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Original Article

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Abstract

Background: Cholecystectomy in patients with idiopathic acute pancreatitis (IAP) is controversial. A randomized trial found cholecystectomy to reduce the recurrence rate of IAP but did not include preoperative endoscopic ultrasonography (EUS). As EUS is effective in detecting gallstone disease, cholecystectomy may be indicated only in patients with gallstone disease. This study aimed to determine the diagnostic value of EUS in patients with IAP, and the rate of recurrent pancreatitis in patients in whom EUS could not determine the aetiology (EUS-negative IAP).

Methods: This prospective multicentre cohort study included patients with a first episode of IAP who underwent outpatient EUS. The primary outcome was detection of aetiology by EUS. Secondary outcomes included adverse events after EUS, recurrence of pancreatitis, and quality of life during 1-year follow-up.

Results: After screening 957 consecutive patients with acute pancreatitis from 24 centres, 105 patients with IAP were included and underwent EUS. In 34 patients (32 per cent), EUS detected an aetiology: (micro)lithiasis and biliary sludge (23.8 per cent), chronic pancreatitis (6.7 per cent), and neoplasms (2.9 per cent); 2 of the latter patients underwent pancreatoduodenectomy. During 1-year follow-up, the pancreatitis recurrence rate was 17 per cent (12 of 71) among patients with EUS-negative IAP *versus* 6 per cent (2 of 34) among those with positive EUS. Recurrent pancreatitis was associated with poorer quality of life.

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Conclusion: EUS detected an aetiology in a one-third of patients with a first episode of IAP, requiring mostly cholecystectomy or pancreatoduodenectomy. The role of cholecystectomy in patients with EUS-negative IAP remains uncertain and warrants further study.

Introduction

No aetiology is found after routine investigations in approximately 25 per cent of patients with acute pancreatitis. These patients are considered to have idiopathic acute pancreatitis (IAP)[1–3], and endoscopic ultrasonography (EUS) may be of use to detect gallstones or other causes of pancreatitis such as neoplasms and chronic pancreatitis[3–6]. Although international guidelines[3] recommend EUS for patients with IAP, this recommendation is weak and based on studies of low quality. Consequently, EUS is not performed routinely.

In a previous *post hoc* analysis[7] of a prospective cohort of 191 patients with a first episode of IAP, more than one-quarter of patients experienced at least 1 recurrence of pancreatitis. This has led to the belief that a subset of these patients has occult gallstone disease. One multicentre randomized trial[8] from Finland of 85 patients with IAP found that cholecystectomy was effective in reducing the recurrence rate of pancreatitis from 30 to 10 per cent, and gallstones were diagnosed in 59 per cent of patients. However, this study was criticized because EUS was not included in the routine evaluation. EUS could have identified gallstones, thereby improving selection of patients for cholecystectomy. Furthermore, other studies on EUS in patients with IAP did not use the current standard diagnostic work-up[9]. Before setting up a multicentre randomized trial to investigate the value of cholecystectomy in patients with IAP, the rate of recurrent pancreatitis in patients with EUS-negative IAP should be established.

This prospective multicentre study was undertaken to determine the diagnostic value of EUS in patients with a first episode of IAP after complete standard diagnostic investigations, and to assess the rate of recurrent pancreatitis in patients with EUS-negative or EUS-positive IAP. It was hypothesized that EUS would be able to detect gallstone disease in a considerable proportion of patients with a first episode of IAP (even after complete standard diagnostic work-up) and that adequate treatment by cholecystectomy would reduce recurrent pancreatitis.

Methods

Study design

The prospective multicentre PICUS (Pancreatitis of Idiopathic origin: Clinical added value of UltraSound) study was conducted in 24 centres of the Dutch Pancreatitis Study Group according to the Declaration of Helsinki and the Guideline for Good Clinical Practice. The Medical Ethics Review Committee of Amsterdam UMC approved the study on 28 May 2018, after which local board approval was obtained in all other participating centres. All patients provided written informed consent. The study protocol was registered at the Netherlands Trial Registry (NL7066) and published[10]. This study was reported in accordance with the STROBE statement for cohort studies[11] and the STARD statement[12] (*Table S1*).

Eligibility

Adult patients with a first episode of IAP after standard diagnostic work-up, as recommended by the 2013 International Association of Pancreatology/American Pancreatic Association evidence-based guidelines on management of acute pancreatitis[3], were eligible to participate. Acute pancreatitis was defined according to the 2012 revised Atlanta criteria[13]. Main exclusion criteria were: known aetiology; chronic pancreatitis, as defined by the M-ANNHEIM criteria[14]; previous episode of acute pancreatitis; altered anatomy prohibiting visualization of the gallbladder, bile ducts, pancreas or pancreatic duct by EUS (for example history of Roux-en-Y gastric bypass); and diagnostic EUS aimed at determining the aetiology before inclusion.

Standard diagnostic investigations comprised: detailed personal and family history (alcohol use, recent endoscopic retrograde cholangiopancreatography (ERCP)); recent start or changes in use of drugs associated with acute pancreatitis; recent major abdominal trauma or abdominal surgery; familial and hereditary pancreatitis, and cystic fibrosis-related pancreatitis); laboratory tests (serum alanine aminotransferase, triglyceride, and calcium level, corrected for serum albumin level on admission); and imaging (transabdominal ultrasonography, MRI or magnetic resonance cholangiopancreatography (MRCP) after clinical recovery).

Study procedure and follow-up

Patients underwent EUS in an outpatient setting after resolution of acute pancreatitis. EUS was performed according to the technique of Hawes and Fockens[15], with a linear or radial scope, at the discretion of the endosonographer. Follow-up was completed 1 year after inclusion. Patients filled out Short Form 36 questionnaires (translated into Dutch) at inclusion, and 6 months and 1 year after inclusion to assess quality of life[16].

Outcome measures

The primary endpoint was the number of patients in whom EUS detected a potential cause of IAP. EUS was considered positive when a highly probable or definitive cause for the acute pancreatitis was found. Chronic pancreatitis was defined according to the M-ANNHEIM criteria[14]. Anatomical anomalies (for example divisum) were not considered a certain cause of IAP and were therefore not considered as positive imaging[17]. More detailed information on the definition of positive EUS and other relevant definitions is provided in the *supplementary material*.

Secondary endpoints included recurrence rate of acute pancreatitis, severity of recurrent acute pancreatitis, readmission, adverse events after EUS, additional invasive procedures (cholecystectomy, endoscopic sphincterotomy), duration of hospital stay, quality of life, and mortality. A cost analysis will be performed and published separately.

Sample size calculation

A diagnostic yield of EUS of 30 per cent was assumed based on two previous studies[18,19] and adjusted for the criteria for inclusion and positive imaging. Assuming a drop-out rate of 10 per cent, using a two-sided significance level of 0.05 and a power of 80 per cent, a total of 106 patients were needed to attain a 95 per cent confidence interval with a range smaller than 10 per cent above and below the assumed yield (95 per cent c.i. 20.8 to 39.2).

Statistical analysis

All included patients were evaluated for primary and secondary endpoints at 1 year after inclusion. All analyses were done according to the intention-to-treat principle. Baseline categorical variables are presented as numbers with percentages, whereas continuous data are presented as mean(s.d.), or median (i.q.r.) if the distribution was skewed. Primary and secondary outcome measures are presented as percentages with 95 per cent confidence intervals, mean(s.d.) or median (i.q.r.), as appropriate.

Predefined subgroup analyses were carried out to identify potential predictors of a positive EUS and recurrence of acute pancreatitis using the χ^2 test or Fisher's exact test for the following variables: BMI (cut-off at 30 kg/m^2), previous cholecystectomy, alcohol use (none *versus* less than 5 units/day), local adverse events from the IAP episode, and imaging after clinical recovery. For recurrence rate, predefined subgroup analyses were also performed using the χ^2 test or Fisher's exact test for patients with a positive or negative EUS, and, among patients with a positive EUS, those who were or were not treated adequately.

The paired *t* test was used to compare quality of life at 6-month follow-up *versus* baseline and to compare 1-year follow-up *versus* baseline for each subcategory of the Short Form 36 questionnaire. A modern repeated-measures analysis was performed using a mixed-effects model to determine the effect of outcome of EUS and of recurrence of acute pancreatitis on overall quality of life at baseline, and 6-month and 1-year follow-up[20].

Missing data were considered as no event; no imputation was used. Missing data were excluded from the quality-of-life analyses. Two-tailed $P < 0.050$ was considered statistically significant. All analyses were performed in SPSS® version 26 for Windows® (IBM, Armonk, NY, USA).

Results

Between 6 September 2018 and 27 September 2019, 957 patients with acute pancreatitis were admitted and screened for inclusion in the study at 24 participating hospitals. Some 106 patients with a first episode of IAP were included (*Fig. 1*). One patient refused EUS after inclusion. No other patients were lost to follow-up.

Patient characteristics

The majority of the patients were men (63, 59.4 per cent), and the mean(s.d.) age was 59.7(14.2) years (*Table 1*). Eight patients had a history of cholecystectomy before IAP. The median duration of hospital stay for IAP was 4 (i.q.r. 2–7) days. The disease course was (moderately) severe in 19 patients (17.9 per cent), with acute necrotic collections in 12 (11.3 per cent), acute (peri) pancreatic fluid collections in 8 (7.5 per cent), walled-off necrosis in 1 (0.9 per cent), and/or splenic vein thrombosis in 1 patient (0.9 per cent).

The median interval from admission to additional imaging (repeat transabdominal ultrasonography or MRI/MRCP) after resolution of acute pancreatitis was 22 (i.q.r. 14–37.5) days. After standard diagnostic evaluation during admission, additional imaging was performed after recovery from acute pancreatitis and was negative for aetiology in all patients: transabdominal ultrasonography in 98 (93 per cent), MRI/MRCP in 15 (13 per cent), and/or CT in 16 (15 per cent) (*Table 1*).

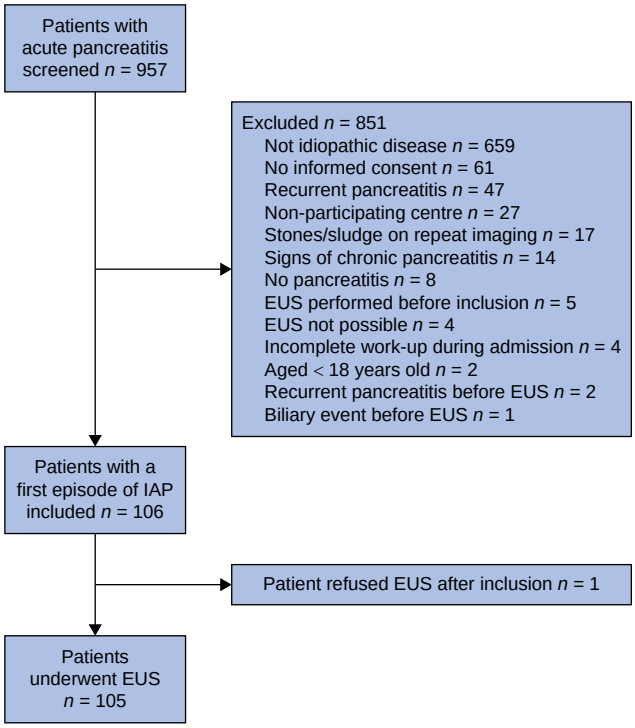

Fig. 1 Patient screening and selection process

EUS, endoscopic ultrasonography; IAP, idiopathic acute pancreatitis.

Endoscopic ultrasonography

Overall, 105 of 106 patients (99 per cent) underwent EUS at a median of 58 (i.q.r. 39.5–84) days after initial admission. The EUS was performed by a gastroenterologist (96, 91.4 per cent) or supervised gastroenterology resident. Eight-four procedures (80.0 per cent) were undertaken by an endoscopist with a cumulative total of more than 400 EUS procedures. In 88 procedures (83.8 per cent), patients received midazolam sedation only, whereas 17 (16.2 per cent) received propofol.

Endoscopic ultrasonographic findings

A highly probable or definitive aetiology was found in 34 of the 105 patients (32.4 (95 per cent c.i. 23.4 to 41.3) per cent). The majority had (micro)lithiasis or biliary sludge (25 patients, 23.8 (16 to 33.1) per cent). Other abnormalities observed were chronic pancreatitis in seven patients (6.7 (2.7 to 13.3) per cent) and periampullary neoplasms in three (2.9 (0.6 to 8.1) per cent) (*Table 2*). One patient had signs of both chronic pancreatitis and biliary stones. In three patients (2.9 per cent) a pancreas divisum was detected during EUS, which was not considered as definitive aetiology.

The three patients (2.9 per cent) with a periampullary neoplasm included one with a papillary adenoma with low-grade dysplasia requiring endoscopic ampullectomy twice during the 1-year follow-up. The second patient was diagnosed with pancreatic cancer derived from a main duct intraductal papillary mucinous neoplasm; this patient underwent pancreatoduodenectomy. The third patient had pancreatic cancer, received neoadjuvant therapy, and also underwent pancreatoduodenectomy. This patient had undergone CT before EUS, which was negative for aetiology, as well as transabdominal ultrasonography after resolution of acute pancreatitis, which was also negative.

Table 1 Patient and disease characteristics

	No. of patients* (*n* = 106)
Age at admission (years), mean(s.d.)	59.7(14.2)
Sex ratio (M : F)	63 : 43
BMI (kg/m^2), mean(s.d.)†	27.7(5.6)
Previous cholecystectomy	8 (7.5)
Nicotine use	
No	52 (49.1)
Stopped	29 (27.4)
Yes	25 (23.6)
Alcohol use	
None	43 (40.6)
Alcohol use (1–5 units/day)	63 (59.4)
Local adverse events after first episode of IAP	19 (17.9)
Acute (peri)pancreatic fluid collection	8 (7.5)
Acute necrotic collection	12 (11.3)
Walled-off necrosis	1 (0.9)
Splenic vein thrombosis	1 (0.9)
Duration of hospital stay (days), median (i.q.r.)	4 (2–7)
Amylase (units/l), median (i.q.r.)	532.5 (143.5–1626.8)
Lipase (units/l), median (i.q.r.)	896 (351–3376)
CRP (mg/l), median (i.q.r.)	14.5 (2.9–46.3)
ALT (units/l), median (i.q.r.)	25.5 (18–37)
Calcium (mmol/l), median (i.q.r.)	2.3 (2.3–2.4)
Albumin (g/l), mean(s.d.)	39.1(4.7)
Triglyceride (mmol/l), median (i.q.r.)	1.3 (0.9–1.8)
Imaging before EUS	105 (100)
CT	16 (15.1)
MRI/MRCP	14 (13.2)
Repeat abdominal ultrasonography	98 (92.5)
Time to additional imaging (days), median (i.q.r.)	22 (14–37.5)

*Values are *n* (%) unless otherwise indicated. †Missing for three patients. No pseudocysts, gastric outlet obstruction, portal vein thrombosis or colonic necrosis were observed in this study. IAP, idiopathic acute pancreatitis; CRP, C-reactive protein; ALT, alanine aminotransferase; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography.

Recurrence rate

During 1-year follow-up, there were 20 recurrent episodes of pancreatitis in 14 patients (13.2 per cent). One-quarter of these were moderate–severe (4) or severe (1). Based on the EUS results, cholecystectomy was performed in 18 patients (17 per cent) and ERCP in 6 (5.7 per cent). No patients died during the course of this study (*Table 2*).

Pancreatitis recurred in 12 of 71 patients (16.9 per cent) with a negative EUS *versus* 2 of 34 (5.9 per cent) with a positive EUS ($P = 0.218$). Subgroup analyses showed that the recurrence rate was higher among patients with a gallbladder *in situ* at initial admission for IAP than in patients who had undergone cholecystectomy previously (14.4 *versus* 0 per cent; $P = 0.594$) (*Table S2*). Patients with hepatic steatosis or cirrhosis had a higher recurrence rate than those who did not (20 *versus* 9.2 per cent; $P = 0.143$). No cholecystectomies were performed after a negative EUS.

Complications and subgroups

In one patient (1 per cent), EUS was complicated by a mild episode of acute pancreatitis, for which the patient was admitted for 1 week. No fine-needle aspiration or biopsy had been performed.

Subgroup analyses were undertaken to determine whether patient and EUS procedural characteristics were associated with a positive EUS (*Table S3*). No statistically significant associations were found between patient or EUS procedural characteristics and the results of EUS.

Table 2 Study endpoints

	No. of patients* (*n* = 105)
Positive EUS and aetiology	34 (32.4)
Biliary	25 (23.8)
Chronic pancreatitis	7 (6.7)
Periampullary neoplasm	3 (2.9)
Recurrence	14 (13.2)
Recurrence in EUS-positive IAP	2 of 34 (5.9)
Recurrence in EUS-negative IAP	12 of 71 (16.9)
Total no. of recurrences	20
Severity of recurrence	
Mild	15 (75)
Moderate–severe	4 (20)
Severe	1 (5)
Duration of hospital stay (for recurrence) (days), median (i.q.r.)	3.5 (2–6)
Cholecystectomy	18 (17)
ERCP	6 (5.7)
Adverse events after EUS	1 (0.9)
Death	0 (0)

*Values are *n* (%) uness otherwise indicated. EUS, endoscopic ultrasonography; IAP, idiopathic acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography.

Quality of life

Six months after inclusion, overall quality of life was similar to that at inclusion (mean (s.d.) difference in score *versus* that at time of inclusion 31.7 (164.2); $P = 0.098$). At 1 year, overall quality of life was better (mean difference in score *versus* at inclusion 39 (129.6); $P = 0.015$). EUS positive for aetiology was not associated with changes in quality of life ($P = 0.867$), whereas readmission for acute pancreatitis was associated with a reduced overall quality of life ($P = 0.022$) (*Table S4*).

Discussion

This prospective multicentre cohort study, including standard work-up for IAP and EUS in 106 patients with a first episode of IAP, detected an underlying cause requiring surgical intervention in one-quarter of patients. Overall, EUS was positive in one-third of patients, indicating the presence of gallstones (23.8 per cent), chronic pancreatitis (6.7 per cent), and periampullary neoplasms (2.9 per cent). No patient-related or EUS procedural factors were significantly associated with a higher yield of EUS. Patients with EUS-negative IAP had a high recurrence rate of 16.9 per cent and require further study.

The diagnostic yield of EUS in this study was lower than that reported in other studies[9]. This may be explained by the strict diagnostic evaluation before EUS in the present study, which reduced the risk of overestimating the accuracy of EUS in IAP. In most patients screened in the present study, a likely cause of pancreatitis was detected after standard work-up during admission (659 of 957 patients, 69 per cent) or during repeat imaging (17 of 957, 2 per cent) (*Fig. 1*). Therefore, the results of this study better reflect current clinical practice. Previous studies included patients with single and recurrent episodes of IAP, had no adequate diagnostic evaluation before EUS, and often did not report systematically on clinically relevant long-term outcomes including recurrent pancreatitis and quality of life[9].

When the study was designed, the minimum clinically relevant added yield of EUS was set at 10 per cent. Based on the observation that detection of aetiology in this study was three times higher than anticipated, routine use of EUS should be advised in patients with a first episode of IAP. The rate of recurrent pancreatitis was nearly three times higher in those with a negative EUS than in patients with a positive EUS. It has been hypothesized that undetected microlithiasis or biliary sludge may cause recurrent IAP episodes. The result of EUS could be false-negative owing to spontaneous passage of the microlithiasis or sludge, limited experience of the endoscopist or technical limitations. Thus, it remains unclear whether patients with a EUS-negative IAP may benefit from cholecystectomy[21].

A recent systematic review[22] reported a lower recurrence rate in 524 patients with IAP who underwent cholecystectomy *versus* non-surgical management from 10 studies (11.1 *versus* 35.2 per cent; risk ratio 0.44). However, EUS was not undertaken routinely in these patients. The present data have been used for the PICUS-2 RCT of cholecystectomy in patients with EUS-negative IAP. This study will give insight into the role of cholecystectomy in EUS-negative IAP as patients will be randomized to conservative management or cholecystectomy.

Follow-up in the present study was limited to 1 year. As such, recurrence of pancreatitis after 1 year is unknown. Furthermore, diagnostic tests were interpreted by different clinicians which may have led to selection bias, and confounding factors could not be ruled out. Despite these limitations, EUS in patients with IAP should be performed routinely, given the small chance of adverse events.

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Author contributions

Devica Umans (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing—original draft), Hester C. Timmerhuis (Data curation, Investigation, Resources, Writing—review & editing), Marie-Paule G. F. Anten (Data curation, Investigation, Writing—review & editing), Abha Bhalla (Data curation, Investigation, Writing—review & editing), Rina A. Bijlsma (Data curation, Investigation, Writing—review & editing), Lotte Boxhoorn (Data curation, Investigation, Methodology, Writing—review & editing), Menno Brink (Data curation, Investigation, Writing—review & editing), Marco Bruno (Conceptualization, Data curation, Investigation, Methodology, Writing—review & editing), Wouter Curvers (Data curation, Investigation, Writing—review & editing), Brechje C. van Eijck (Data curation, Investigation, Writing—review & editing), G. Erkelens (Data curation, Investigation, Writing—review & editing), E. van Geenen (Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing—review & editing), Wouter Hazen (Data curation, Investigation, Writing—review & editing), Chantal Hoge (Data curation, Investigation, Writing—review & editing), L. Hol (Data curation, Investigation, Writing—review & editing), Akin Inderson (Data curation, Investigation, Writing—review & editing), Liesbeth M. Kager (Data curation, Investigation, Writing—review & editing), Sjoerd D. Kuiken (Data curation, Investigation, Writing—review & editing), Lars Perk (Data curation, Investigation, Writing—review & editing), R. Quispel (Data curation, Investigation, Methodology, Writing—review & editing), Tessa E .H. Römkens (Data curation, Investigation, Writing—review & editing), Christina J. Sperna Weiland (Data curation, Formal analysis, Investigation, Writing—review & editing), Annemieke Y. Thijssen (Data curation, Investigation, Writing—review & editing), N. Venneman (Data curation, Investigation, Writing—review & editing), Robert Verdonk (Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Writing—review & editing), Roy L. J. van Wanrooij (Data curation, Investigation, Writing—review & editing), Ben Witteman (Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing—review & editing), Marc Besselink (Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Writing—review & editing), and Jeanin van Hooft (Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Data will be available upon reasonable request from the authors.

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