Endoscopic ultrasonography can detect a cause in the majority of patients with idiopathic acute pancreatitis: a systematic review and meta-analysis

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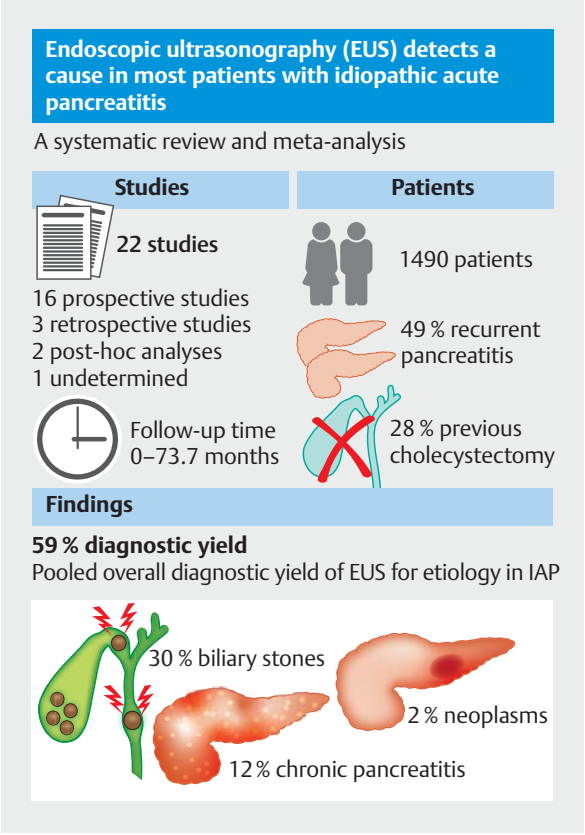
GRAPHICAL ABSTRACT



ABSTRACT

Background Idiopathic acute pancreatitis (IAP) has a 25 % pancreatitis recurrence rate. Endoscopic ultrasonography (EUS) may diagnose treatable causes of IAP and hence prevent recurrence. The goal of this systematic review with meta-analysis is to determine the diagnostic yield of EUS and its impact on recurrence.

Methods PubMed, EMBASE and the Cochrane Library were systematically searched for English studies on EUS in adults with IAP. The primary outcome was diagnostic yield. Secondary outcomes included recurrence. Methodological quality was assessed using the QUADAS-2 score. Meta-analysis was performed to calculate the pooled diagnostic yield and risk ratio with 95 % confidence intervals (CI) using a random-effects model with inverse variance method.

Results 22 studies were included, with 1490 IAP patients who underwent EUS. Overall diagnostic yield was 59 % (874 / 1490; 95 %CI 52 % – 66 %). The most common etiologies were biliary (429 / 1490; 30 %, 95 %CI 21 % – 41 %) and chronic pancreatitis (271 / 1490; 12 %, 95 %CI 8 % – 19 %). In 2 % of patients, neoplasms were detected (45 / 1490; 95 %CI 1 % – 4 %). There was no difference in yield between patients with or without recurrent IAP before EUS (risk ratio 0.89, 95 %CI 0.71 – 1.11).

Conclusions EUS is able to identify a potential etiology in the majority of patients with IAP, detecting mostly biliary origin or chronic pancreatitis, but also neoplasms in 2 % of patients. EUS may be associated with a reduction of recurrence rate. Future studies should include complete diagnostic work-up and preferably include patients with a first episode of IAP only.

Introduction

The incidence of acute pancreatitis continues to rise [1]. Although biliary lithiasis and/or sludge, and alcohol abuse remain the most common causes of acute pancreatitis, in approximately 25 % of cases a causative factor cannot be determined during standard diagnostic work-up [1]. Standard diagnostic work-up consists of: a personal and family history; laboratory tests including serum alanine transaminase (ALT), calcium, and triglycerides; and transabdominal ultrasonography during admission and after discharge. Patients in whom such work-up is negative are referred to as having idiopathic acute pancreatitis (IAP) [2].

In comparison to pancreatitis with a known origin, IAP has a relatively high pancreatitis recurrence rate of 25 % within 3 years. Furthermore, the risk of recurrence in patients who have already had one recurrent IAP episode is twice as high as in patients with a first episode of IAP [3].

For many years, undetected microlithiasis and biliary sludge have been considered to be the major causes of IAP, and even routine cholecystectomy has been suggested in these patients [4]. In recent years, however, a more diverse view has arisen as studies have shown that other etiologies such as pancreatic cancer may not be as rare in this situation as previously thought [5].

Partly owing to the heterogeneity of occult etiologies in IAP, no consensus existed among physicians regarding the use of various additional diagnostic modalities. The International Association of Pancreatology/American Pancreatic Association (IPA/APA) evidence-based guidelines on management of acute pancreatitis recommend endoscopic ultrasonography (EUS) as the first step after negative standard diagnostic work-up (GRADE 2C, weak agreement) [2], with discussion as to whether this should be performed after the first episode or only after recurrent episodes of IAP. Considering the hypothesis that IAP recurrences may be caused by occult and subsequently untreated underlying causes, it is suggested that by improving the detection rate of etiology in IAP by implementing EUS in the diagnostic work-up, recurrence rate in this patient group could be reduced [3].

The goal of this study was to determine the diagnostic yield of EUS for etiological factors in IAP. Secondary objectives were to determine whether the diagnostic yield is altered by the presence of the gallbladder during EUS and in recurrent pancreatitis, as opposed to a first episode of pancreatitis; and whether the detection of etiology by EUS and subsequent treatment of underlying etiologies may be associated with a reduced pancreatitis recurrence rate and occurrence of biliary events.

Methods

Study design and registration

This study was designed as a systematic review with meta-analysis of the diagnostic yield of EUS in patients with IAP. The review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [6] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines (see the PRISMA and MOOSE checklists in **Appendix 1 s**, available in online-only Supplementary Material) [7]. This study was registered in the PROSPERO database under registration number CRD42019120730.

Search strategy

With the aid of an expert librarian, the databases PubMed, EMBASE, and the Cochrane library were systematically searched for relevant articles between inception and 19 November 2019. The search contained the following key words: pancreatitis, pancreas, acute, recurrent, relapsing, idiopathic, unexplained, unknown, endoscopic, ultrasonography, ultrasound, and EUS. The complete searches are listed in **Appendix 2 s**. After performing the search, duplicates were removed and the search results were uploaded to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia).

Study selection

Two independent reviewers (D.U. and C.R.) screened potentially relevant articles by title and abstract. Disagreements were resolved in a discussion between the two reviewers. The full text of the potentially eligible studies was read by both reviewers individually. Mutual agreement was required for inclusion of potential studies, while disagreement on the eligibility of an article was resolved after joint re-evaluation of the article by the two reviewers. Reasons for exclusion were recorded during screening by title and abstract, and full-text screening.

Peer-reviewed articles in English that included patients with IAP in whom, after presentation with IAP, a diagnostic EUS was performed, and articles reporting the diagnostic yield of EUS by etiology were considered. Studies with patients younger than 18 years or with known chronic pancreatitis, of animals, or where the EUS was performed for indications other than detection of etiology were excluded. Letters, comments, case reports, reviews, book sections, conference abstracts, and case–control studies were excluded as well. Finally, all patients in whom an etiology was found prior to EUS were excluded from the meta-analysis.

Outcome measures

The primary outcome was the diagnostic yield of EUS for detection of etiology in IAP. Subgroup analyses were made for diagnostic yield of EUS for biliary etiology, chronic pancreatitis, and neoplasms. Comparative analyses were made for diagnostic yield in patients with a first episode of IAP versus patients with recurrent pancreatitis and in patients with a gallbladder in situ versus post-cholecystectomy patients.

Secondary outcome measures were the treatment of underlying etiologies, pancreatitis recurrence rate, and the occurrence of biliary events (i.e. cholangitis, cholecystitis, acute biliary pancreatitis, and biliary colic) during follow-up.

Data extraction

After the studies that met the inclusion criteria had been selected, all relevant data from these studies were extracted by two reviewers using a standardized form. Relevant data included: study characteristics (period and country of inclusion, year and journal of publication, study design, number of patients, and follow-up time); patient characteristics (sex, age, recurrence and severity of pancreatitis, previous cholecystectomy); the use of diagnostic tests prior to EUS; type of scope and EUS technique used; definitions of positive imaging; diagnostic yield (including yield for biliary etiology, chronic pancreatitis, neoplasms, and other anomalies); treatment of etiology after EUS; and pancreatitis recurrence and occurrence of biliary events during follow-up. The definition of positive imaging used in each of the included studies is provided in **Appendix 3s**.

No attempt was made to communicate with the corresponding authors concerning missing data. Missing data were reported as "not reported" and excluded from pooled analyses.

Quality assessment

The quality of the included articles was appraised at study level by two independent reviewers (D.U. and C.R.) using the QUADAS-2 score for quality assessment of diagnostic accuracy studies, adjusted for the study designs of the included studies by omitting the third domain regarding the reference standard [8]. Risk of bias in patient selection was scored based on whether the study included a consecutive or random sample, the type of center in which patients were included, and whether additional diagnostics were performed before EUS. Risk of bias in the use of EUS was scored based on whether the type of scope, expertise level of the endoscopist, use of sedation, and definitions for biliary etiology and chronic pancreatitis were reported. Risk of bias in the timing of EUS was scored based on whether the EUS was performed before or after clinical recovery from the acute pancreatitis episode. Applicability in patient selection was scored based on whether a minimal standard diagnostic work-up was performed before EUS, and applicability in use of EUS was scored based on whether the EUS technique described was similar to conventional EUS techniques [9].

Disagreement on the appraisal was resolved by joint re-evaluation by the two reviewers.

Data analyses

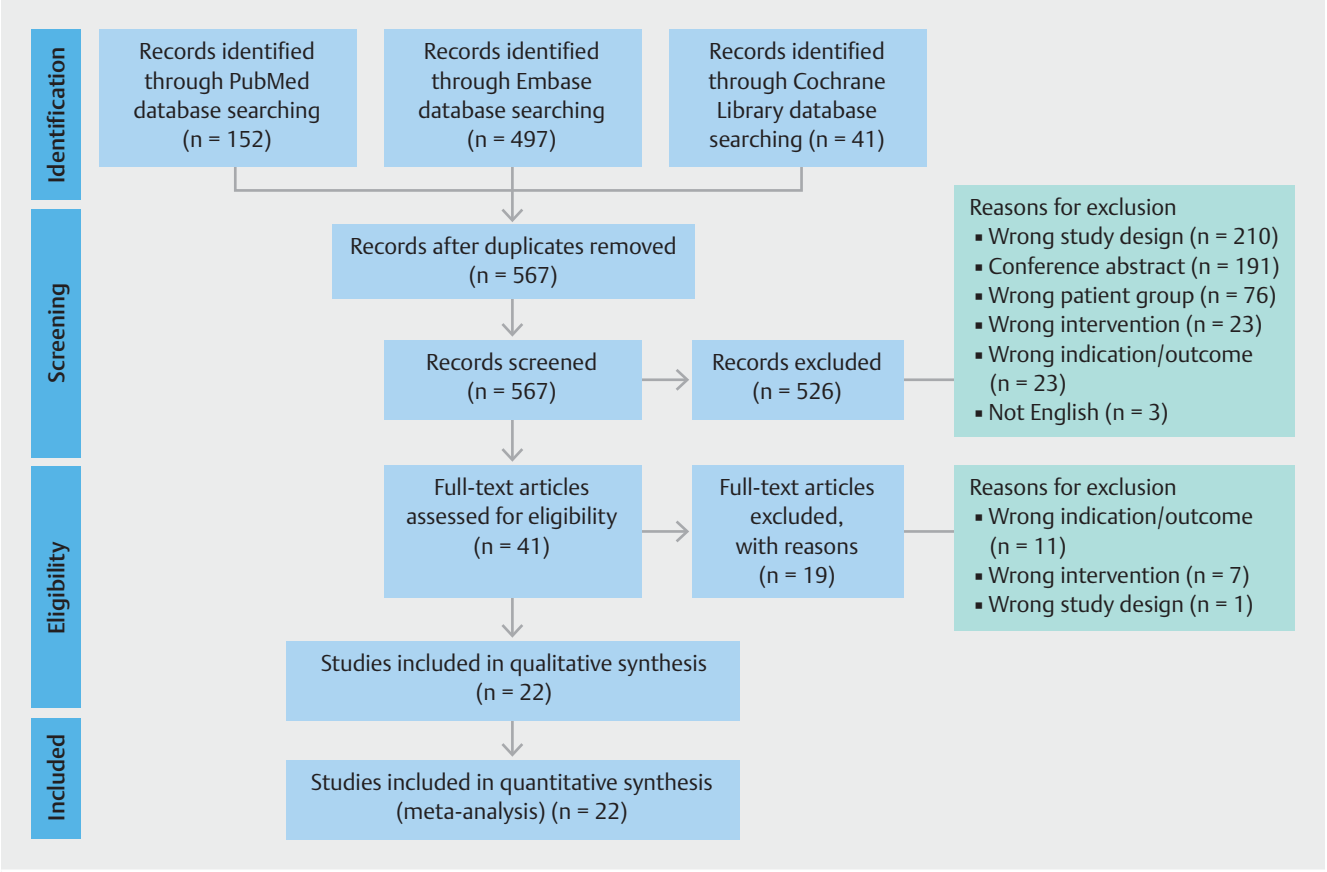
The study and patient characteristics, as well as the diagnostic work-up prior to EUS were reported using descriptive statistics.

The pooled estimates of the primary outcome measure, diagnostic yield, were reported as proportions with a 95 % confidence interval (CI) with 95 % prediction intervals (PI), estimated using a random-effects model with DerSimonian – Laird estimator [10], implemented in R [11]. A random-effects model, in which some studies are appointed more weight in pooled proportions than others, as opposed to a fixed-effects model, was chosen to correct for the between-study heterogeneity on baseline level.

Sensitivity analyses for diagnostic yield were performed based on study type, year of publication, type of pancreatitis (first versus recurrent disease), presence of the gallbladder, timing of EUS, definition of chronic pancreatitis, and diagnostic work-up prior to EUS. For comparative analyses of diagnostic yield in patients with a first episode of IAP versus recurrent pancreatitis and post-cholecystectomy patients versus patients with a gallbladder in situ and pancreatitis recurrence rate, the risk ratio with 95 %CI was also reported. This was done in a random-effects model with the inverse variance method and DerSimonian – Laird estimator [10], using Review Manager software [12]. Other secondary outcome measures were reported descriptively. No correction for multiple testing was performed.

Between-study heterogeneity was assessed using the I^2 statistic. I^2 values of < 25 %, 25 % – 50 %, 50 % – 75 %, and > 75 % were classified as low, moderate, high, and very high heterogeneity [13].

Publication bias was evaluated using the Egger's linear regression method [14].



▶ **Fig. 1** PRISMA flowchart of study screening and selection, as per Moher et al. [6]. More information available from: www.prisma-statement.org.

Results

Search results and included studies

A systematic literature search yielded 567 unique records. After screening and full-text eligibility assessment, 22 studies with 1490 patients with IAP who underwent EUS were included in the qualitative and quantitative synthesis [3, 15–35]. The exclusion criteria for the excluded studies are listed in ▶ **Fig. 1**.

Study characteristics

The 22 included studies, published between 1999 [23] and 2019 [22], comprised 16 prospective cohort studies [3, 15–21, 23, 24, 27, 28, 30, 32–34], two post-hoc analyses of prospective cohorts [22, 31], three retrospective cohort studies [25, 29, 35], and one study with unclear design [26]. Mean or median follow-up time ranged between 0 and 73.7 months. A complete overview of the study characteristics is provided in ▶ **Table 1**.

Patient characteristics

In total, 1679 IAP patients were included, of whom 1490 underwent diagnostic EUS. The average ages ranged between 22.25 and 53.75 years, with 53 % of the patients (869/1647) being men (reported in 21 studies [3, 15–25, 28–35]), and 49 % (649/1318) had had more than one episode of acute pancreatitis before undergoing EUS (reported in 16 studies [3, 15, 16, 18–21, 23, 24, 29–35]). Cholecystectomy was performed before EUS in 28 % (343/1217; reported in 13 studies [3, 16, 19, 20, 22, 24, 26, 28, 30–34]) and 13 % (117/919) had severe pancreatitis before EUS (reported in 14 studies [3, 15, 17–21, 23–25, 30, 32, 33, 35]). All patient characteristics are listed in ▶ **Table 2**.

Critical appraisal

A comprehensive quality assessment is provided in **Appendix 4s**. There were 10 studies that were considered to have a low risk of bias regarding patient selection [3, 15, 17, 24, 27, 28, 30, 32–34], while one study was appraised as having low applicability concerns [23]. Regarding risk of bias in the use of EUS, four studies were assessed as having high risk of bias [15, 23, 25, 35] and 10 studies were considered to have low applicability concerns in the use of EUS [17, 19, 21, 24–26, 28–30, 35]. Finally, five studies were appraised as having high risk of bias in flow and timing of the study [23, 25, 27, 28, 35].

An Egger's linear regression indicated low risk of publication bias ($P = 0.74$) (**Appendix 5s**).

Diagnostic work-up prior to EUS

Standard diagnostic work-up, as defined by the IAP/APA evidence-based guidelines for management of acute pancreatitis

▶ **Table 1** Characteristics of the 22 included studies of endoscopic ultrasonography (EUS) for the investigation of idiopathic acute pancreatitis (IAP).

First author	Year of publication	Country	Study design	Period of inclusion	Follow-up time, months
Ammori [15][1]	2003	UK	Prospective cohort study	2000 – 2001	NR
Choudhary [16]	2016	India	Prospective cohort study	Period of 2 years	NR
Frossard [17][2]	2000	France	Prospective cohort study	1991 – 1995	NR
Garg [18]	2007	India	Prospective cohort study	1995 – 2003	17.63 (mean)
Govil [19]	2014	India	Prospective cohort study	2010 – 2012	NR
Kim [20][3]	2011	South Korea	Prospective cohort study	NR	36.4 (median)
Liu [21][4]	2000	China	Prospective cohort study	1996 – 1997	20, 22 (median)
Lopes [22]	2019	Brazil	Post-hoc analysis of a prospective EUS database	2012 – 2017	31.7 (mean)
Maes [23]	1999	France	Prospective cohort study	1994 – 1995	3.65 (mean or median not reported)
Mariani [24]	2009	Italy	Prospective cohort study	NR	NR
Morris-Stiff [25]	2009	UK	Retrospective cohort	2000 – 2004	73.7 (median)
Norton [26]	2000	UK	NR	NR	3 – 28 (range)
Poves [27]	2010	Spain	Prospective cohort study	Period of 18 months	21.5 (mean)
Queneau [28]	2002	France	Prospective cohort study	1995 – 1997	36 (median)
Rana [29][5]	2012	India	Retrospective cohort	NR	5 – 36 (range)
Repiso Ortega [30]	2011	Spain	Prospective cohort study	2005 – 2009	16 (mean)
Tandon [31]	2001	USA	Post-hoc analysis of a prospective EUS database	NR	16 (mean)
Thevenot [32]	2013	France	Prospective cohort study	2008 – 2010	22 (mean)
Vila [33]	2010	Spain	Prospective cohort study	2004 – 2007	28.95 (mean)
Wilcox [3]	2016	USA	Prospective cohort study	2003 – 2013	37 (mean)
Yusoff [34]	2004	Canada	Prospective cohort study	2000 – 2003	NR
Zhan [35]	2011	China	Retrospective cohort	2006 – 2009	NR

NR, not reported.
[1] Ammori et al. included eight patients with IAP who underwent EUS but four of these patients has significant liver enzyme abnormalities and were for that reason excluded from this review.
[2] Frossard et al. included 168 patients with IAP who underwent EUS but one of these patients had furosemide-induced pancreatitis and another had Coxsackie virus-related pancreatitis. These patients were also excluded from the review.
[3] Kim et al. included 31 patients with IAP who underwent EUS but seven of them already had signs of biliary etiology on previous imaging (i. e. a dilated common bile duct). These patients were excluded. Kim et al. also included two patients with cholecystolithiasis but owing to missing data these patients could not be excluded.
[4] Liu et al. reported a median follow-up time of 20 and 22 months for EUS-positive patients and EUS-negative patients, respectively.
[5] Rana et al. did not report the years of inclusion but did mention they included patients during "the last 3 years."

(i. e. personal and family history; laboratory tests including serum ALT, calcium, and triglycerides; and transabdominal ultrasonography during admission and after discharge) [2], and additional diagnostic tests are listed in **Appendix 6 s**. Definitions of positive tests are summarized in **Appendix 7 s**. The majority of studies excluded patients with known alcohol abuse, drugs associated with acute pancreatitis, hypercalcemia, and hypertriglyceridemia, although definitions for all of these exclusion criteria differed among studies.

Regarding the diagnosis of biliary etiology, most studies required at least one transabdominal ultrasound, while only two studies required a repeat ultrasound after clinical recovery from the episode of pancreatitis in all included patients [18, 26], and six studies explicitly excluded patients with abnormal liver function tests [3, 15, 16, 18 – 20].

Importantly, none of the studies performed a complete standard diagnostic work-up, according to the IAP/APA guidelines, prior to EUS.

Diagnostic yield of EUS

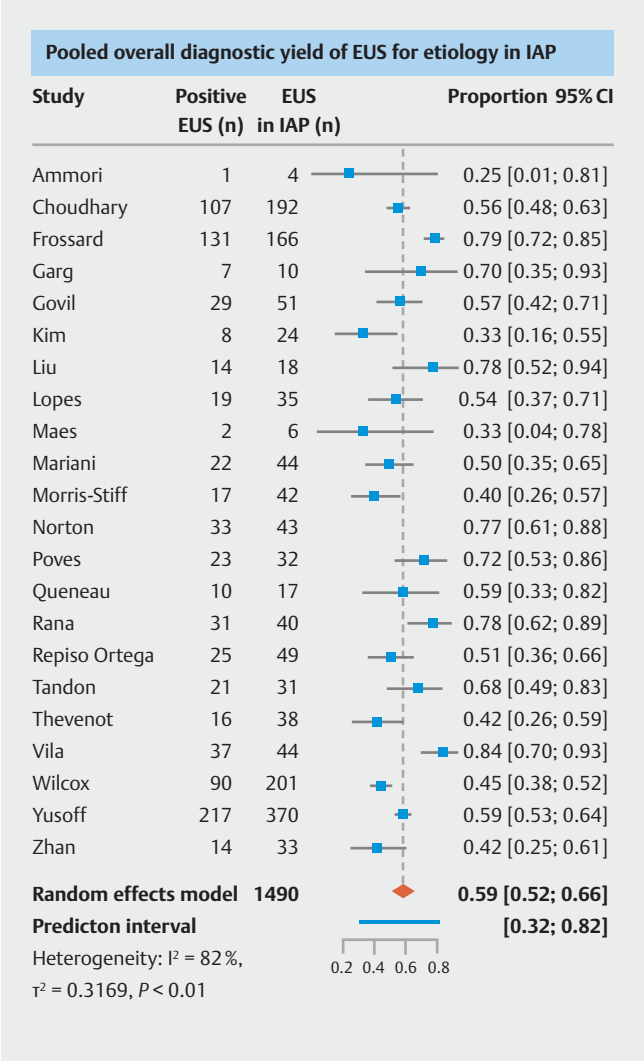
Out of the 1490 IAP patients who underwent EUS, EUS found a possible etiology in 874 patients (59 % in random-effects mod-

▶ **Table 2** Patient characteristics in the 22 included studies of endoscopic ultrasonography (EUS) for the investigation of idiopathic acute pancreatitis (IAP).

Study	All included IAP patients, n	IAP patients with EUS, n	Male sex, n (%)[1]	Age, years	Recurrent pancreatitis, n (%)[1]	Previous chole-cystectomy, n (%)[1]	Severe pancreatitis, n (%)[12]
Ammori [15]	68	4	23 (34)	55 (median)	NR	NR	12 (18)
Choudhary [16]	192	192	131 (68)	34.6 (mean)	102 (53)	57 (30)	NR
Frossard [17]	168	166	102 (61)	50 (mean)	NR	NR	15 (9)
Garg [18]	75	10	60 (80)	31.9 (mean)	75 (100)	NR	15 (20)
Govil [19]	51	51	35 (69)	36.7 (mean)	0 (0)	2 (4)	6 (12)
Kim [20]	31	24	11 (35)	51.3 (mean)	31 (100)	6 (19)	8 (26)
Liu [21]	18	18	9 (50)	68 (median)	13 (72)	NR	10 (56)
Lopes [22]	35	35	10 (29)	51.9 (mean)	NR	10 (29)	NR
Maes [23]	18	6	11 (61)	55.5 (mean)	3 (17)	NR	3 (17)
Mariani [24]	44	44	20 (45)	48.9 (mean)	44 (100)	7 (16)	0 (0)
Morris-Stiff [25]	42	42	25 (60)	53 (mean)	NR	NR	0 (0)
Norton [26]	44	43	20 (45)	53.5 (median)	10 (23)	8 (18)	NR
Poves [27]	32	32	NR	NR	NR	NR	NR
Queneau [28]	48	17	21 (44)	51 (mean)	NR	0 (0)	NR
Rana [29]	40	40	26 (65)	17 – 72 (range)	17 (43)	NR	NR
Repiso Ortega [30]	49	49	24 (49)	58 (mean)	16 (33)	9 (18)	5 (10)
Tandon [31]	31	31	12 (39)	48.8 (mean)	17 (55)	3 (10)	NR
Thevenot [32]	45	38	25 (56)	53.8 (mean)	8 (18)	7 (16)	7 (16)
Vila [33]	44	44	31 (70)	61.45 (mean)	19 (43)	11 (25)	9 (20)
Wilcox [3]	201	201	95 (47)	53 (mean)	121 (60)	99 (49)	27 (13)
Yusoff [34]	370	370	165 (61)	53.4 (mean)	169 (63)	124 (46)	NR
Zhan [35]	33	33	13 (39)	46.5 (mean)	4 (12)	NR	0 (0)
Total	**1679**	**1490**	**869 (53)**	**22.25 – 53.75 (range)**	**649 (49)**	**343 (28)**	**117 (13)**

NR, not reported.
[1] Only concerns the studies that reported this parameter.
[2] Severity was defined by the Atlanta score in four studies (Ammori et al., Maes et al., Repiso Ortega et al., Thevenot et al.); by the Ranson criteria in four studies (Frossard et al., Kim et al., Liu et al., Zhan et al.); by clinical criteria in two studies (organ failure at the time of admission [Govil et al.]) and hospitalization of more than 10 days [Wilcox et al.]); and was not reported in four studies (Garg et al., Mariani et al., Morris-Stiff et al., Vila et al.).

el, 95 %CI 52 % – 66 %, 95 %PI 32 % – 82 %), as shown in ▶ **Fig. 2**. In random-effects models, biliary etiology was detected in 30 % of patients (429 / 1490; 95 %CI 21 % – 41 %, 95 %PI 5 % – 77 %), chronic pancreatitis in 12 % (271 / 1490; 95 %CI 8 % – 19 %, 95 % PI 2 % – 51 %), and neoplasms in 2 % (45 / 1490; 95 %CI 1 % – 4 %, 95 %PI 0 % – 17 %), as shown in ▶ **Table 3**. The neoplasms included 22 intraductal papillary mucinous neoplasms (IPMNs), 12 pancreatic carcinomas, three ampullary adenomas, two ampullary cancers, one malignant IPMN, one gastric adenocarcinoma invading the pancreatic parenchyma, two (suspected) neu-



▶ **Fig. 2** Pooled overall diagnostic yield of endoscopic ultrasonography (EUS) for the etiology of idiopathic acute pancreatitis (IAP). CI, confidence interval.

roendocrine tumors, one cystic lesion not further specified, and one pancreatic mass suspicious for malignancy where pathology after resection showed inflammation.

Other reported etiologies included: pancreas divisum (n = 87), ascariasis (n = 3), autoimmune pancreatitis (n = 3), cystic fibrosis (n = 3), impaired outflow through the papilla of Vater (n = 2), abnormal pancreaticobiliary junction (n = 1), choledochocele (n = 1), and diverticulum (n = 1). Impaired outflow through the papilla of Vater was diagnosed in one study by measuring the diameter of the pancreatic duct after secretin injection, and was considered suggestive of sphincter of Oddi dysfunction [24].

A sensitivity analysis showed no statistically significant difference in the diagnostic yields reported by prospective versus non-prospective studies, studies published before 2010 versus after 2009, studies using the Rosemont criteria for chronic pancreatitis [36] versus other criteria, or studies performing only standard diagnostic work-up prior to EUS versus additional diagnostic work-up (▶ **Table 3**).

In random-effects models, there was no difference in diagnostic yield between patients with a first episode of IAP and patients with recurrent pancreatitis before EUS (264/494 [56 %] versus 299/594 [52 %]; risk ratio 0.89, 95 %CI 0.71 – 1.11). Diagnostic yield of EUS in random-effects models was, however, significantly higher in patients with their gallbladder in situ compared with those patients who had undergone a previous cholecystectomy (105/211 [50 %] versus 310/496 [64 %]; risk ratio 0.81, 95 %CI 0.70 – 0.95). When EUS was performed after clinical recovery from the pancreatitis episode, the diagnostic yield in a random-effects model was 61 % (80/1360; 95 %CI 53 % – 68 %), while the diagnostic yield in EUS before clinical recovery was 48 % (24/50; 95 %CI 35 % – 62 %).

Between-study heterogeneity was very high in the analyses of overall diagnostic yield, yield for biliary etiology, yield for chronic pancreatitis, and yield for EUS after clinical recovery, as exemplified by I^2 statistics of 82 %, 92 %, 89 %, and 84 %, respectively. The I^2 statistic showed high heterogeneity in the analyses of yield for neoplasms and in the comparison of yield between patients with a first episode of IAP versus patients with recurrent IAP (68 % and 69 %, respectively). The heterogeneity of the analyses of yield in EUS after clinical recovery and the comparison of yield between post-cholecystectomy patients versus patients with gallbladder in situ was low (0 and 1 %, respectively).

Interventions, pancreatitis recurrence, and biliary events after EUS

Interventions and adverse events during follow-up were scarcely reported and not systematically assessed. Thirteen studies reported performing endoscopic sphincterotomy and/or cholecystectomy after the EUS uncovered a biliary etiology [3, 19 – 22,25 – 27,29 – 33]; in one study, endoscopic sphincterotomy was performed during endoscopic retrograde cholangiopancreatography (ERCP) in one patient with choledocholithiasis and in three patients without evidence of biliary etiology [23]. Other treatments included enzyme replacement therapy and endoscopic therapy for chronic pancreatitis [19, 20], surgery and/or chemoradiation for malignancies [20, 23, 30, 33], and pancreatic stenting for pancreas divisum [3, 26, 29].

Six studies reported no recurrence during follow-up [19, 21, 27 – 29, 32]. Seven studies reported seven recurrences in 76 patients with confirmed biliary etiology versus 49 recurrences in 138 patients with unknown etiology (9.2 % versus 35.5 %, respectively; risk ratio 0.71, 95 %CI 0.21 – 2.41) (**Appendix 8 s**) [3, 18, 20, 22, 26, 30, 31].

Regarding biliary events, one study reported jaundice in a patient in whom biliary etiology was confirmed during EUS [25], and one study reported acalculous cholecystitis in a patient in whom no etiology was found during EUS [26].

▶ **Table 3** Diagnostic yield of endoscopic ultrasonography (EUS) in patients with idiopathic acute pancreatitis (IAP).

	Diagnostic yield, n[1]	Proportion, %	95 %CI	95 %PI	Risk ratio (95 %CI)	Heterogeneity, I^2, %
Overall positive for etiology	874/1490	59	52 – 66	32 – 82	NA	82
Overall negative for etiology	616/1490	41	34 – 48	18 – 68	NA	82
Biliary disease	429/1490	30	21 – 41	5 – 77	NA	92
Chronic pancreatitis	271/1490	12	8 – 19	2 – 51	NA	89
Neoplasms	45/1490	2	1 – 4	0 – 17	NA	68
Other	138/1490	4	2 – 8	0 – 32	NA	87
Prospective studies	739/1266	58	50 – 66	31 – 81	NA	83
Non-prospective studies	135/224	61	47 – 73	31 – 84	NA	73
Studies < 2010	475/751	62	53 – 71	36 – 83	NA	75
Studies > 2009	399/739	56	47 – 65	29 – 81	NA	82
Rosemont criteria for chronic pancreatitis	264/403	65	52 – 77	40 – 85	NA	78
Other criteria for chronic pancreatitis	610/1087	57	50 – 65	30 – 81	NA	80
EUS after standard diagnostics	302/475	67	52 – 80	31 – 91	NA	86
EUS after additional diagnostics	572/1015	56	50 – 62	37 – 73	NA	62
First episode	264/494	56	46 – 65	33 – 76	0.89 (0.71 – 1.11)	69
Recurrent disease	299/594	52	34 – 69	11 – 91		
Previous cholecystectomy	105/211	50	43 – 56	43 – 56	0.81 (0.70 – 0.95)	1
Gallbladder in situ	310/496	64	54 – 73	42 – 82		
Early EUS[2]	24/50	48	35 – 62	NA	NA	0
Late EUS[3]	80/1360	61	53 – 68	33 – 83	NA	84

CI, confidence interval; PI, prediction interval; NA, not applicable.
[1] The overall diagnostic yield as well as the yield for several etiologies in a random-effects model is shown. See **Appendix 9 s** for the forest plots made to facilitate the subgroup analyses.
[2] Before clinical recovery from pancreatitis episode.
[3] After clinical recovery from pancreatitis episode.

Discussion

This meta-analysis including 1490 patients who underwent EUS for IAP found an overall diagnostic yield of 59 %. EUS mostly detected a biliary etiology (30 %), while chronic pancreatitis was diagnosed in 12 % of patients. Strikingly, in 2 % of patients, neoplastic lesions were detected.

While the number of pancreatitis episodes before EUS did not affect the diagnostic yield, we did establish that the diagnostic yield is higher in patients with a gallbladder in situ. Additionally, we found that an EUS after clinical recovery has a higher yield than EUS during acute pancreatitis (61 % versus 48 %). This was not statistically significant, potentially because only 50 patients had EUS during an acute pancreatitis episode versus 1360 patients thereafter.

Owing to limited reporting on interventions and biliary events after EUS, no meta-analysis could be performed for these secondary outcome measures. However, we did establish that the pancreatitis recurrence rate after EUS tended to be lower when biliary etiology was detected compared with when no etiology was uncovered. This finding supports the hypothesis that uncovering the etiology by EUS may prevent recurrence.

None of the studies included in this systematic review performed diagnostic work-up according to the IAP/APA Guidelines on management of acute pancreatitis [2]. This is exemplified by the fact that in the quality assessment, 21 out of 22 studies were deemed to have selected patients that were not representative of the IAP patient population. Most importantly, only two studies required a repeat transabdominal ultrasound after clinical recovery, five studies performed magnetic reso-

nance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) before EUS, and only six studies excluded patients based on abnormal liver function tests. It has previously been established that a repeat ultrasound has a diagnostic yield of 20 % for biliary stones and sludge [37], and that in particular an elevated ALT level on admission indicates high probability of biliary etiology [15]. This incomplete diagnostic work-up may have led to an overestimation of the overall diagnostic yield and of the diagnostic yield for biliary etiology using EUS.

There appeared to be considerable between-study heterogeneity in this systematic review, particularly with regard to the inclusion of patients with a first IAP or recurrent episode of IAP, inclusion of post-cholecystectomy patients, timing of the EUS, and the definition of a positive EUS. This is demonstrated by a high I^2 statistic in the meta-analysis. In this review, we have attempted to make the data more homogeneous by performing a sensitivity analysis.

In this systematic review, most detected etiologies were treatable (e. g. biliary etiology), and EUS appeared to lower recurrence rates. Additionally, some neoplastic lesions were found. Early detection of neoplasm is obviously essential. In a considerable proportion of the included patients, a pancreas divisum was present. As the prevalence of divisum is similar in the general population and in patients with a first episode of IAP, the role of pancreas divisum in acute pancreatitis is debated [38]. This may imply that the reported diagnostic yield of EUS in the studies included in this systematic review is higher than the clinically relevant diagnostic yield of EUS.

The diagnostic yield of EUS in a first episode of IAP was as high as the yield in recurrent IAP. Although the diagnostic yield was significantly higher in patients with a gallbladder in situ, the diagnostic yield in post-cholecystectomy patients was still 50 %. These findings underline the importance of additional diagnostic work-up for etiology in IAP, even in a first episode of IAP and in post-cholecystectomy patients. EUS also appeared to have a higher yield when performed after clinical recovery. Therefore, physicians should consider delaying EUS until patients have recovered.

The results of this systematic review are similar to those of a recently published review, in which a diagnostic yield of 62 % (CI 56 % – 68 %) was reported [39]. However, this review does not report on the quality of the included studies, the definitions of a positive EUS, gallbladder status, timing of cholecystectomy, or on the statistical methods used to perform and interpret the meta-analyses. Therefore, although they report considerable between-study heterogeneity with an I^2 of up to 87 %, no sensitivity analysis was performed. In our systematic review, we have attempted to increase the quality of the meta-analyses by including only peer-reviewed studies, critically appraising these studies, and extracting sufficient data to perform a sensitivity analysis.

The main limitations of this systematic review are that all studies lacked a complete standard diagnostic work-up of IAP before EUS, including consideration of abnormal liver functions tests and repeat imaging after clinical recovery, and that most of the included studies lacked homogeneous data on patients with either first episode IAP or recurrent disease. Multiple previous studies have confirmed the association between elevated liver function tests and biliary etiology, with a positive predictive value of 85 % for an ALT above 150 U/L within 48 hours after onset of symptoms [15]. Future studies should focus on including homogeneous patient groups who truly have IAP, according to current guidelines. Therefore, the Dutch Pancreatitis Study Group has decided to conduct the multicenter, prospective cohort PICUS study, including 106 patients after a first episode of IAP with complete standard diagnostic work-up.

In conclusion, this systematic review shows that EUS can detect a potential etiology in the majority of patients with IAP and that detection and subsequent treatment of the etiology may be associated with a reduction of pancreatitis recurrence. There is, however, a paucity of prospective homogeneous data on the diagnostic yield of EUS in IAP after a complete standard diagnostic work-up according to international guidelines. The etiology appears to be mostly biliary stones or sludge, and chronic pancreatitis, but neoplastic causes are also found in a substantial proportion of these patients.

The protocol for this systematic review was registered on PROSPERO (CRD42019120730) and is available in full on the NIHR website (https://www.crd.york.ac.uk/prospero/).

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Competing interests

The authors declare that they have no conflict of interest.

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