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ORIGINAL ARTICLE

Exocrine Pancreatic Insufficiency Following Acute Pancreatitis: Systematic Review and Meta-Analysis

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Abstract

Background/Objectives The epidemiology of exocrine pancreatic insufficiency (EPI) after acute pancreatitis (AP) is uncertain. We sought to determine the prevalence, progression, etiology and pancreatic enzyme replacement therapy (PERT) requirements for EPI during follow-up of AP by systematic review and meta-analysis.

Methods Scopus, Medline and Embase were searched for prospective observational studies or randomized clinical trials (RCTs) of PERT reporting EPI during the first admission (between the start of oral refeeding and before discharge) or follow-up (≥ 1 month of discharge) for AP in adults. EPI was diagnosed by direct and/or indirect laboratory exocrine pancreatic function tests.

Results Quantitative data were analyzed from 370 patients studied during admission (10 studies) and 1795 patients during follow-up (39 studies). The pooled prevalence of EPI during admission was 62% (95% confidence interval: 39–82%), decreasing significantly during follow-up to 35% (27–43%; risk difference: −0.34, −0.53 to −0.14). There was a two-fold increase in the prevalence of EPI with severe compared with mild AP, and it was higher in patients with pancreatic necrosis and those with an alcohol etiology. The prevalence decreased during recovery, but persisted in a third of patients. There was no statistically significant difference between EPI and new-onset pre-diabetes/diabetes (risk difference: 0.8, 0.7–1.1, $P = 0.33$) in studies reporting both. Sensitivity analysis showed fecal elastase-1 assay detected significantly fewer patients with EPI than other tests.

Conclusions The prevalence of EPI during admission and follow-up is substantial in patients with a first attack of AP. Unanswered questions remain about the way this is managed, and further RCTs are indicated.

Keywords Acute pancreatitis · Exocrine pancreatic insufficiency · Pancreatic enzyme replacement therapy · Necrotizing pancreatitis · Severe pancreatitis

Introduction

Patients presenting with acute pancreatitis (AP) are at risk of local and systemic complications, some of which persist beyond the hospital admission [1]. This includes both endocrine and exocrine pancreatic insufficiency (EPI). Recent studies have shown that prediabetes and diabetes mellitus (DM) occur following the first attack of AP in up to 40% patients and increase over 5 years [2]; they are associated with a marked reduction in the quality of life [3, 4]. Another study found that 10% of first-attack AP patients will then develop chronic pancreatitis [5]. A recent meta-analysis [6] investigated EPI after AP, but not during hospital admission, and found that a quarter of all AP patients develop EPI

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during follow-up. The risk of EPI is higher when patients have alcoholic etiology, severe and necrotizing pancreatitis.

The prevalence of EPI following AP and the use of pancreatic enzyme replacement therapy (PERT) are variably reported in the literature. The aim of this study was to undertake a systematic review and meta-analysis to determine the prevalence of EPI using formal exocrine function tests during AP hospitalization and follow-up to determine the contributing factors and time course and define strategies for PERT to treat EPI after AP.

Methods

Data Sources and Searches

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [7]. Electronic databases (Scopus, Embase and Medline) were searched (IB-R, CC-S and JL-N) for relevant studies from 1 January 1946 to 31 July 2018. References from searched studies were also examined. The keywords are listed in Supplementary Methods. Two authors (WH and DdlI-G) scrutinized all identified studies independently and agreed on those for inclusion. Citations from included studies and relevant reviews were also evaluated. When there was a discrepancy, the senior authors (JED-M and RS) arbitrated.

Study Selection

Included studies fulfilled the following criteria: (1) prospective observational studies or randomized clinical trials (RCTs) of PERT that reported on EPI during the index admission (between the start of oral refeeding and before discharge) or follow-up (≥ 1 month after discharge) for AP in adults; (2) EPI diagnosed by direct and/or indirect laboratory exocrine function tests [8, 9]; (3) with multiple publications with overlapping patient groups the most recent study was included unless an earlier study had a larger sample size. Editorials, expert opinions, reviews, abstracts, case reports, letters, small sample size (< 10 patients), pre-existing EPI, population-based studies and retrospective studies were excluded.

Data Extraction and Quality Assessment

Two authors (WH and DdlI-G) independently collected data from included studies using a standardized pro forma designed by two senior authors (JED-M and RS). The data items are provided in Supplementary Methods. Three authors (XZ, NS and WC) independently scored the included studies, and two further authors (WH and DdlI-G) resolved any disagreement. The quality of observational studies was assessed using the Newcastle-Ottawa scale [10] with a total score ≥ 5 (up to 4 for selection, 2 for comparability and 3 for outcome) indicative of high quality; the quality of RCTs was assessed using the Jadad system [11] with a total score ≥ 3 (randomization 0 or 1; allocation concealment 0 or 1; double blinding 0, 1 or 2; recording of dropouts and/or withdrawals 0 or 1) indicative of high quality.

Outcomes of Interest

The primary outcome was the number (proportion) of patients diagnosed with EPI following development of AP during both hospitalization for the first attack of AP and follow-up. EPI was diagnosed by either direct pancreatic function tests, including the Lundh meal test, secretin-caerulein (or pancreozymin) test (SCT), amino acid consumption test (AACT), fecal chymotrypsin test or fecal elastase-1 (FE-1) test, or indirect tests including the triolein breath test, serum fluorescein-dilaurate test, serum pancreolauryl test, urinary pancreolauryl test, urinary *N*-benzoyl-L-tyrosyl-*P*-aminobenzoic acid (NBP-PABA) test, urinary D-xylose excretion test and fecal fat excretion (FFE) test. An FE-1 of 100–200 μg/g was defined as mild to moderate EPI and < 100 μg/g as severe EPI.

Secondary outcomes included symptoms of EPI [12], treatment with PERT [12], recurrence of AP [1, 13], new-onset prediabetes and/or DM [2, 14], changes in pancreatic morphology, quality of life and employment status.

Definition of AP Severity, Complications and Pancreatic Intervention

AP was classified as severe when fulfilling one or more of the following criteria: (1) the "severe" category of the original Atlanta classification (OAC) [15]; (2) the "moderately severe" and "severe" grades of the revised Atlanta classification (RAC) [16]; (3) the presence of necrosis ($> 30\%$), pseudocyst or abscess; (4) a clinical severity score, imaging severity indices or biomarkers greater than their respective cutoff values. Other cases of AP were classified as mild. Studies were analyzed separately if they only included infected pancreatic necrosis (IPN), and IPN was defined as those with definitive diagnosis of pancreatic infection [17] and/or unresolving sterile necrosis that was treated by pancreatic necrosectomy that became infected [17, 18]. Necrosectomy included open and minimally invasive procedures, while conservative management included no procedure, percutaneous drainage or an endoscopic procedure only [19].

Data Synthesis and Statistical Analysis

Pooled data were expressed as prevalence with 95% confidence interval (CI). Data for two group comparisons were expressed as relative risk (RR) or risk difference (RD) with 95% CI. Stats Direct V3.1 (StatsDirect Ltd, Cheshire, UK) was used to generate forest plots of pooled data using a random effects model to deliver the most conservative estimates. Heterogeneity was evaluated using χ^2. $P < 0.1$ was considered significant. Statistical heterogeneity was assessed using I^2 values with cutoffs of 25%, 50% and 75% to indicate low, moderate and high heterogeneity, respectively [20]. Meta-analyses generated the RR and RD for each comparison between two groups. For studies of EPI during the index admission and follow-up, the prevalence of EPI during the index admission was compared with EPI during follow-up between gallstone versus alcohol etiology and OAC mild versus severe AP. For all the follow-up studies, the prevalence of EPI was compared between females versus males; gallstones versus alcohol etiology; OAC mild versus severe AP; RAC mild versus moderate to severe AP; edematous versus necrotizing AP; necrosis < 50% versus necrosis ≥ 50%; necrosis in the head versus body and/or tail; conservative management versus necrosectomy. Pooled prevalence of recurrent AP, pre-diabetes and/or DM and pancreatic morphologic changes were also generated.

Subgroup analyses examined high-quality studies, studies with sample sizes ≥ 40, Western population, etiology (gallstone or alcohol) and follow-up periods (up to 12 months, > 12–36 months, > 36–60 months and > 60 months). Sensitivity analyses considered studies restricted to first AP episodes, pre-existing DM, studies with a proportion of patients undergoing pancreatic intervention for necrosis and/or infection during the index admission, direct EPI tests, indirect EPI tests, FFE test only and FE-1 test only.

Meta-regression analyses determined the impact of publication year, patient age, gender, AP etiology, disease severity, type of EPI test and study quality on the pooled prevalence estimate using Stata SE version 13 software (StataCorp LP, College Station TX, USA); $P < 0.05$ was considered significant. Publication bias was assessed visually by funnel plots [21] and using P values generated from the pooled prevalence of EPI during index admission and follow-up as well as by subgroups according to Begg-Mazumdar [22] and Egger et al. [23]; $P < 0.05$ was considered significant.

Results

Characteristics of Included Studies

A PRISMA flow diagram for study selection is shown in Fig. 1. A final total of 41 studies [24–64] from 16 countries were included. The study designs are summarized in Table 1. Thirty-seven studies were published in English, two [27, 29] in Spanish, one [41] in Italian and one [59] in Russian. There were two RCTs [30, 55] for PERT versus placebo and one for the endoscopic versus surgical step-up approach [64]. Ten studies [36, 44, 46, 47, 49, 51, 53, 54, 57, 64] had a consecutive cohort design, and the remainders were non-consecutive cohort studies. Three studies [55, 56, 64] were multicenter. The shortest median follow-up was 1 month [27] and the longest 180 months [51]. Ten studies [25, 27, 29–31, 40, 44, 48, 49, 55] assessed EPI during hospitalization and 39 studies [24–48, 50–54, 56–64] during follow-up.

Of the 38 studies scored by the Newcastle-Ottawa scale with Selection, Comparability and Outcome compositions (Supplementary Table 1A), 32 (84%) were of high quality [24–29, 31–54, 56–62, 64]. The three RCTs [30, 55, 64] were all of high quality (Supplementary Table 1B). Regarding the *Selection* section, 22 (58%) studies had no *"selection of the non-exposed cohort*," while 35 (92%) did not report *"demonstration that outcome of interest was not present at start of study."* In the *Comparability* section, 33 (87%) did not show *"comparability of cohorts on the basis of the design or analysis."* In the *Outcome* section, ten had no *"adequacy of follow-up of cohorts."*

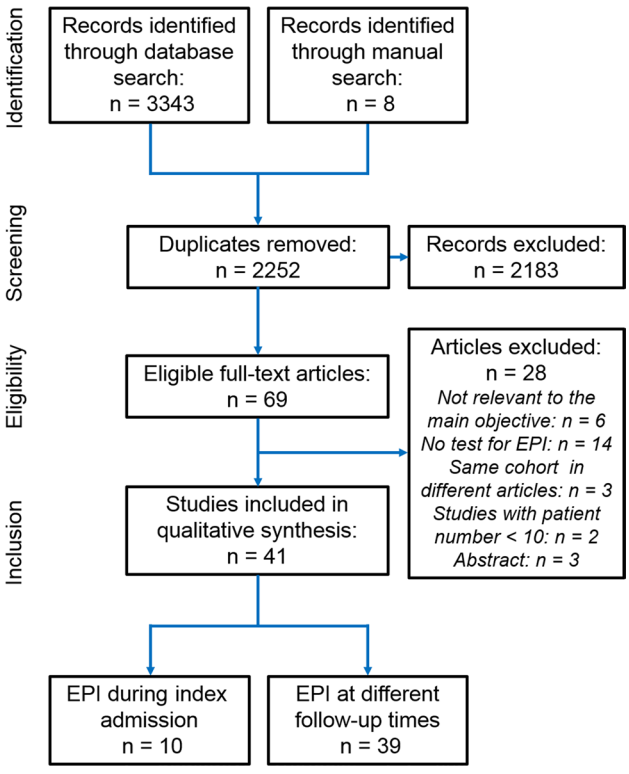

Fig. 1 Preferred reporting items for the systematic reviews flow chart of study selection for this systematic review

Table 1 Design and quality assessment of included studies

Study	Year	Country	Follow-up design	Single or multi-center	Index hospitalization period of source cohort	Study AP population[a]	Type of comparison	Follow-up time (months)[b]	Quality score
Braganza et al.	1973	UK	Prospective cohort	Single	NR	NR	None	> 3	NOS, 6
Seligson et al.	1982	Sweden	Prospective cohort	Single	1969–1978	Severe[c]	None	59 (18–108)	NOS, 5
Mitchell et al.	1983	UK	Prospective cohort	Single	NR	All severity	Index admission versus follow-up; mild versus severe; biliary versus alcohol	Index admission, 2–12	NOS, 6
Angelini et al.	1984	Italy	Prospective cohort	Single	NR	Severe[c]	Biliary versus alcohol	13–36	NOS, 5
Arenas et al.	1986	Spain	Prospective cohort	Singe	NR	All severity	Index admission versus follow-up; biliary versus alcohol	Index admission, 1	NOS, 4
Büchler et al.	1987	Germany	Prospective cohort	Single	1981 to 1985	All severity	Edematous versus necrotizing; biliary versus alcohol	2–12, 13–40	NOS, 6
Garnacho Montero et al.	1989	Spain	Prospective cohort	Single	NR	All severity; biliary and alcohol	Index admission versus follow-up; biliary versus alcohol	Index admission, 3–12	NOS, 6
Airely et al.	1991	UK	Prospective RCT	Single	NR	Mild[c]	Index admission versus follow-up; placebo versus PERT	Index admission, 1.5	Jadad, 3
Glasbrenner et al.	1992	Germany	Prospective cohort	Single	NR	Mild[c]	Index admission versus follow-up; biliary versus alcohol	Index admission, 1.5	NOS, 5
Bozkurt et al.	1995	Germany	Prospective cohort	Single	NR	IPN	None	3–12, 18	NOS, 5
Seidensticker et al.	1995	Germany	Prospective cohort	Single	1976 to 1992	All severity	Biliary versus alcohol	< 12, 12–60, > 60	NOS, 5
Malecka-Panas et al. (a)	1996	Poland	Prospective cohort	Single	NR	Severe[c]; alcohol	None	48–84	NOS, 4
Malecka-Panas et al. (b)	1996	Poland	Prospective cohort	Single	NR	All severity; biliary	None	6–12; 36–60	NOS, 4
John et al.	1997	South Africa	Prospective consecutive cohort	Single	NR	All severity	None	9 (2–16)	NOS, 4
Tsiotos et al.	1998	USA	Prospective cohort	Single	1983 to 1995	IPN	None	48 (3–132)	NOS, 5
Appelros et al.	2001	Sweden	Prospective cohort	Single	1985 and 1994	Severe[c]	None	84 (24–144)	NOS, 4

Table 1 (continued)

Study	Year	Country	Follow-up design	Single or multicenter	Index hospitalization period of source cohort	Study AP population[a]	Type of comparison	Follow-up time (months)[b]	Quality score
Ibars et al.	2002	Spain	Prospective cohort	Single	July 1994 to December 1995	All severity; biliary	Mild versus severe	6–12	NOS, 6
Boreham et al.	2003	UK	Prospective cohort	Single	December 2000 to November 2001	All severity	Index admission versus follow-up; mild versus severe	Index admission, 3	NOS, 7
Napolitano et al.	2003	Italy	Prospective cohort	Single	NR	Mild[c]; biliary	None	48	NOS, 7
Sabater et al.	2004	Spain	Prospective cohort	Single	1994 to 1998	Severe (included a proportion of IPN)[c]; biliary	Conservative versus necrosectomy	12	NOS, 8
Migliori et al.	2004	Italy	Prospective cohort	Single	NR	All severity; biliary and alcohol	Edematous versus necrotizing; biliary versus alcohol	18	NOS, 6
Bavare et al.	2004	India	Prospective consecutive cohort	Single	January 2001 to June 2003	IPN	Index admission versus follow-up	Index admission, 6–12, 13–18	NOS, 5
Symersky et al.	2006	Netherlands	Prospective cohort	Single	1990 to 1996	All severity; nonalcoholic	Mild versus severe	55 (12–90)	NOS, 4
Reszetow et al.	2007	Poland	Prospective consecutive cohort	Single	January 1993 to December 1999	IPN; biliary and alcohol	Biliary versus alcohol; female versus male	61 (24–96)	NOS, 5
Reddy et al.	2007	India	Prospective consecutive cohort	Single	1996 to 1998	IPN	Biliary versus alcohol; female versus male	22 (15–36)	NOS, 5
Pelli et al.	2009	Finland	Prospective cohort	Single	January 2001 to February 2004	All severity, alcoholic	Index admission versus follow-up; mild versus severe	Index admission, 24	NOS, 5
Pezzilli et al.	2009	Italy	Prospective consecutive cohort	Single	January 2006 to December 2006	All severity	Mild versus severe; biliary versus alcohol; female versus male	Index admission	NOS, 3
Gupta et al.	2009	India	Prospective cohort	Single	July 2005 to December 2006 (and prior to 2005)	Severe (included a proportion of IPN)[c]	Conservative versus necrosectomy	31 (7–118)	NOS, 4
Uomo et al.	2010	Italy	Prospective consecutive cohort	Single	January 1994 to December 2006	Severe[c]	None	180 (156–203)	NOS, 6
Andersson et al.	2010	Sweden	Prospective cohort	Single	2001–2005	All severity	Mild versus severe	42 (36–53)	NOS, 8
Xu et al.	2012	China	Prospective consecutive cohort	Single	2003 to 2008	All severity	Mild versus severe	29	NOS, 7

Table 1 (continued)

Study	Year	Country	Follow-up design	Single or multicenter	Index hospitalization period of source cohort	Study AP population[a]	Type of comparison	Follow-up time (months)[b]	Quality score
Garip et al.	2013	Turkey	Prospective consecutive cohort	Single	March 2003 to October 2007	All severity	Mild versus severe; edematous versus necrotizing	32 (6–48)	NOS, 6
Kahl et al.	2014	Germany	Prospective RCT	Multicenter	NR	All severity	Placebo versus PERT	Index admission	Jadad, 4
Vujasinovic et al.	2014	Slovenia	Prospective cohort	Multicenter	NR	All severity	Mild versus severe (mild versus moderate versus severe[d]); biliary versus alcohol; female versus male	32	NOS, 5
Winter Gasparoto et al.	2015	Brazil	Prospective consecutive cohort	Single	January 2002 to April 2012	Severe[c]	None	35 (12–90)	NOS, 4
Chandrasekaran et al.	2015	India	Prospective cohort	Single	July 2009 to December 2010	Severe (included a proportion of IPN)[c]	Conservative versus necrosectomy	26 ± 18	NOS, 8
Ermolov et al.	2016	Russia	Prospective cohort	Single	2003 to 2012	Severe (included a proportion of IPN)[c]	Conservative versus necrosectomy	102 ± 36	NOS, 6
Nikkola et al.	2017	Finland	Prospective cohort	Single	January 2001 to February 2005	All severity; alcoholic	Mild versus severe[d]	126 (37–155)	NOS, 5
Koziel et al.	2017	Poland	Prospective cohort	Single	2011 and 2012	Mild and severe	Mild versus severe (mild versus moderate to severe[d]); biliary versus alcohol	14 ± 4	NOS, 8
Tu et al.	2017	China	Prospective cohort	Single	January 2016 to April 2016	All severity (included a proportion of IPN)	Mild versus moderate versus severe[d]	43 ± 4	NOS, 5
van Brunschot et al.	2018	Netherland	Prospective RCT	Multicenter	September 2011 to January 2015	Infected pancreatic necrosis	Endoscopic versus surgical step up approach	6	Jadad, 5

AP acute pancreatitis, *NOS* Newcastle-Ottawa Scale, *NR* not reported, *RCT* randomized controlled trial, *PERT* pancreatic enzyme replacement therapy, *IPN* infected pancreatic necrosis and/or unresolving sterile necrosis that needed necrosectomy and became infected

[a]Included all etiologies if not otherwise stated

[b]Index admission refers to between the start of oral refeeding and before discharge

[c]Severe was defined by original Atlanta classification or the authors own clinical criteria

[d]Severe was defined by the revised Atlanta classification

Characteristics of Included Patients

The overall baseline characteristics of patients are shown in Table 2. For ten inpatient studies, the pooled median age was 51 years (males, 59%); etiology was 70% gallstones, 17% alcohol and 13% other causes; six studies were restricted to first AP episodes [30, 31, 40, 44, 48, 49], while four [25, 27, 29, 55] did not report. For the 39 follow-up studies, the pooled median age was 51 years (males, 63%); etiology was 55% gallstone, 28% alcohol and 17% other causes; 16 studies were restricted to first AP episodes [30–34, 39, 40, 43–46, 48, 50, 53, 57, 60], while 5 [28, 35, 38, 56, 62] were not so restricted, and the remaining 18 [24–27, 29, 36, 37, 41, 42, 47, 51, 52, 54, 58, 59, 61, 63, 64] did not report.

Pancreatic Function During Admission and Follow-Up

Detailed pancreatic function data and clinical outcomes at follow-up are shown in Table 3. For the 10 inpatient studies, 1 [48] reported pre-existing DM in 8 of 54 patients (15%), 2 [40, 49] reported none, and the remaining studies [25, 27, 29–31, 44, 55] did not report; 2 [44, 49] had a proportion of patients who had undergone pancreatic interventions, 4 [25, 30, 31, 40] had none, and 4 [27, 29, 48, 55] did not report.

In the 39 follow-up studies, body mass index, alcohol history, cigarette smoking and symptoms of EPI were rarely recorded (data not shown). Nine studies [24, 38, 48, 51, 52, 54, 60, 61, 64] had a minor proportion of pre-existing DM (1.3–18%), 8 [40, 46, 47, 50, 53, 57, 58, 62] had none, and the remaining 22 [25–37, 39, 41–45, 56, 59, 63] did not report; 22 [26, 28, 32, 33, 37, 38, 42, 44–47, 50–54, 57–59, 61, 62] had a proportion of patients who had undergone pancreatic interventions; 10 [25, 30, 31, 34, 39–41, 43, 60, 63] reported no pancreatic interventions, and the remaining 7 [24, 27, 29, 35, 36, 48, 56] did not report.

Results of the Meta-Analysis

There were insufficient data for quantitative meta-analysis of the effects of PERT versus placebo in the two RCTs [30, 55]. The results of meta-analysis are shown in Table 4.

Prevalence of EPI During Admission and Follow-Up

In the 10 index admission studies, 389 patients were enrolled and 370 analyzed (Supplementary Figure 1A). The pooled prevalence of EPI was 62% (95% CI 39–82%), with high statistical heterogeneity among studies ($I^2 = 95\%$). Of the eight studies [25, 27, 29–31, 40, 44, 48] that also provided data on EPI during follow-up, the pooled prevalence of EPI was 71% (50–89%) during the index admission and 33% (17–53%) during follow-up, respectively (Supplementary Figure 1B and 1C), showing that the prevalence of EPI halved (RD: −0.34, −0.53 to −0.14) during follow-up (Fig. 2a).

Five studies [25, 27, 29, 31, 49] of EPI during the index admission compared alcohol versus gallstone etiology (RR: 1.79, 0.59–5.43, $P = 0.35$; Fig. 2b), and three [25, 40, 49] compared OAC severe versus mild AP (RR: 2.9, 0.5–16.7, $P = 0.24$; Fig. 2c), both showing no significant difference. No data were quantitively synthesized for gender and necrosis.

Prevalence of EPI During Follow-Up Alone

In the 39 follow-up studies, 2168 patients were enrolled and 1795 analyzed (Table 4 and Supplementary Figure 2). The pooled prevalence of EPI was 35% (27–43%), with high statistical heterogeneity among studies ($I^2 = 92\%$). The pooled prevalence of EPI was 21% for OAC mild AP (13 studies) (Supplementary Figure 3A), 42% for OAC severe AP (23 studies) (Supplementary Figure 3B), 16% for RAC mild AP (4 studies) (Supplementary Figure 4A), 27% for RAC moderately severe AP (2 studies) (Supplementary Figure 4B) and 30% for RAC severe AP (3 studies) (Supplementary Figure 4C). The pooled prevalence of EPI was 24% for edematous AP (8 studies) (Supplementary Figure 5A), 47% for necrotizing AP (15 studies) (Supplementary Figure 5B) and 48% for IPN (11 studies) (Supplementary Figure 5C).

There was no significant difference in the prevalence of EPI during follow-up for gender (RR: 1.5, 0.4–6.3, $P > 0.5$; 3 studies) [46, 47, 56] (Table 4). There was a significantly higher prevalence of EPI for patients with alcohol etiology compared with gallstones (RR: 1.6, 1.1–2.3, $P = 0.01$; 11 studies) [26, 28, 29, 31, 33–35, 43, 46, 47, 56, 61] (Fig. 3a). There was a higher prevalence of EPI in patients with OAC severe AP versus mild AP (RR: 1.5, 1.2–2, $P = 0.003$, 10 studies) [40, 45, 48, 52–54, 56, 60–62] (Fig. 3b); in RAC moderately severe/severe versus mild AP (RR: 2, 1.1–3.4, $P = 0.018$, 3 studies) [56, 61, 62] (Fig. 3c); in necrotizing versus edematous AP (RR: 1.8, 1–3.2, $P = 0.06$; 6 studies) [28, 40, 43, 50, 54, 62] (Fig. 4a). There was no significant difference in the prevalence of EPI for ≥ 50% necrosis versus < 50% necrosis (RR: 1.2, 1–1.6, $P = 0.172$, 6 studies) [28, 40, 46, 47, 50, 62] (Fig. 4b), for pancreatic head versus body and/or tail necrosis (RR: 1.1, 0.6–2, $P > 0.5$; 3 studies) [46, 47, 62] (Table 4) or for patients having necrosectomy versus conservative management (RR: 1.62, 0.8–3.44, $P = 0.205$; 5 studies) [42, 50, 58, 59, 64] (Fig. 4c).

The pooled prevalence for recurrent AP, pre-diabetes and/or DM and pancreatic morphologic changes was 24% (17–31%), 38% (31–45%) and 36% (27–45%), respectively (Table 4). In the studies [24, 26, 28, 34, 37–42, 44–48, 50–52, 54, 56–62] that reported on the occurrence of EPI

Table 2 Baseline characteristics of patients in the included studies

Study	Patients enrolled (analyzed for EPI)	Age, year[a]	Male, *n* (%)	Biliary	Alcoholic	Others	First AP episode	Severity criteria	Severity status
Braganza et al.	12 (12)	NR	NR	NR	NR	NR	NR	NR	NR
Seligson et al.	10 (10)	54 ± 12	8 (80)	2	7	1	NR	Necrotizing AP	10 severe
Mitchell et al.	30 (30)	22–89	15 (50)	13	6	11	NR	Clinical complication	25 mild, 5 severe
Angelini et al.	27 (20)[b]	NR	24 (89)[b]	14[b]	10[b]	3[b]	NR	Necrotizing AP	27 severe
Arenas et al.	26 (26)	24–82	9 (35)	16	4	7	NR	NR	NR
Büchler et al.	79 (79)	46	48 (61)	28	37	14	Partially[c]	Necrotizing AP	27 edematous, 32 minor necrotizing, 20 major necrotizing
Garnacho Montero et al.	19 (19)	23–75	9 (47)	11	8	0	NR	NR	NR
Airey et al.	59 (41)	62 (30–82)	19 (46)	30	6	5	All	Local or systemic complication	41 mild, 0 severe
Glasbrenner et al.	29 (29)	37 (22–68)	17 (59)	15	14	0	All	Pancreatic necrosis and CRP > 120 mg/l	Mean ranson score 1.6
Bozkurt et al.	89 (53)[b]	21–83[b]	59 (66)[b]	21[b]	56[b]	12[b]	All	IPN	53 IPN
Seidensticker et al.	38 (38)	41 ± 14	25 (66)	8	16	14	All	Ranson score > 3	21 ranson score ≤ 3, 4 ranson score > 3
Malecka-Panas et al. (a)	47 (47)	44 ± 10	33 (70)	47	0	0	All	Imrie criteria 3–4	47 severe
Malecka-Panas et al. (b)	30 (30)	53 ± 17	8 (27)	30	0	0	Partially (70%)	Imrie criteria ≥ 3	NR
John et al.	50 (50)	39	38 (76)	5	42	3	NR	OAC	NR
Tsiotos et al.	72 (44)	58 (20–93)	33 (75)	17	5	22	NR	IPN	44 IPN
Appelros et al.	79 (26)	60 (27–92)[b]	52 (66)[b]	19[b]	30[b]	30[b]	Partially (87%)	OAC	79 severe[b]
Ibars et al.	63 (61)	62 ± 14[b]	17 (27)[b]	63[b]	0[b]	0[b]	All	OAC and area of necrosis	45 mild, 18 severe; 6 necrosis 30–50%, 3 necrosis ≥ 50%[b]
Boreham et al.	23 (23)	55 (21–77)	13 (57)	15	5	3	All	OAC	16 mild, 7 severe
Napolitano et al.	35 (35)	NR	NR	35	0	0	NR	NR	NR
Sabater et al.	39 (27)	No surgery: 61 ± 14; necrosectomy: 64 ± 11	12 (44.4)	27	0	0	NR	OAC; IPN	27 severe (11 necrosis ≥ 50%); 12 IPN, 15 sterile necrosis
Migliori et al.	75 (75)	46 (17–80)	57 (76)	39	36	0	All	Necrotizing AP	42 edematous, 33 necrotizing
Bavare et al.	18 (18)	36 (25–47)	18 (100)	4	10	4	All	IPN	18 IPN
Symersky et al.	34 (34)	53 ± 3	16 (47)	26	0	8	All	OAC	22 mild, 12 severe
Reszetow et al.	28 (28)	48 ± 10	20 (71)	10	18	0	All	IPN	28 IPN (26 APACHE II > 8)
Reddy et al.	10 (10)	35 (22–47)	8 (80)	4	6	0	NR	IPN	IPN (5 necrosis < 50%, 4 necrosis ≥ 50%, 1 unspecified)
Pelli et al.	54 (54)	49 (25–71)	47 (87)	54	0	0	All	OAC	41 mild, 13 severe
Pezzilli et al.	75 (75)	62 (20–94)	37 (49)	61	1	13	All	OAC	60 mild, 15 severe
Gupta et al.	30 (30)	38 ± 2	24 (80)	12	13	5	All	OAC; IPN	22 IPN, 8 sterile necrosis

Table 2 (continued)

Study	Patients enrolled (analyzed for EPI)	Age, year[a]	Male, *n* (%)	Biliary	Alcoholic	Others	First AP episode	Severity criteria	Severity status
Uomo et al.	65 (40)	48±18	17 (42.5)	28	0	12	NR	NR	25 necrosis < 50%, 15 necrosis ≥ 50%
Andersson et al.	40 (40)	61 (48–68)	16 (40)	20	10	10	NR	OAC	26 mild (3 APACHE II ≥ 8), 14 severe (9 APACHE II ≥ 8)
Xu et al.	65 (65)	59 (27–82)	33 (51)	50	7	8	All	OAC	Mild 27, severe 38
Garip et al.	109 (109)	57 ± 16	58 (53)	72	9	28	NR	APACHE II ≥ 8	39 severe (APACHE II ≥ 8), 70 mild (APACHE II < 8); necrosis 30
Kahl et al.	56 (55)	51 (23–81)	34 (62)	NR	NR	NR	NR	APACHE II ≥ 4; CRP > 120 mg/L	Placebo: APACHE II 5.1 ± 3.2, CRP 172 ± 108 mg/l; PERT: APACHE II 5.3 ± 2.9, CRP 176 ± 79 mg/l
Vujasinovic et al.	100 (100)	58 ± 12	65 (65)	36	42	22	Partially (75%)	RAC	67 mild, 15 moderate, 18 severe
Winter Gasparoto et al.	16 (16)	48 ± 13	9 (56)	10	4	0	Yes	APACHE II ≥ 8 or 12 CRP ≥ 150 mg/l	4 APACHE II ≥ 8, 12 CRP ≥ 150 mg/l; 9 necrosis < 30%, 4 30–50%, 3 ≥ 50%
Chandrasekaran et al.	35 (35)	37 ± 10	30 (86)	11	19	5	NR	OAC; IPN	35 severe (1 necrosis < 30%, 7 30–50%, 27 ≥ 50%; 15 APACHE II < 8, 20 APACHE II > 8); 21 IPN, 14 sterile necrosis
Ermolov et al.	210 (80)[b]	55 ± 13[b]	144 (69)[b]	NR	NR	NR	NR	OAC; IPN	Severe 210[b]; 34 IPN
Nikkola et al.	77 (45)	48 (25–71)	69 (90)	45	0	0	All	RAC	53 mild, 20 moderate, 4 severe
Koziel et al.	150 (150)	53 ± 15	94 (63)	64	46	40	NR	RAC	51 mild, 99 severe
Tu et al.	113 (113)	47 ± 1	75 (66)	65	3	45	Partially (83%)	RAC; IPN	10 mild, 12 moderate, 91 severe (73 IPN)
van Brunschot et al.	98 (83)	62 ± 13	63 (64)	56 (57)	14 (14)	28 (29)	NR	RAC	55 moderate, 43 severe

EPI exocrine pancreatic insufficiency, *AP* acute pancreatitis, *NR* not reported, *CRP* C-reactive protein, *IPN* infected pancreatic necrosis, *OAC* original Atlanta classification, *APACHE* Acute Physiology and Chronic Health Evaluation, *PERT* pancreatic enzyme replacement therapy, *RAC* revised Atlanta classification

[a]Year is expressed as mean (standardized deviation), mean (range), median (range) or range

[b]Data are derived from original enrolled patients rather than actual analyzed patients

[c]Included two cases of chronic pancreatitis

Table 3 Pancreatic function at baseline and follow-up

Study	Patients enrolled (analyzed for EPI)	Pre-existing DM (%)	Pancreatic intervention (%)[a]	EPI diagnostic criteria	EPI (%)[b]	Use of PERT	RAP (%)	New prediabetes and/or DM (%)	Pancreatic morphology changes (%)	Health status
Braganza et al.	12 (12)	NR	0 (0)	SCT < lower reference range[c]	1 (0.8)	NR	NR	NR	NR	NR
Seligson et al.	10 (10)	1 (10)	NR	Lundh meal test < lower reference range[d]	7 (70)	2 (20)	NR	5 (50)	6 (60)	NR
Mitchell et al.	30 (30)	NR	0 (0)	NBT-PABA test with urinary PABA recovery < 57%	7/15 (47); Index admission: 30 (100)	NR	NR	NR	NR	NR
Angelini et al.	27 (20)	NR	27 (100)[e]	SCT < lower reference range[c]	8/20 (40)	NR	NR	12 (44)[e]	13 (48)[e]	NR
Arenas et al.	26 (26)	NR	NR	NBT-PABA test with urinary PABA recovery < 45%	2/11 (18) Index admission: 12 (46)	NR	NR	NR	NR	NR
Büchler et al.	79 (79)	NR	52 (65.8)	SCT < lower reference range[c]; urine or serum fluorescein-dilaurate test < lower reference range (NR)	42 (53)	NR	NR	19 (24)	34 (43)	NR
Garnacho Montero et al.	19 (19)	NR	NR	NBT-PABA test with urinary PABA recovery < 45%	8 (42); Index admission: 19 (100)	NR	NR	NR	NR	NR
Airey et al.	59 (41)	NR	0 (0)	NBT-PABA test with urinary PABA recovery < 55%	29 (71); Index admission: 26 (63)	20 (49)[f]	NR	NR	NR	NR
Glasbrenner et al.	29 (29)	NR	0 (0)	Fluorescein dilaurate test with peak serum fluorescein < 4.5 µg/ml; fecal chymotrypsin < 3 U/g	Index admission: 23 (79)	0 (0)	NR	NR	NR	NR
Bozkurt et al.	89 (53)	NR	42 (47)[d]	Lundh meal test < lower reference range[d]	45 (85)	NR	NR	NR	NR	NR
Seidensticker et al.	38 (38)	NR	1 (3)	SCT < lower reference range[c]	5 (13)	NR	0 (0)	NR	7 (18)	NR

Table 3 (continued)

Study	Patients enrolled (analyzed for EPI)	Pre-existing DM (%)	Pancreatic intervention (%)[a]	EPI diagnostic criteria	EPI (%)[b]	Use of PERT	RAP (%)	New prediabetes and/or DM (%)	Pancreatic morphology changes (%)	Health status
Malecka-Panas et al. (a)	47 (47)	NR	0 (0)	SCT < lower reference range[c]	30 (64)	6 (13)	NR	14 (30)	30 (64)	NR
Malecka-Panas et al. (b)	30 (30)	NR	NR	SCT < lower reference range[c]	19 (63)	NR	NR	NR	4 (13)	NR
John et al.	50 (36)	NR	NR	Fecal chymotrypsin level < 3 U/g	11 (31)	NR	NR	NR	9 (18)	NR
Tsiotos et al.	72 (44)	NR	44 (100)	FFE > 7 g/d with or without fecal weight > 20%	11 (25)	11 (25)	2 (5)	16 (36)	NR	ECOG score
Appelros et al.	79 (26)	1 (1)	31 (39)	Pathologic triolein breath test (1 point) with weight loss > 10% (1 point), low level of serum amylase (1 point), low fat diet to avoid diarrhea (1 point); ≥ 2	18 (69)	NR	12 (34)	19 (73)	NR	Working capacity
Ibars et al.	63 (61)	NR	0 (0)	FFE > 7 g/d; SCT < lower reference range[c]; urinary pancreolauryl test < 25%; fecal chymotrypsin < 3 U/g	2 (3)	NR	NR	13 (21)	NR	NR
Boreham et al.	23 (23)	0 (0)	0 (0)	FE-1 < 200 µg/g[g]	6 (26); Index admission: 8 (35)	NR	NR	4 (17)	NR	NR
Napolitano et al.	35 (35)	NR	0 (0)	FE-1 < 200 µg/g	4 (11)	NR	NR	2 (6)	NR	NR
Sabater et al.	39 (27)	NR	12 (44)	FFE > 7 g/d for 3 days; fecal chymotrypsin < 6 U/g; SCT < lower reference range[c]	9 (33)	NR	NR	13 (48)	NR	NR

Table 3 (continued)

Study	Patients enrolled (analyzed for EPI)	Pre-existing DM (%)	Pancreatic intervention (%)[a]	EPI diagnostic criteria	EPI (%)[b]	Use of PERT	RAP (%)	New prediabetes and/or DM (%)	Pancreatic morphology changes (%)	Health status
Migliori et al.	75 (75)	NR	0 (0)	SCT with bicarbonate < 15 mmol, lipase < 150 U × 10^3; chymotrypsin < 160 U × 10^2; AACT < 14%	41 (55)	NR	NR	NR	NR	NR
Bavare et al.	18 (18)	NR	18 (100)	FFE > 7 g/d with or without steatorrhea and use of PERT	9 (50); index admission: 13 (72)	2 (11)	3 (17)	13 (72)	16 (89)	Back to work
Symersky et al.	34 (34)	NR	6 (18)	FFE > 7 g/d for 2 days; NBT-PABA test with urinary PABA < 50%	22 (65)	10 (29)	0 (0)	12 (35)	NR	GIQLI
Reszetow et al.	28 (28)	0 (0)	28 (100)	FE-1 < 200 µg/g[g]	4 (14)	NR	NR	22 (79)	12 (42)	Core FACIT scale
Reddy et al.	10 (10)	0 (0)	10 (100)	FFE > 7 g/d	8 (80)	NR	NR	5 (50)	7 (70)	Back to work
Pelli et al.	54 (54)	8 (15)	NR	FE-1 < 200 µg/g with or without plasma fat-soluble vitamin A < 1 µmol/l or vitamin E < 12 µmol/l	5 (9); index admission 21 (39)	NR	10 (19)	17 (37)	18 (51)	NR
Pezzilli et al.	75 (75)	0 (0)	5 (7)	FE-1 < 200 µg/g[g]	Index admission: 9 (12)	0 (0)	NR	NR	NR	NR
Gupta et al.	30 (30)	0 (0)	25 (83)	FFE > 7 g/d; urinary D-xylose excretion < 20%	12 (40)	4 (13)	12 (40)	12 (40)	13 (43)	NR
Uomo et al.	65 (40)	2 (5)	19 (48)	Serum pancreoauryl test < 4.5 µg/ml; FE-1 < 200 µg/g	9 (23)	0 (0)	0 (0)	6 (16)	2 (5)	NR
Andersson et al.	40 (40)	1 (2.5)	4 (10)	FE-1 < 200 µg/g	1 (3)	3 (8)	NR	22 (55)	NR	SF-36
Xu et al.	65 (65)	0 (0)	5 (8)	FE-1 < 200 µg/g[g]	38 (59)	33 (51)	NR	NR	20 (31)	NR
Garip et al.	109 (109)	13 (12)	5 (5)	FE-1 < 200 µg/g[g]	15 (14)	NR	NR	33 (30)	NR	NR
Kahl et al.	56 (56)	NR	NR	FE-1 < 200 µg/g	Index admission: 20 (36)	26 (46)[f]	NR	NR	NR	FACT-Pa

Table 3 (continued)

Study	Patients enrolled (analyzed for EPI)	Pre-existing DM (%)	Pancreatic intervention (%)[a]	EPI diagnostic criteria	EPI (%)[b]	Use of PERT	RAP (%)	New prediabetes and/or DM (%)	Pancreatic morphology changes (%)	Health status
Vujasinovic et al.	100 (100)	NR	NR	FE-1 < 200 µg/g[g] with measuring serum iron, magnesium, folic acid and vitamins A, D, E and B12	21 (21)	NR	25 (25)	14 (14)	NR	NR
Winter Gasparoto et al.	16 (16)	0 (0)	5 (31)	FFE with positive Sudan stain	1 (6)	1 (6)	NR	12 (75)	2 (13)	SF-36
Chandrasekaran et al.	35 (35)	0 (0)	21 (60)	FFE > 7 g/d	14 (40)	21 (60)	3 (8.6)	17 (48.6)	NR	NR
Ermolov et al.	210 (80)	NR	136 (65)[e]	FE-1 < 200 µg/g[g]	28 (35)	NR	58 (28)	62 (30)	12 (15)	GIQLI
Nikkola et al.	77 (45)	5 (7)[e]	0 (0)	FE-1 < 200 µg/g	11 (24)	NR	27 (35)[e]	20 (26)[e]	9 (12)[e]	NR
Koziel et al.	150 (150)	17 (11)	18 (12)	FE-1 < 200 µg/g[g]	21 (14)	NR	44 (29)	18 (14)	58 (39)	SF-36
Tu et al.	113 (113)	0 (0)	73 (65)	FE-1 < 200 µg/g[g]	40 (35)	NR	NR	67 (59)	NR	NR
van Brunschot et al.	98 (83)	18 (18)	98 (100)	FE-1 < 200 µg/g[g]	41 (49)	29 (35)	NR	19 (23)	NR	NR

EPI exocrine pancreatic insufficiency, *DM* diabetic mellitus, *RAP* recurrent acute pancreatitis, *NR* not reported, *NBT-PABA N*-benzoyl-L-tyrosyl-*P*-aminobenzoic acid, *SCT* secretin-cerulein (or pancreozymin) test, *FFE* fecal fat excretion, *FE-1* fecal elastase-1, *AACT* amino acid consumption test, *PERT* pancreatic enzyme replacement therapy, *GIQLI* Gastrointestinal Quality of Life Index, *FACIT* Functional Assessment of Chronic Illness Therapy, *SF-36* Short Form 36 Health Survey Questionnaire, *FACT* Functional Assessment of Cancer Therapy

[a]Included necrosectomy, drainage and local lavage procedures

[b]Data refer to follow-up studies if not otherwise stated and with maximal numbers of EPI during observational period

[c]Bicarbonate < 70 mEq/l, lipase < 97 kUI/h, chymotrypsin > 11 kUI/h

[d]Lundh test meal amylase < 11,000 U/h, lipase < 110,000 U/h and trypsin < 7000 U/h

[e]Data are derived from original enrolled patients rather than actual analyzed patients

[f]Contained all the patients in the PERT arm in a randomized controlled trial comparing placebo versus PERT

[g]These studies defined severity of EPI with FE-1 levels: 100–200 µg/g mild to moderate and < 100 µg/g severe

Table 4 Results of meta-analyses

Variable	No. of studies	No. of patients	No. of EPI	Effect estimate	Heterogeneity	
				Pool prevalence, % (95% CI)	I^2 (%)	*P* value
Overall during index admission	10	370	183	62 (39–82)	95	< 0.0001
Index admission versus follow-up[a]						
Index admission	8	240	154	71 (50–89)	92	< 0.0001
Follow-up	8	210	69	33 (17–53)	88	< 0.0001
Mild versus severe (OAC)						
Mild	3	101	34	46 (0–99)	98	< 0.0001
Severe	3	27	13	66 (11–99)	90	< 0.0001
Biliary versus alcohol						
Biliary etiology	5	116	51	72 (26–99)	96	< 0.0001
Alcohol etiology	6	87	50	87 (71–97)	26	0.248
Overall at follow-up	39	1795	618	35 (27–43)	91	< 0.0001
Mild versus severe (OAC)						
Mild	13	467	100	21 (11–33)	89	< 0.0001
Severe	23	847	345	42 (33–52)	86	< 0.0001
Mild versus moderate to severe (RAC)						
Mild	4	160	24	16 (10–23)	23	0.275
Moderate	2	27	7	27 (13–45)	0	0.453
Severe	3	208	58	30 (15–47)	82	0.004
Biliary versus alcohol						
Biliary etiology	15	335	72	22 (12–33)	81	< 0.0001
Alcohol etiology	14	388	155	44 (27–60)	91	< 0.0001
Other etiologies	3	72	13	19 (11–29)	0	0.726
Female versus male						
Female	3	45	6	23 (1–64)	79	0.01
Male	5	119	45	48 (26–71)	82	0.0003
Edematous versus necrotizing versus IPN						
Edematous	8	261	54	24 (14–36)	77	< 0.0001
Necrotizing	15	538	244	47 (36–58)	84	< 0.0001
IPN	11	398	188	48 (35–62)	86	< 0.0001
Necrosis < 50% versus necrosis ≥ 50%						
< 50%	6	121	49	41 (17–68)	86	< 0.0001
≥ 50%	6	81	45	58 (34–79)	76	0.001
Head versus body and/or tail						
Head	3	20	8	41 (22–62)	0	0.661
Body/tail	3	79	27	34 (11–61)	70	0.036
Conservative versus necrosectomy						
Conservative	4	74	16	23 (12–35)	24	0.267
Necrosectomy	9	183	73	48 (32–63)	77	< 0.0001
Recurrent AP	13	937	188	24 (17–31)	82	< 0.0001
Prediabetic and/or DM versus EPI[b]						
Prediabetes and/or DM	27	1454	494	38 (31–45)	87	< 0.0001
EPI	27	1357	409	32 (24–40)	90	< 0.0001
Pancreatic morphologic changes	18	810	272	36 (27–45)	87	< 0.0001

EPI exocrine pancreatic insufficiency, *CI* confidence interval, *OAC* original Atlanta classification, *RAC* revised Atlanta classification, *IPN* infected pancreatic necrosis, *AP* acute pancreatitis, *DM* diabetic mellitus

[a]Included studies that simultaneously reported prevalence of EPI during index admission and at follow-up

[b]Included studies that simultaneously reported prevalence of EPI and prediabetic and/or DM

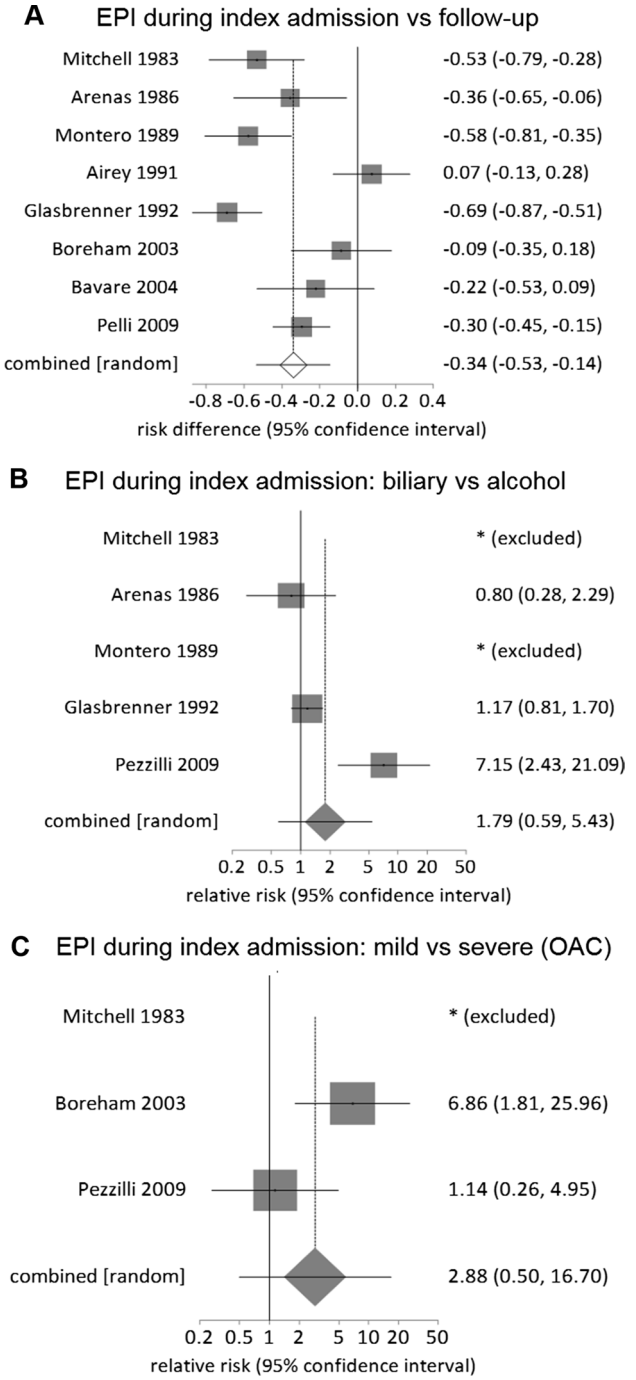

Fig. 2 Relative risk comparison for prevalence of exocrine pancreatic insufficiency during index admission of acute pancreatitis: **a** index admission versus follow-up, **b** biliary versus alcohol (original Atlanta classification, OAC) and **c** mild versus severe (OAC)

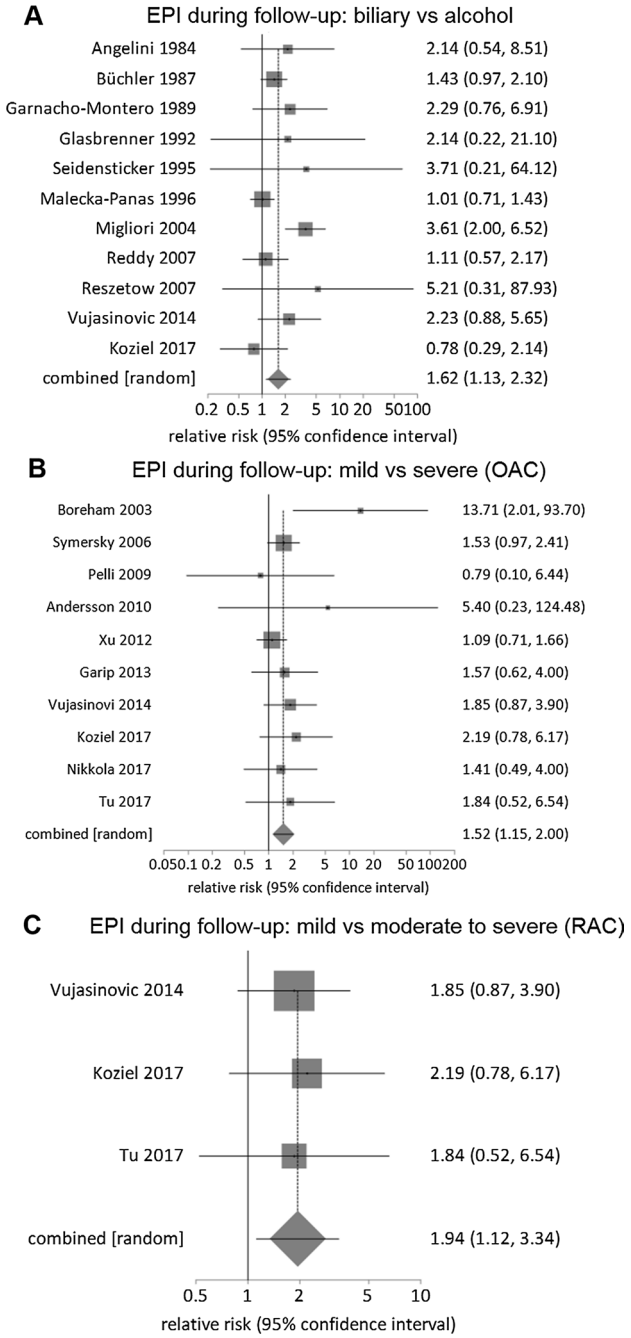

Fig. 3 Relative risk comparison for prevalence of exocrine pancreatic insufficiency for all follow-up studies of acute pancreatitis: **a** biliary versus alcohol (original Atlanta classification, OAC), **b** mild versus severe (OAC) and **c** mild versus moderate to severe (revised Atlanta classification, RAC)

and new-onset pre-diabetes and/or DM, the pooled prevalence of EPI was 32% (24–40%), without any statistically significant difference between the two (RR of EPI in patients developing new-onset pre-diabetes and/or DM: 0.8, 0.7–1.1, $P = 0.33$) (Fig. 5).

In eight studies [40, 46, 53, 54, 56, 59, 61, 62] that reported the severity of EPI and used the FE-1 test, the pooled prevalence of mild to moderately severe EPI was 16% (CI 10–24%) (Supplementary Figure 6A) and of severe EPI was 11% (CI 6–17% (Supplementary Figure 6B).

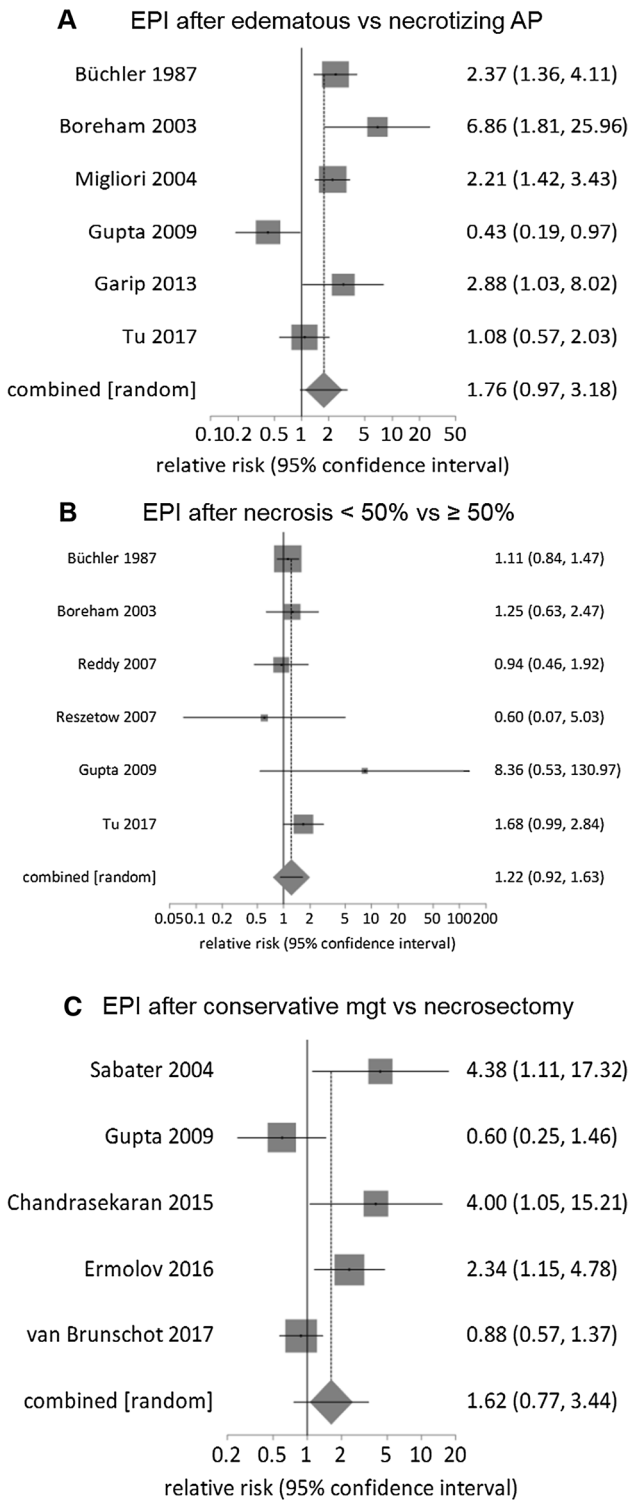

Fig. 4 Relative risk comparison for prevalence of exocrine pancreatic insufficiency at follow-up focused on acute necrotizing pancreatitis: **a** edematous versus necrotizing; **b** necrosis < 50% versus ≥ 50%; **c** conservative management (mgt) versus necrosectomy

The prevalence of EPI for long-term follow-up is shown in Fig. 6 and Supplementary Table 2. These data demonstrate that there was a steady decrease in the prevalence of EPI after AP from the index admission over the subsequent 5 years of follow-up (OAC severe AP 59–38%, OAC mild AP 56–18%), but beyond 5 years there was a modest rise in prevalence.

Subgroup Analyses

Subgroup analyses found that study quality, sample size and Western population did not affect the primary meta-analysis results (Supplementary Table 2). Gallstone etiology had a decreased prevalence of EPI compared with the primary analysis, whereas alcohol etiology had an increased prevalence of EPI. None of these factors significantly affected the statistical heterogeneity.

Sensitivity Analyses

Sensitivity analyses found that in the studies that used the FE-1 test there was a lower pooled prevalence of EPI (Supplementary Table 3). In contrast, the sensitivity analyses found that the primary meta-analysis results were not affected by restriction to first episodes of AP, the proportion of patients with pre-existing DM, the proportion of patients who had undergone pancreatic intervention or the use of direct, indirect or FFE tests to diagnose EPI. None of these factors significantly affected statistical heterogeneity.

Meta-regression Analysis

Meta-regression analyses did not identify any significant contributing factor to study heterogeneity by any pre-defined criterion except the year of publication for the follow-up study (Supplementary Table 4).

Publication Bias

Funnel plots for publication bias are shown in Supplementary Figure 6. There was no publication bias identified for admission studies ($n = 10$), follow-up studies ($n = 39$) or OAC severe AP patients (Begg-Mazumdar and Egger tests $P > 0.1$). There was significant publication bias for the follow-up studies of OAC mild AP patients (both Begg-Mazumdar and Egger tests $P < 0.05$).

Discussion

By combining data from a total of 41 studies, we found EPI in over half (62%) of all AP patients during their index admission, including patients of all grades of severity. One

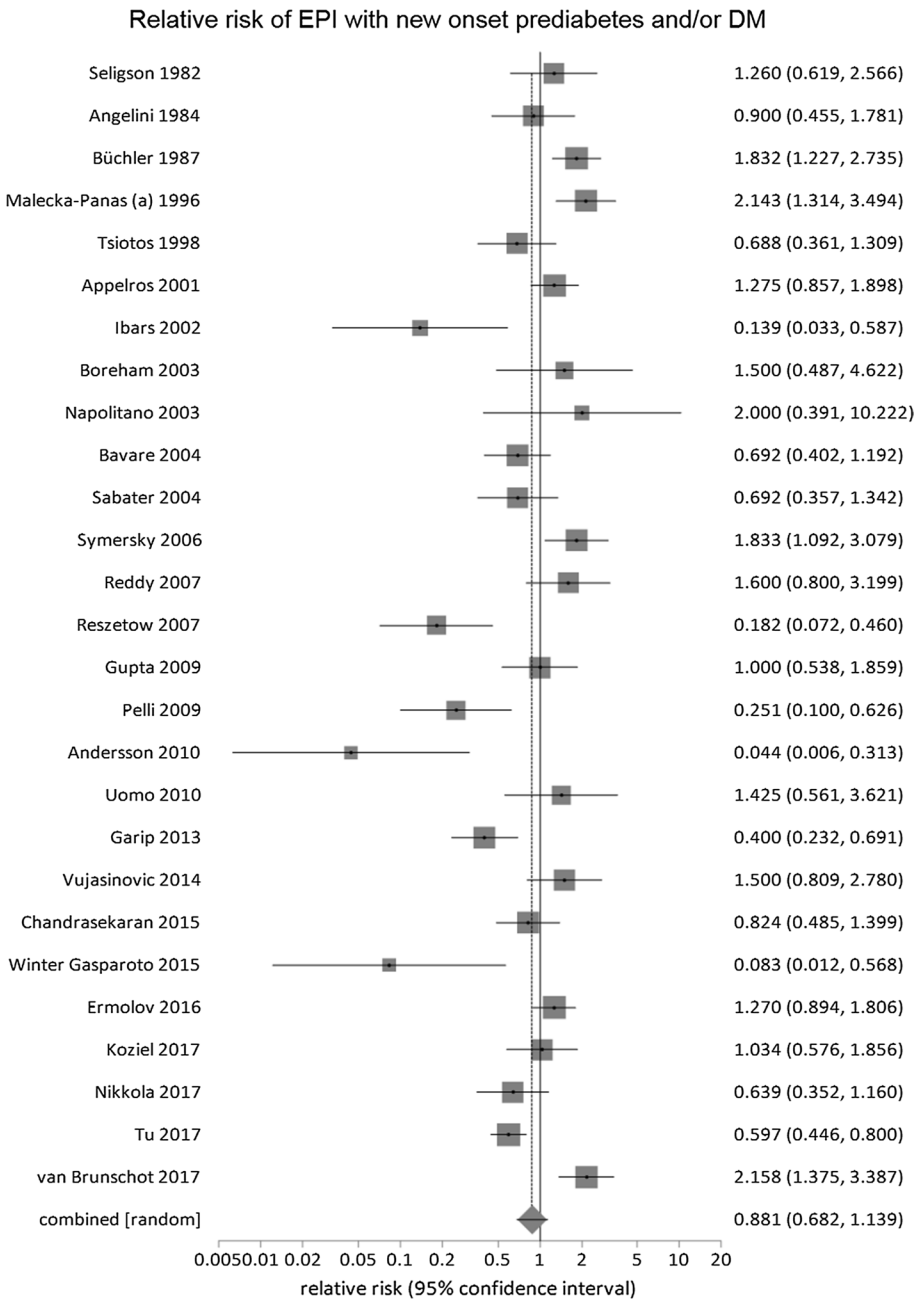

Fig. 5 Relative risk comparison for prevalence of exocrine pancreatic insufficiency (EPI) versus pre-diabetes and/or diabetes mellitus (DM) for all follow-up studies of acute pancreatitis that reported these two parameters simultaneously

third (35%) of all AP patients were found to have EPI during follow-up, significantly more after severe AP compared with mild AP or necrotizing AP compared with edematous AP. Note that EPI was not restricted to patients who had extensive pancreatic necrosis, as almost half (46%) of patients who had mild AP were found to have EPI during their index admission and one fifth during follow-up. Patients who had pancreatic necrosis $\geq 50\%$, underwent necrosectomy and head necrosectomy had increased, but not statistically significantly, RR of EPI compared with those who had necrosis $< 50\%$, conservative procedures and body/tail necrosectomy, respectively. The prevalence of EPI and new-onset pre-diabetes/diabetes was similar in studies reporting both complications.

There was a progressive decrease in the prevalence of EPI during the follow-up period, to about half at 5 years. Beyond 5 years, prevalence rose modestly, which may have resulted from a focus on more severe and/or progressive disease evidenced by biased reports for mild AP from our publication bias analysis. These data show that recovery from EPI after AP may take many months. AP can be associated with patchy necrosis of many different cell types in the pancreatic parenchyma, exacerbated in inflammation, with disruption of the normal microscopic architecture and

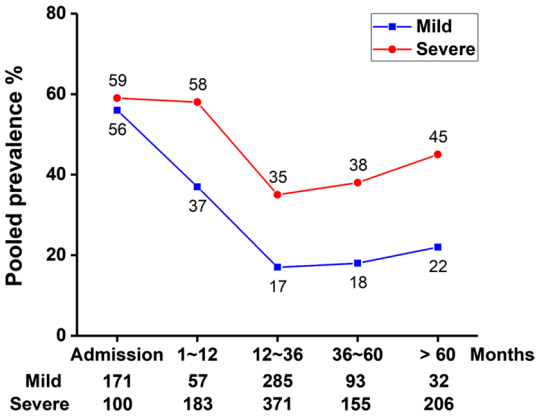

Fig. 6 Time course of the pooled prevalence of exocrine pancreatic insufficiency during and for > 5 years after an attack of acute pancreatitis obtained from all included studies

complex, coordinated machinery of secretion [65]. The high prevalence of EPI in patients with AP during their index admission is consistent with such microscopic changes and their effects on exocrine function. There are many data indicating that the murine exocrine pancreas has the capacity to recover or regenerate after experimental AP, but no direct evidence of human exocrine pancreatic regeneration after AP has previously been provided [65]. There is thus a notable and consistent decrease in the prevalence of EPI over the first 12 months after index admission, which is likely to result from resolution of inflammation, repair, remodeling and regeneration. However, it is also noteworthy that at 5 years this recovery remains incomplete in over a third of affected patients, including 15–20% of all those who had mild AP. In these patients EPI persists and can increase in the long term.

Estimates of the prevalence of EPI after AP made without formal exocrine function tests may be misleading. For example, a large population-based study [66] from Taiwan included 12,284 patients after a first episode of AP, of whom 94% had OAC mild AP and 46% were prescribed PERT for EPI during follow-up. A US multicenter retrospective study of 167 patients found 30 (28%) of 106 who had a first episode of necrotizing AP were subsequently prescribed PERT for EPI [67]. In contrast, an Italian multicenter retrospective questionnaire study of 631 patients found 10 (2%) of 558 who had OAC mild AP and 6 (8%) of 73 who had severe AP developed overt steatorrhea [68]. In a meta-analysis investigating the relationship between exocrine and endocrine failure after AP [14], summary data from a total of 8 studies including 234 patients identified new-onset prediabetes and/or DM in 91 (41% of 221 identified by standard criteria or requirement for therapy) and EPI (by either formal exocrine function testing or reported requirement for PERT) in 59 (27% of 220). This study did not explore the impact of gender, etiology or AP severity, EPI during the index admission, the progression of EPI over time, the role of PERT or the potential effects of EPI on quality of life. The recent meta-analysis by Hollemans et al. [6] used diagnostic laboratory testing for EPI and found a pooled prevalence of EPI was 27.1% of 1495 AP patients analyzed at 36 months (median).

An alcohol etiology had a twofold RR for EPI after AP compared with other etiologies. This is consistent with the repeated injury that occurs with prolonged and excessive consumption of alcohol [69] with the risk of atrophy and fibrosis. In these patients there is an increased risk of recurrent AP and/or chronic pancreatitis [12]. Smoking, more common among those who consume excess alcohol, is known to increase the risk of chronic pancreatitis [70–72]. Given that repair and the reduction in EPI occurs over many months, it is important to cease alcohol consumption and to maintain prolonged abstinence. This is supported by the low incidence of EPI (6%) during long-term follow-up of abstinent patients who had alcohol-associated AP [73].

Regarding testing (direct and indirect) for EPI, all the tests found similar prevalence rates for EPI except FE-1. This was used in more recent studies and identified a significantly lower prevalence of EPI. While the FE-1 test is easy to perform and cost-effective for RAC severe patients (sensitivity and specificity > 90%) [74], the sensitivity for RAC mild/moderately severe AP is low (~60%) and fails to identify many patients with EPI.

Subgroup and sensitivity analyses did not alter our findings, despite the significant heterogeneity between studies. Tests used to diagnose EPI contributed to this heterogeneity, but it was not possible to determine the contribution of the definitions and methods of identification of etiology, application of severity classification, follow-up periods and time points of investigation. Nor did we contact authors for further data, as we considered it highly unlikely that this would alter our principal findings.

The prevalence and persistence of EPI after AP indicate that up to a third of patients are at risk of malnutrition and malabsorption for prolonged periods after AP, and they may well increase after 5 years. AP induces many catabolic responses, resolution of which EPI may delay; the longer EPI persists, the greater the potential impact of malabsorption and malnutrition; thus, early PERT requirement may be indicated. Hollemans et al. [6] and our findings confirm that EPI may develop after AP of any severity, justifying routine symptom enquiry and a simple test of exocrine pancreatic function during follow-up, e.g., the FE-1 test.

Apart from the limitations reported by Hollemans et al. [6] for such a meta-analysis, different methods used to measure EPI may create the high heterogeneity between studies. Also, healthy inequalities that may cause unexplained heterogeneity were rarely reported by the included studies. This

study also highlighted the high prevalence of EPI during AP admission regardless of disease severity, and there was a lack of studies to investigate the effect of PERT on EPI during admission and at follow-up.

In conclusion, there is a significant and largely unrecognized prevalence of EPI after AP. Taking into account the data from this study and other published studies, a number of practical recommendations can be made:

1. EPI should be tested for in all patients with AP before discharge from index admission, irrespective of the predicted severity.
2. PERT may be considered for patients with persistent EPI (e.g., FE-1 < 100–200 µg/g) after AP has resolved. Patients who were likely to develop persistent EPI included those with moderately severe and severe AP, those with pancreatic necrosis, those who have had a necrosectomy and those with an alcohol etiology.
3. Re-testing for EPI (off treatment) should be done at 3 months after discharge in all patients, e.g., a normal FE-1 test result would mean that PERT can be discontinued. For those who remain on PERT, testing should be repeated at 6 and 12 months.

These recommendations will require prospective validation studies, but withholding PERT until further evidence is available is not justified. Further research is needed to refine diagnostic methods for EPI, to determine optimal PERT strategies and to address the impact of health inequalities.

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Authors' contributions WH and DdlIG are co-first authors. WH, DdlIG, JED-M and RS conceived and designed the study. WH, DdlIG, IB-R, CC-S, JL-N, JI-G, NS, XZ, WC, LD and DM acquired, analyzed and interpreted the data. WH, DdlIG, JED-M and RS drafted the manuscript. VKS, QX, JAW, JED-M and RS undertook critical revision of the manuscript for important intellectual content. WH and DdlIG performed the statistical analyses. WH, QX, JED-M and RS obtained the funding. All authors approved the final version of the article.

Compliance with ethical standards

Conflict of interest JED-M has provided consultancy to and received financial support from Abbott (Mylan) for lecture fees and travel expenses outside of the submitted work; RS has provided consultancy to Abbott (Mylan); no further support from any organization for the submitted work; no the financial relationships with any organizations that might have had an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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