographic and clinical factors that might identify patients with a high probability of recurrences.

Table 3 Recurrence rate in patients with biliary findings related to lithiasis on EUS in which an ERCP or cholecystectomy was performed and in patients with non-biliary findings on EUS and follow up

Recurrence	Total	EUS lithiasis + Cholecystectomy and/or ERCP	EUS non-lithiasis Follow up	P
First episode IAP	63	34	29	
Recurrence, n (%)		4 (11.8)	7 (24.1)	0.3
Recurrent IAP	19	8	11	0.35
Recurrence, n (%)		2 (25)	6 (54.5)	
Total	82	42	40	
Recurrence, n (%)		6 (14.3)	13 (32.5)	0.05
Follow up in months (mean ± SD)		52.71 ± 21.42	57.58 ± 26.14	0.35

IAP, idiopathic acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound

Table 4 Factors associated with recurrence

Factors	Total	Recurrence	No recurrence	P
N	106	29 (27.4)	77 (72.6)	
Normal ALT/ALP, n (%)	56	20 (68.9)	36 (46.7)	0.04
Male sex, n (%)	52	16 (55.1)	36 (46.75)	n.s.
No lithiasis findings in EUS, n (%)	54	21 (72.4)	33 (42.8)	<0.01
Age <65, n (%)	65	22 (75.8)	43 (55.8)	0.06
Current or previous smoker, n (%)	37 (3.1)	10 (34.4)	27 (35)	n.s.
Previous cholecystectomy, n (%)	28 (4.9)	13 (44.8)	15 (19.4)	<0.01

ALT, alanine transaminase; ALP, alkaline phosphatase

Indeed, we found that biliary tract disease, particularly when related to stones, was the most common finding on EUS in patients with a first episode of AP (51.1%), with a more usual diagnosis of CP in the RIAP group, being significantly higher than in patients with a single episode (32.1% vs. 6.4%; P=0.01). Regarding gallbladder status, we found that biliary tract disease was significantly more prevalent in patients with a gallbladder, whereas rates of CP were higher in patients with a previous cholecystectomy. A higher proportion of intact gallbladder was found in patients with a first episode of AP (84.6% vs. 42.9%; P<0.001), which could explain the higher rate of biliary findings related to stones in these patients. Yusoff *et al*, in 2004, performed one of the largest studies of IAP in 340 patients. They found that CP was the most common finding on EUS, although the only criterion established by the authors to avoid alcoholic pancreatitis was the absence of binge alcohol consumption within 14 days prior to the index episode [14]. The ACG guideline for the management of AP in 2013 established that consumption of >50 g of alcohol per day for at least 5 years is required to define an alcoholic etiology, so patients with previous or current significant alcohol consumption may have been included in this study and, therefore, the occurrence of CP may have been higher [6]. Our results show biliary tract disease as the most common finding on EUS (49.1%), consistent with a previous systematic review that found very similar rates of biliary tract disease to ours (41%) [13]. The study of Rana *et al* also found biliary tract disease to be the most common finding in patients with a negative initial study for IAP (50%), especially when due to findings in the gallbladder [21]. In our study, only 19 patients underwent ERCP, more frequent in patients with RIAP (42.9% vs. 9.1%), although few conclusions about these findings can be drawn because of the small sample size. The performance of more diagnostic and therapeutic procedures in patients with RIAP, due to the recurrent nature of this condition, was determined by a lower threshold for their indication by clinicians, as well as a higher patient acceptance of those medical interventions, longing as they were for improvements in their quality of life. This could be an alternative explanation for this finding, but greater sample sizes are needed to address the real impact of ERCP on both groups.

The diagnostic yield of EUS did not differ between patients with single or multiple episodes (65.4% vs. 71.4%), as has already been described in many other studies [13,14,22]. However, we found a better diagnostic yield in patients with an intact gallbladder compared to those who had a prior cholecystectomy, with differences that almost reached statistical significance, as has also been previously described [23-25]. Considering relapsing AP, we found an overall recurrence of 27.4%, with the highest proportion in patients with multiple attacks (57.1%) and in patients with a previous cholecystectomy (46.4%). These results are similar to those of previous studies, which found relapsing rates of 11-32% after a first episode when the cause was not identified and treated [26,27], and in which recurrence rates were higher in patients with multiple attacks than in those with a single episode [28]. In this setting, we found a group of

patients with a first episode of AP, a high proportion of intact gallbladder and biliary disease, mainly stones. We also found a second group of individuals with multiple AP episodes, a higher proportion of previous cholecystectomy, and with both stones and CP as the most common diagnostic findings, also with different recurrence rates. It is likely that the higher rates of relapse in patients with a previous cholecystectomy were caused by conditions with no specific treatment, such as genetic mutations or currently unknown causes, since this group of patients had lower rates of biliary etiology. However, our study lacked the design to establish the causes and further studies with larger sample sizes are needed.

Previous studies have shown that EUS performance is especially useful in patients with a gallbladder, in whom it has also been proven in a cost analysis to be the least expensive procedure for the diagnosis of IAP [29]. Besides its cost-related benefits, it is also necessary to perform further invasive procedures with a therapeutic intention, aiming to decrease the number of relapsing episodes [30]. Taking this into account, we compared recurrence rates in patients with biliary findings on EUS followed by ERCP or cholecystectomy, and patients with normal EUS or with findings other than stones in which follow up without specific intervention was decided upon, observing a higher recurrence rate in the second group (32.5% vs. 14.3%; P=0.05). Relapsing rates of AP in patients with non-biliary findings on EUS were similar to the relapsing rates found by Stigliano *et al* in patients with biliary AP without further treatment (31%) [31]. In this study, recurrence was lowered to 18% in patients referred only for ERCP, 16% when only cholecystectomy was performed, while no relapse was found in patients who underwent both procedures [31]. All these findings support the goal of finding and treating the etiologic factor in order to prevent further episodes of AP, and the essential role of EUS in targeting a specific intervention, but also in identifying patients with an early or an already established CP [32-34].

However, when performing EUS for IAP assessment, physicians must be concerned not only about patients' characteristics that can help find the underlying etiology, but also about the factors that might be related to relapsing episodes of AP. In this sense, we found that normal ALT or ALP at the time of admission during the index episode, findings on EUS other than lithiasis, and previous cholecystectomy were significantly related to recurrence. Multivariate analysis showed that age below 65 years, previous cholecystectomy, and findings other than stones on EUS were independent risk factors related to recurrence. These factors might be included in a predictive model of recurrence, and all of them should be taken into account in a global assessment of patients with IAP. Although a number of previous studies have tried to search for patients' characteristics, such as age or liver enzymes, that could improve the diagnostic yield of EUS [14,24,25,35], few of the studies concerning IAP have focused on long-term recurrences. Wilcox *et al* emphasized the role of EUS in IAP diagnosis and prognosis, in a large cohort with a long follow up [28]. They found that a normal EUS in patients with a single AP episode is a predictive factor for a low recurrence rate. Our results could also add that patients with previous cholecystectomy, age below 65 and findings on EUS other than lithiasis or sludge have an increased probability of recurrences. Nevertheless, further multicenter studies should be carried out specifically to search for clinical or diagnostic features that can be predictors of IAP recurrence.

Our study had several limitations. First, it was a single-center study with a relatively low sample size, especially regarding patients with RIAP and a previous cholecystectomy. Second, recruitment was based on the index EUS, so patients with a first episode of IAP or RIAP who had not been referred for an EUS might be missed. Finally, recurrences were documented in chart reviews. In future studies, prospective data collection should be done, starting with the index episode.

In conclusion, IAP is a common problem, being the third most likely diagnosis after initial evaluation of an AP episode in Spain [36]. Undeniably, it requires further assessment to treat the cause and prevent more episodes [34]. Our study found a subgroup of patients with a first episode of AP, a higher proportion of intact gallbladder, less need for ERCP and MRCP, and low recurrence rates; we also identified another group with multiple attacks, higher rates of previous cholecystectomy, more need for ERCP and MRCP, and a high recurrence rate. EUS findings are essential to address mainly biliary disease that can lead to an ERCP or cholecystectomy, with the aim of lowering recurrence rates, as well as findings suggestive of CP leading to a close monitoring schedule and further studies of pancreatic function [34]. Furthermore, in combination with

Summary Box

What is already known:

- Endoscopic ultrasound (EUS) is a valuable tool in the diagnostic work up of idiopathic acute pancreatitis (IAP)
- Treatment of the cause in IAP can prevent relapsing episodes of acute pancreatitis (AP), especially in patients with biliary AP
- Biliary tract disease is the most common finding on EUS in patients with IAP

What the new findings are:

- Recurrence rates are significantly higher in patients referred for EUS for recurrent IAP, compared with those with a first episode of IAP
- EUS leads to endoscopic retrograde cholangiopancreatography and cholecystectomy when biliary tract disease is found, lowering the recurrence rates compared with patients in whom no lithiasis is found on EUS and further conservative management is performed
- Age below 65 years, previous cholecystectomy, and findings other than lithiasis on EUS are independent risk factors for relapsing episodes

other factors, such as age or gallbladder status, it provides predictive information about recurrence likelihood. All this information must be taken into account by pancreatologists in order to perform close monitoring in patients with high recurrence rates, or to avoid pointless costs in patients who have a low probability of relapse, although further multicenter studies should be performed in this setting.

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