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Original article

Recurrence rates and risk factors for recurrence after first episode of acute pancreatitis: A systematic review and meta-analysis

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ABSTRACT

Background: There are a certain number of acute pancreatitis (AP) patients who may suffer from multiple episodes and develop recurrent acute pancreatitis (RAP), but recurrence rates and associated risk factors for RAP vary significantly in the published literature.

Methods: We searched PubMed, Web of Science, Scopus, and Embase databases to identify all publications reporting AP recurrence until October 20th, 2022. Meta-analysis and meta-regression were performed to calculate the pooled estimates using the random-effects model.

Results: A total of 36 studies met the inclusion criteria and all were used in pooled analyses. The overall rate of recurrence after first-time AP was 21% (95% CI, 18%- 24%), and pooled rates in biliary, alcoholic, idiopathic, and hypertriglyceridemia etiology patients were 12%, 30%, 25%, and 30%, respectively. After managing underlying causes post-discharge, the recurrence rate decreased (14% versus 4% for biliary, 30% versus 6% for alcoholic, and 30% versus 22% for hypertriglyceridemia AP). An increased risk of recurrence was reported in patients with a smoking history (odds ratio [OR] = 1.99), alcoholic etiology (OR = 1.72), male sex (hazard ratio [HR] = 1.63), and local complications (HR = 3.40), while biliary etiology was associated with lower recurrence rates (OR = 0.38).

Conclusion: More than one-fifth of AP patients experienced recurrence after discharge, with the highest recurrence rate in alcoholic and hypertriglyceridemia etiologies, and managing underlying causes post-discharge was related to decreased incidence. In addition, smoking history, alcoholic etiology, male gender, and presence of local complications were independent risks for the recurrence.

1. Introduction

Acute pancreatitis (AP) has become a prevalent gastrointestinal disorder over the past few decades, with a growing impact on healthcare [1,2]. While most patients with AP experience mild symptoms and fully recover, some may face recurring attacks of AP and ultimately develop recurrent acute pancreatitis (RAP), leading to chronic pancreatitis (CP) or even pancreatic cancer with repeated episodes [3,4]. Furthermore, previous research has shown that RAP can result in a decrease in the physical, and mental aspects and quality of life of patients, even if there are no overt changes associated with CP [5].

However, the published investigations on incidence and risk factors

Abbreviations: AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CI, confidence intervals; OR, odds ratio; HR, hazard ratio; CP, chronic pancreatitis; PRISMA, Preferred Reporting Items for Systematic Reviews; MOOSE, Meta-analysis Of Observational Studies in Epidemiology reporting guidelines; NOS, Newcastle–Ottawa Quality Assessment Scale; SAP, severe acute pancreatitis; HTG-AP, hypertriglyceridemia-induced acute pancreatitis.

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for RAP have shown contradictory results. On the one hand, the recurrence rates have been found to vary greatly from 11% to 36% due to factors such as small sample sizes, short follow-up evaluation periods, and baseline patient characteristics differences [6,7]. Furthermore, several potential circumstances such as smoking, drinking, biliary and alcohol etiology, diabetes, and local complication have been postulated as risk factors for recurrence [8–10]. Nevertheless, there is no consensus on the specific risk factors that offer the greatest predictive effects on recurrence, prompting researchers to make generalizations and summarizations.

Therefore, this study aims to present the recurrence rate of AP after the first episode by systematically reviewing and synthesizing the available literature, as well as describing the risk factors that affect recurrence.

2. Material and methods

2.1. Literature search and study selection

This meta-analysis was performed by two reviewers (SL and LG) independently in adherence with the guidelines for Preferred Reporting Items for Systematic Reviews (PRISMA) [11] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidelines [12]. PubMed, Web of Science, Scopus, and Embase electronic databases were reviewed to complete a systematic search of the literature for relevant studies from inception to October 20th, 2022. The terms acute pancreatitis and recur* OR relaps* OR readmi* and follow up OR followup OR follow-up OR followed up OR follow* OR risk OR predict* OR associat* were combined to retrieve, detailed search strategies were shown in Supplementary Table S1. The present study and the corresponding protocol have been registered in the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO) as CRD42023388443.

Studies were screened for potential eligibility based on title and abstract by two independent investigators (SL and LG). Then full-text articles that appeared to be relevant were obtained for further evaluation of eligibility and selection. A consensus was used to resolve any disagreements, with a third reviewer involved if a consensus could not be achieved (HWG). The references of all review and primary studies retrieved were manually screened to find additional articles considered relevant.

2.2. Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria:

(1) adult patients (aged $\geq$ 18 years) with a diagnosis of AP;
(2) the studies investigated the recurrence of AP and evaluated risk factors influencing the recurrence;
(3) the length of follow-up was greater than 12 months.

Studies were excluded from the meta-analysis if they met the following criteria:

(1) studies did not include or report the first episode of acute pancreatitis patients;
(2) studies enroled only chronic, hereditary, gestational, and autoimmune pancreatitis patients;
(3) studies lack sufficient or detailed data to extract or evaluate the associations of risk factors with RAP.
(4) review articles, case reports, editorials, conference abstracts, and studies carried out in animals or *in vitro*.

2.3. Quality assessment

The quality of included studies was assessed according to the Newcastle–Ottawa Quality Assessment Scale (NOS) for case-control or cohort studies by two independent reviewers (SL and LG), with discrepancies resolved by consensus (HWG)[13]. The scale has eight elements under three categories: selection, comparability and exposure. Each element was marked with one or two stars if eligible, with a maximum of 9 stars for each study. Studies with scores of 7 or greater were classified as high quality, 5 to 7 were classified as medium quality, and lower than 4 were classified as low quality [13].

2.4. Study outcomes

The primary outcome of interest was the natural recurrence rate of AP after the initial episode, across all etiologies. The secondary outcome were the recurrence after the control of underlying causes, and the number and proportion of patients who were diagnosed with RAP following the first episode within each specific etiology. Beside, risk factors associated with the incidence of RAP were explored.

2.5. Data extraction

All pertinent data from included studies was extracted by two independent investigators (SL and LG), and discrepancies were resolved by consensus with a third reviewer involved (HWG). For each study, the following data were extracted: authors, year of publication, single-center or multi-center, study design, study duration, methods used to confirm recurrence, mean or median age of patients, number and proportion of male and severe acute pancreatitis (SAP) patients, follow-up period, the total number of patients, number of patients followed up, the incidence of RAP in patients with different etiologies, and risk factors included in multivariate regression analysis in each study and their respective effect sizes.

2.6. Statistical analysis

The crude recurrence rate was extracted as an outcome. Pooled estimates and 95% confidence intervals (CI) were obtained using a random-effects model and forest plots were created. Statistical heterogeneity was assessed by the I^2 test. High statistical heterogeneity was defined as greater than 70%, medium as 50–70%, and low heterogeneity as 0–50% [14]. Subgroup and meta-regression analyses were conducted and stratified by general characteristics of the included studies and patients. Continuous data were converted to dichotomous ones based on their mean or median. Univariate and multivariate meta-regression analyses were used to examine associations between covariates and outcomes. Variables with a p-value less than 0.05 in univariate meta-regression were included in multivariate meta-regression. The degree of heterogeneity in the outcome was evaluated with the R^2 index. Publication bias was assessed by visual inspection of the funnel plots and the Egger test [15]. Relevant data was quantitatively summarized when a factor was investigated in at least three studies.

For all analyses, a p-value less than 0.05 was considered statistically significant. All analyses and graphics were completed in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Literature selection

An initial search yielded 4377 records, from which we identified 3036 studies after the removal of duplicates. Of these, 136 full-text articles were screened for eligibility based on title and abstract.

After excluding studies in which patients were non-first episode (n = 6), only included CP or other uncommon etiology (n = 35), lack of sufficient data (n = 31), and reviews or case reports (n = 28), finally, 36 studies were eligible and enroled in this systematic review and meta-analysis [6–10,16–46]. The flow diagram is shown in Supplementary

Fig. S1.

3.2. General study characteristics

The general characteristics of the included studies and patients were presented in Table 1 and Supplementary Table S2. Over a period of twenty years, a total of 23 studies focused on natural AP recurrence and 13 studies focused on recurrence after control of underlying causes post-discharge were included. Nine of the 36 studies followed up patients prospectively [8,19–21,25,27,28,41,42], while the remaining 27 were retrospective in design [6,7,9,10,16–18,22–24,26,29–40,44–46]. In addition, the duration of follow-up varied significantly across studies, with the mean or median duration ranging from 20 to at least 156 months. Most studies confirmed recurrence through a medical records review, but few followed up with outpatient or telephone visits.

3.3. Risk of bias assessment

The quality assessment results of included studies focused on natural AP recurrence are shown in Table 1, with most studies receiving high ratings. Specifically, seventeen studies earned a high quality, while the rest six studies were classified as medium quality. More details on the quality evaluation are available in Supplementary Table S3.

3.4. Natural recurrence rate

3.4.1. Recurrence rate in all etiologies

There was considerable variation in reported natural recurrence rates, with a range of 11% [6] to 36% [7]. The forest plot for crude and pooled rates is presented in Fig. 1A. The pooled overall recurrence rate was 21% (95% CI, 18%- 24%), and heterogeneity between the included studies was high ($I^2 = 96\%$; $p < 0.01$). Publication bias was not detected (Egger test $p = 0.703$) (Supplementary Fig. S4).

3.4.2. Recurrence rate in each etiology

Regarding the recurrence rate in AP patients with each etiology, a total of 20 studies reported the number of patients who had RAP in biliary AP patients [7–10,18–33]. These studies comprised 5756 patients, and the pooled recurrence rate was 12% (95% CI: 9%−15%). As for alcoholic etiology, the pooled rate of recurrence was 30% (95% CI: 26%−35%) from a total of 2977 patients in 19 studies [8–10,18–33]. In the patients of idiopathic and hypertriglyceridemia-induced AP (HTG-AP), the pooled rate of recurrence was 25% (95% CI: 20%−31%) and 30% (95% CI: 21%−44%), with a total of 3377 and 635 patients from 11 [20–22,24–30,32] and 5 [9,18,28,31,33] studies respectively. High heterogeneity was found between these studies and I^2 was 87%, 89%, 75%, and 73% for biliary, alcoholic, idiopathic, and hypertriglyceridemia etiologies, respectively (Fig. 2).

3.4.3. Subgroup analysis and meta-regression

Subgroup analyses were conducted and the results showed that the pooled recurrence rate was lower in studies with the number of followed-up patients greater than 500, compared with studies less than 500 (18% vs 25%; $p = 0.01$) (Fig. 1B), detailed findings are displayed in Supplementary Figs. S2–3 and Table S4. Univariate meta-regression revealed that the number of followed-up patients less than 500, earlier year of publication, and proportion of SAP more than 20% were significantly associated with a higher recurrence rate ($p = 0.047$, 0.015 and 0.045), accounting for 11.19%, 19.74%, and 19.4% of overall heterogeneity, respectively. Multivariate meta-regression demonstrated a significant 9.2% decrease in recurrence rate associated with the number of followed-up patients exceeding 500 (95% CI: 4.6%–13.8%; $p < 0.001$). However, there was no significant association between the recurrence rate and the proportion of SAP (Table 2). The publication year was not evaluated by multivariate meta-regression due to the limited number of included studies.

3.5. Recurrence after control of underlying causes for each etiology

There are 7 studies [28,34–39] conducted to investigate the impact of cholecystectomy on the recurrence of biliary pancreatitis, and a meta-analysis showed a recurrence rate of 14% for patients who did not undergo cholecystectomy and 4% for those who did, statistical difference was observed between the groups (14% vs. 4%; $p < 0.01$; $I^2 = 100\%$). In addition, 4[40-43] and 3[44-46] studies examined the effect of alcohol abstinence and blood lipid control on recurrence, respectively. The results also revealed that alcohol or lipid control was significantly associated with a decreased risk of recurrence (alcohol: 30% vs. 6%; $p < 0.01$; $I^2 = 50\%$; lipid: 30% vs. 22%; $p < 0.01$; $I^2 = 74\%$), and the forest plots are displayed in Fig. 3.

3.6. Factors associated with recurrence

In the 36 studies included, there were 30 different predictors associated with the risk of recurrence identified by multivariate regression in 11 studies [8,9,18,22,24–26,29–31,33]. The most commonly reported factors were alcoholic AP (8 studies [8,9,18,22,26,29–31]), followed by smoking history (7 studies [8,9,22,24,26,29,30]), biliary AP (6 studies [9,22,24,25,31,33]), idiopathic AP (5 studies [8,22,24,26,29]), and age (5 studies [22,26,30,31,33]) (Table 3). Further details regarding the pooled results of these predictors are presented in Fig. 4 and Supplementary Table S5.

3.6.1. Age

There were 5 studies that reported age was a predictor for AP recurrence. A significant correlation between younger age and the elevated recurrence rate was observed in 2 studies [22,30], in which age was deemed a categorical variable. While the meta-analysis of the remaining 3 studies [26,31,33] which deemed age a continuous variable, revealed no discernible correlation between age and recurrence (odds ratio [OR] = 1.00 [95% CI, 0.97–1.04]; $p = 0.87$; $I^2 = 0\%$).

3.6.2. Gender

Gender was reported in 4 studies [29–31,33], and 1 study [33] was excluded due to utilizing males as the reference and a lack of detailed effect estimates. Meta-analysis of the remaining three studies showed a significantly higher recurrence rate in male patients compared with females (hazard ratio [HR] = 1.60 [95% CI, 1.24–2.05]; $p < 0.001$; $I^2 = 0\%$).

3.6.3. Smoking history

The data relating to smoking history before the first attack of AP from seven separate studies was aggregated. The pooled results indicated that patients with a smoking history had a significantly increased recurrence rate of AP compared with non-smokers (OR = 1.99 [95% CI, 1.42, 2.78]; $p < 0.001$), while high heterogeneity between included studies was observed ($p = 0.96$; $I^2 = 78.2\%$).

3.6.4. AP etiology

There were 8 studies deeming alcoholic AP as a predictor in multivariate regression, and after omitting one study [22] defining alcoholic etiology as the reference, the meta-analysis of the remaining seven studies showed increased risks of recurrence for patients with alcoholic etiology (OR = 1.72 [95% CI, 1.07–2.76]; $p = 0.026$; $I^2 = 68\%$). In the subgroup analysis conducted by combining OR and HR separately, the pooled OR in 3 studies [8,18,26] was 1.74 [1.09, 2.78] ($p = 0.02$; $I^2 = 1\%$), while the pooled HR in 4 studies [9,29–31] was 1.71 [0.76, 3.85] ($p = 0.20$; $I^2 = 82\%$).

Biliary etiology was deemed a predictor in six studies and among them, 2 studies [9,31] used biliary etiology as a reference. Meta-analysis of the 4 studies revealed that biliary etiology was a significant protective factor for recurrence (OR = 0.37 [95% CI, 0.32–0.43]; $p < 0.001$; $I^2 = 0\%$).

Table 1
Characteristics of included studies and patients focused on natural recurrence of AP.

Refs.	Year of publication	Country	Number of centers, n	Study design	Study period	Recurrence confirmation methods	Median or mean time of follow-up (range), months	Total cases, n	Cases followed up, n	Recurrence, n	Etiology (recurrence / total), n					Males (%)	Mean or median (SD or range) age, years	No. of severe patients (%)	NOS
											Biliary	Alcoholic	HTG	Idiopathic	Other				
Gullo et al. [16]	2002	Europe	Multicentric	Retrospective	1990–1994	NS	NS	1068	1068	288	72/NS	164/NS	NS	30/NS	22/NS	211 (73.3)†	43 (16–95)*	NS	5
Zhang et al. [17]	2005	China	Unicentric	Retrospective	1997–2000	Clinical visits	26 (12–60)*	245	245	77	48/NS	3/NS	3/NS	21/NS	2/NS	109 (44.5)	58.04 ±15.43#	13(16.9)†	6
Chen et al. [18]	2006	China	Unicentric	Retrospective	1999–2001	Medical record	20 (5–36)*	106	80	24	2/16	19/53	3/5	0/6		64(80)	43.5± 12.9#	51 (63.75)	7
H. Lund et al. [7]	2006	Denmark	Unicentric	Retrospective	1995–1998	Medical record	43–79*	155	138	49	18/50		31/64			99 (71.7)	48 (12-87)*	55(36.6)	8
Gao et al. [6]	2006	China	Multicentric	Retrospective	1992–2002	NS	NS	1471	1471	157	41/NS	32/NS	13/NS	42/NS	29/NS	99 (63.1)†	41.0 (13–82)*	24(15.4)†	5
Yasuda et al. [19]	2008	Japan	Unicentric	Prospective	1990–2006	Clinical visits	56 ± 6#	145	42	8	0/10	5/23	NS	3/12		36(80)	52 ± 2#	45(100)	6
Lankisch et al. [20]	2009	Germany	Unicentric	Prospective	1987–2004	Medical record	93.6 ± 63.6#	532	501	88	25/214	47/144	NS	14/100	2/43	289 (57.7)	56 ± 18#	199 (39.7)	9
Takeyama [21]	2009	Japan	Multicentric	Prospective	1987	Clinical visits	Shortest 156	2533	714	145	9/121	91/281	NS	29/162	16/150	NS	NS	311 (43.6)	6
Yadav et al. [22]	2012	US	Multicentric	Retrospective	1996–2005	Medical record	40*	7456	6010	1752	302/1647	640/1223	NS	567/2171	182/969	3318 (44.5)	58 (43–74)*	NS	8
Castoldi et al. [23]	2013	Italy	Multicentric	Retrospective	2001–2003	NS	51.7 ± 8.4#	1173	631	80	36/439	11/36	NS	NS	33/156	313 (49.6)	60.6 ± 18.5#	73(11.6)	8
Vipperla et al. [10]	2014	US	Multicentric	Retrospective	2003–2010	NS	36 (9.5–65)*	256	127	22	7/59	7/15	NS	0/17	8/36	66(52)	54 (38–68)*	NS	9
Bertilsson S, et al. [24]	2015	Sweden	Unicentric	Retrospective	2003–2012	Medical record	50.4 (26.6–82.3)*	1457	1416	329	122/690	91/240	NS	102/416	14/70	772 (53)	61 ± 19#	NS	8
Cavestro et al. [25]	2015	Italy	Unicentric	Prospective	2002–2011	Medical record	52.5 ± 26.8#	432	196	40	11/122	5/16	NS	19/40	5/18	125 (63.8)	58.8 ± 16.9#	50(25.5)	8
Ahmed Ali et al. [8]	2016	Netherlands	Multicentric	Prospective	2003–2007	Medical record	57(49–65)*	669	669	117	47/384	37/153	NS	33/132		366 (54.7)	57 (42-70)*	669 (100)	9
Jiao et al. [26]	2017	China	Unicentric	Retrospective	2012–2014	NS	30.4*	489	411	113	57/265	8/19	30/61	12/45	6/21	219 (53.3)	NS	108 (26.3)	8
Kalaria et al. [27]	2018	India	Unicentric	Prospective	2013–2014	Medical record	4–22*	112	97	27	4/37	5/19	NS	14/31	4/10	74 (76.3)	47.2 ± 16.9#	8(8.2)	7
Stigliano et al. [28]	2018	Italy	Unicentric	Prospective	2007–2015	Clinical visits	42 ± 33#	337	266	66	28/125	9/41	4/8	8/38	17/54	158 (59.4)	58 ± 17#	55(20.7)	9
Magnusdottir et al. [29]	2019	Iceland	Multicentric	Retrospective	2006–2015	NS	52 (0–124)*	1589	1102	225	62/450	82/227	NS	54/283	27/142	593 (53.8)	56 ± 18 (men), 56 ± 20 (women)#	64(5.8)	6
Cho et al. [30]	2020	Korea	Unicentric	Retrospective	2009–2014	Medical record	38.4*	617	617	100	31/304	48/182	NS	14/56	7/75	380 (61.6)	60.6 ± 16.8#	51(8.3)	8
Yu et al. [31]	2020	China	Unicentric	Retrospective	2016	Medical record	27.2 ± 14.0#	522	522	56	16/326	7/34	25/116	NS	8/46	305 (58.4)	52.9 ± 16.2#	71(13.6)	8
Patra et al. [32]	2021	India	Unicentric	Retrospective	2011–2012	NS	61.7#	122	100	15	3/31	1/21	NS	9/35	2/13	64(64)	42 (14–88)*	18(18)	7
Song et al. [33]	2021	China	Unicentric	Retrospective	2017–2019	Medical record	NS	870	834	163	9/177	33/182	105/349	NS	16/126	582 (69.8)	NS	NS	7
Sun et al. [9]	2022	China	Unicentric	Retrospective	2018–2021	Medical record	25(3–45)*	644	592	81	26/289	12/68	31/157	NS	12/78	383 (64.7)	49 ± 26#	73(12.3)	8

AP: acute pancreatitis; HTG: hyperlipidemia; NS: Not stated; NOS: the Newcastle–Ottawa Quality Assessment Scale score. *:median or median (range); #:mean or mean ± SD; †: proportion in recurrences. Clinical visits mean that patients were confirmed with recurrence by outpatient or telephone visits.

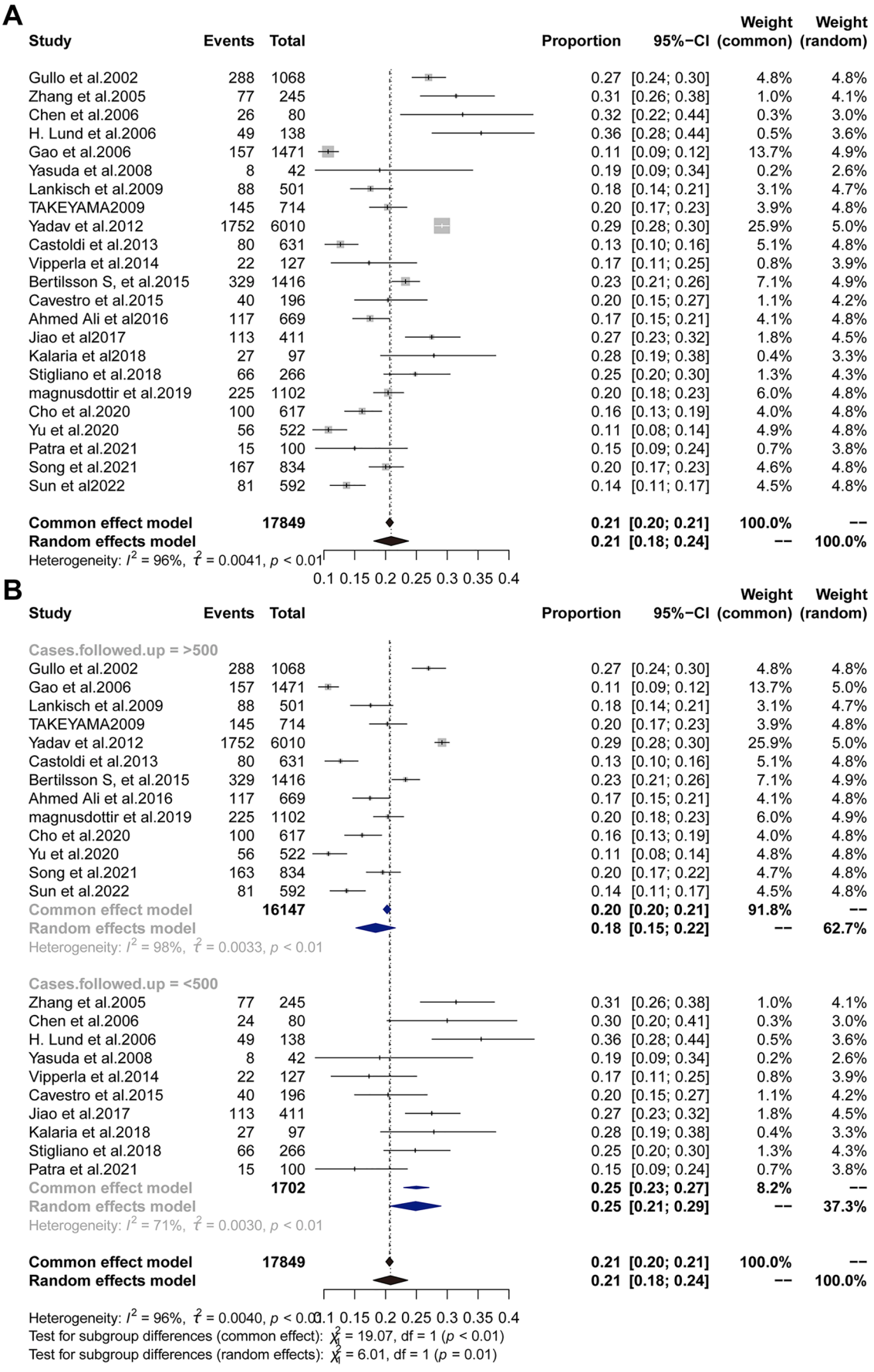

Fig. 1. (A) Overall recurrence rate of AP in studies included in the meta-analysis. (B) Forest plot of pooled estimates and stratified by number of cases followed up. AP: acute pancreatitis.

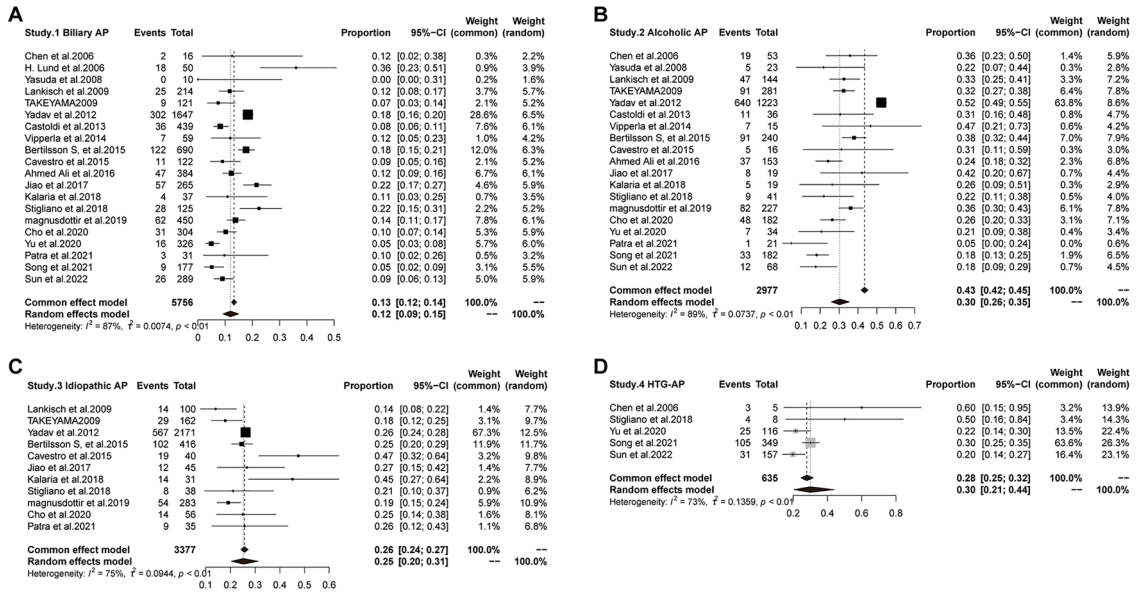

Fig. 2. Recurrence rates of AP in different etiologies. (A) biliary etiology; (B) alcoholic etiology; (C) idiopathic etiology; (D) hypertriglyceridemia etiology. AP: acute pancreatitis; HTG-AP: hypertriglyceridemia-induced acute pancreatitis.

Table 2
Predictors of recurrence rate and risk factors in first episode of acute pancreatitis by univariate and multivariate meta-regression.

	Studies, n	Patients, n	β	SE	95%CI	Z	P	I^2	R^2
Univariate									
Publication year	23	17,849	−0.0045	0.0023	−0.0090 to −0.0001	−1.9826	0.047	93.96%	11.19%
Centers, Multicentric	23	17,849	0.0222	0.0297	−0.0360 to 0.0805	0.7480	0.455	94.71%	0.00%
Age (yr)	20	15,890	0.0001	0.0025	−0.0049 to 0.0050	0.0199	0.984	95.17%	0.00%
Proportion of males (%)	22	17,135	0.0005	0.0016	−0.0025 to 0.0036	0.3413	0.733	94.67%	0.00%
Confirmation methods of recurrence, Clinical visits	16	12,939	0.0296	0.0413	−0.0514 to 0.1106	0.7161	0.474	94.37%	0.00%
Study location, Europe & America	23	17,849	0.0260	0.0283	−0.0294 to 0.0814	0.9205	0.357	94.36%	0.62%
Study design, Prospective	23	17,849	−0.0003	0.0321	−0.0632 to 0.0626	−0.0087	0.993	94.99%	0.00%
Study period, Over 5 years	23	17,849	−0.0159	0.0292	−0.0731 to 0.0413	−0.5457	0.585	94.76%	0.00%
Length of follow-up duration, Over than 48 months	20	14,476	−0.0244	0.0306	−0.0844 to 0.0355	−0.7990	0.424	93.22%	0.00%
Cases followed up, n >500	23	17,849	−0.0650	0.0268	−0.1175 to −0.0125	−2.4275	0.015	93.70%	19.74%
Proportion of SAP, >20%	18	8394	0.0617	0.0308	0.0014 to 0.1220	2.0047	0.045	91.96%	19.40%
Multivariate									
Cases followed up, n >500			−0.0918	0.0235	−0.1380 to −0.0457	−3.9012	<0.0001	82.92%	66.64%
Proportion of SAP, >20%			0.0325	0.0229	−0.0123 to 0.0774	1.4208	0.155		

SE: standard error; CI: confidence intervals; AP: acute pancreatitis; SAP: severe acute pancreatitis; HTG-AP: hypertriglyceridemia-induced acute pancreatitis.

Five studies examined idiopathic AP as a risk factor for RAP, and a meta-analysis of the 5 studies found no significant association between idiopathic etiology and AP recurrence (OR = 1.03 [95% CI: 0.59–1.79]; $p = 0.92$; $I^2 = 90.8\%$). Subgroup analysis revealed that the pooled OR in 2 studies [8,26] was 1.78 [0.83, 3.85] ($p = 0.14$; $I^2 = 61\%$), the pooled HR in 3 studies [22,24,29] was 0.77 [0.44, 1.35] ($p = 0.36$; $I^2 = 90\%$).

Lastly, 3 studies [9,26,31] examined HTG-AP and its effect on recurrence. However, a meta-analysis of the three studies found no significant relationship between hypertriglyceridemia etiology and RAP (OR = 2.31 [95% CI, 0.93–5.72]; $p = 0.07$; $I^2 = 70.3\%$).

3.6.5. Local complication

Three studies [24,30,31] investigated the value of local complications as a predictor of AP recurrence. Through meta-analysis, it was shown that the presence of a local complication was associated with an increased risk of AP recurrence, while high heterogeneity was observed between the studies (HR = 3.40 [95% CI, 1.37–8.40]; $p = 0.008$; $I^2 = 87.6\%$).

4. Discussion

In the present study, we systematically reviewed and meta-analyzed the literature on AP recurrence, and the results showed that 21% of patients may experience AP natural recurrence, with a pooled recurrent rate of 12%, 30%, 25%, and 30% in biliary, alcoholic, idiopathic, and hypertriglyceridemia AP patients, respectively. A significant reduction in the recurrence rate was observed in large-scale (>500 cases) studies and effective management of the underlying causes post-discharge group. Furthermore, the meta-analysis indicated that patients with a smoking history, alcoholic etiology, male gender, and presence of local complications had a higher risk of AP recurrence, and biliary etiology seemed to be a protective factor for recurrence compared with other etiologies.

In 2015, Sankaran et al. conducted a meta-analysis on the natural progression of pancreatitis [3], and their findings revealed that 22% of patients who experienced AP progressed to RAP. Our study similarly found a pooled prevalence of 21%, and there were some differences between our study and theirs in terms of the key populations of interest. Only studies that reported the development of CP after an attack of AP were included in their review, while we included studies focusing on the recurrence after the first AP attack, which allowed us to focus on a wider range of populations and include more patients in our study.

Notably, we observed a significant decrease in recurrence rates in larger-scale studies, which was identified as a potential source of

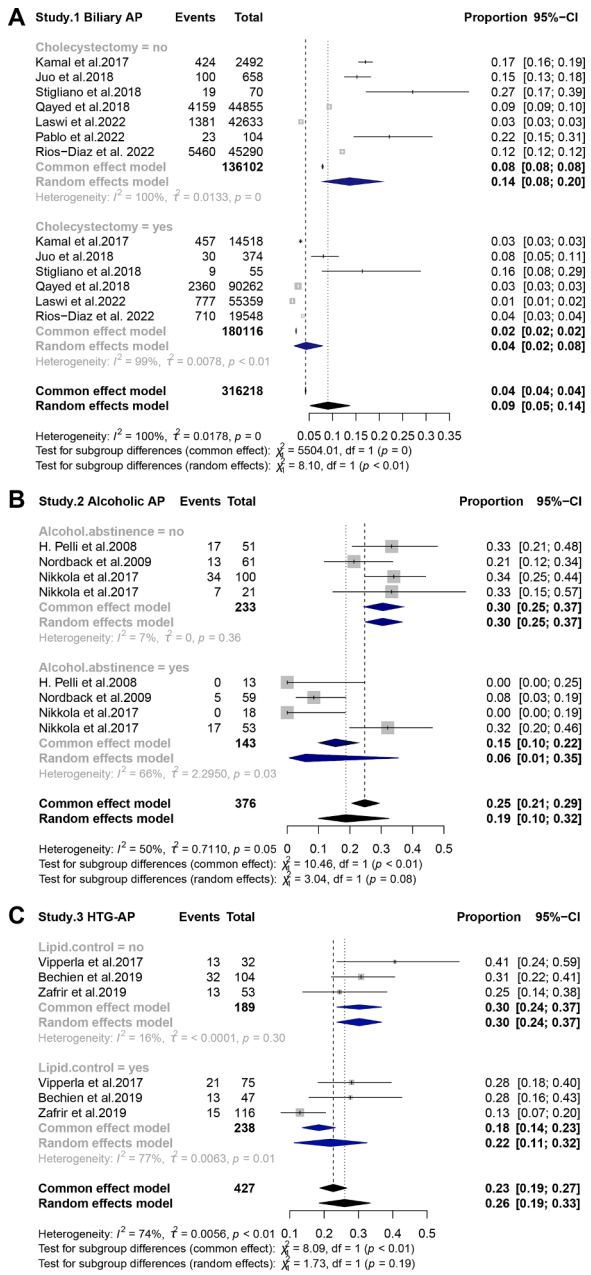

Fig. 3. Recurrence rates of AP associated with etiology control. (A) biliary etiology; (B) alcoholic etiology; (C) idiopathic etiology; (D) hypertriglyceridemia etiology. AP: acute pancreatitis; HTG-AP: hypertriglyceridemia-induced acute pancreatitis.

heterogeneity via multivariate meta-regression. The main reasons contributing to this phenomenon are as follows: First, the majority of large-scale studies collaboratively collected data from multiple centers, which helps avoid biases caused by regional disparities, differences in living circumstances, and variations in the levels of medical facilities. In addition, large-scale studies, which are unicentric, are mostly conducted in top tertiary hospitals in Europe or China, where physicians may have a deep understanding of the disease post-discharge, leading to lower recurrence rates.

To prevent recurrence, it is crucial to timely, effectively, and comprehensively address the underlying causes post-discharge [47]. For biliary pancreatitis, the likelihood of recurrence depends largely on whether cholecystectomy was performed and the timing of the procedure after the first AP attack [48]. According to some recent investigations, cholecystectomy during the same hospital admission might be an optimal strategy to reduce the risk of recurrence, compared with the more commonly used strategy, namely interval or delayed cholecystectomy [49,50]. As for alcoholic and hypertriglyceridemia AP patients, they are at risk of recurrence commonly due to poor lifestyle control [51]. Therefore, eliminating the risk factors for AP after discharge is vital to reduce the recurrence, and motivating lifestyle change seems to be an effective solution.

As stated previously, it is clear that alcoholic etiology is a risk factor for recurrence, which could be partly attributed to pancreatic tissue damage, including perturbation in mitochondrial function, autophagy, ectopic exocytosis, etc. [52,53], and partly to the addictive properties of alcohol, which diminish the efficacy of preventive strategies [54]. The influence of tobacco intake on the natural course of AP has been investigated and confirmed. The two main metabolites from cigarette smoke, nicotine and 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanone (NNK), also can induce damage to pancreatic acinar cells or zymogen secretion through multifactorial events [55–58]. Similar to alcohol, tobacco contains addictive properties, and individuals post-discharge often face difficulties in relinquishing their grasp [59].

Previous studies have revealed an association of variants in trypsin-associated genes, such as cationic trypsinogen (PRSS1), serine protease inhibitor (SPINK1), or the cystic fibrosis transmembrane conductance regulator gene with AP, and the frequencies of the genetic mutations did not differ between recurrent and sentinel pancreatitis upon examination [60,61]. Whitcomb et al. reported two significant genome-wide associations at PRSS1-PRSS2 and x-linked CLDN2 through a two-stage genome-wide study, and the homozygous (or hemizygous male) CLDN2 genotype conferred the greatest risk of AP, which may partially explain the high frequency of RAP in males [62]. Beside, Polonikov et al. confirmed a robust relationship between polymorphism rs10273639 of the PRSS1-PRSS2 locus and pancreatitis development, with the association seen only in men and significantly modified by alcohol consumption and cigarette smoking [63].

According to our meta-analysis, the local complication was a significant risk factor for RAP, which can be explained by the theory that local complications are presumably related to structural changes of the pancreas after recovery, which made patients more susceptible to AP relapse or progression to CP [30]. In the study by Nikkola et al., they found that even a single episode of AP may induce chronic morphological changes to the pancreas, as confirmed by secretin-stimulated magnetic resonance cholangiopancreatography. Moreover, the study indicated that morphological pancreatic changes may aggravate the number of recurrences increases [64].

This research is also not without limitations. First of all, significant heterogeneity between the included studies was detected, and the conclusions drawn in this study needed to be interpreted with caution. Secondly, since most of the studies were retrospective, the evidence level of the included studies was limited. Additionally, although most studies on RAP provide descriptions of incidence and related risk factors, pooled data on effective approaches to limit recurrence remains sparse. To this end, it is crucial to conduct more meticulously designed studies to investigate the effects of these measures, including cholecystectomy, abstinence from alcohol, and lipid level lowering on AP recurrence for future systematic reviews and meta-analyses. In addition, despite the higher recurrence rate in the HTG-AP population, especially in China, research in this area is scarce compared to other etiologies, and more large-scale, prospective studies on HTG-AP recurrence and prevention measures are necessary.

5. Conclusions

In conclusion, this review indicated that 21% of AP patients after the first episode would develop at least one recurrence, with the recurrence rate in biliary AP being 12%, 30% in alcoholic AP, 25% in idiopathic AP, and 30% in HTG-AP, and addressing the underlying causes post-discharge may reduce the risk of recurrence. Several factors were

Table 3
Independent risk factors investigated by studies.

Risk Factor	Sun et al.2022 [9]	Song et al.2021 [33]	Yu et al.2020 [31]	Cho et al.2020 [30]	Magnusdottir et al.2019 [29]	Jiao et al.2017 [26]	Ahmed Ali et al.2016 [8]	Cavestro et al.2015 [25]	Bertilsson S, et al.2015 [24]	Yadav et al.2012 [22]	Chen et al.2006 [18]	No. of Studies
Smoking history												7
Alcoholic AP												8
Biliary AP												6
Idiopathic AP												5
HTG-AP												3
Age												5
Gender												4
Local complication												3
Drinking												2
TG level												2
Diabetes												2
Necrotizing pancreatitis												2
APFC												1
PP												1
IPN												1
MCTSI-Mild												1
MCTSI-Moderate												1
MCTSI-Severe												1
MAP												1
MSAP												1
SAP												1
High-FBG												1
High-LDLc												1
HDL												1
Cholesterol												1
BMI												1
Fatty liver												1
History of BS												1
APACHE II score												1
Pancreas divisum												1
Systemic complications												1
Organ failure												1
LOS												1

Cells highlighted in blue indicate that the study found no significant association between AP recurrence and the factor of interest. Cells highlighted in orange indicate that the study found a significant association between AP recurrence and factor of interest. Cells highlighted in green indicate that the study used this factor as a reference in the category variable. The number "1″ denotes that a study reported investigating the factor for its risk of recurrence [65].
AP: acute pancreatitis; HTG-AP: hypertriglyceridemia-induced acute pancreatitis; TG: triglyceride; BMI, body mass index; HTG, hypertriglyceridemia; APFC: acute peripancreatic fluid collection; ANC: acute necrotic collection pancreatic pseudocyst; WON: walled-off necrosis; IPN: infected pancreatic necrosis; MCTSI: modified computed tomography severity index; MAP: mild acute pancreatitis; MSAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDLc, low-density lipoprotein cholesterol; BS: biliary surgery; APACHE II: Acute Physiology and Chronic Health Evaluation II; LOS: length of stay.

independently associated with a higher risk of recurrence, including smoking history, alcoholic etiology, male gender, and presence of local complication, while biliary etiology was associated with a lower risk of recurrence compared with other etiologies. Further high-quality and large-scale studies are warranted to investigate the effects of control of underlying causes after discharge on AP recurrence.

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Ethical approval

Ethics committee approval is not required, since the present article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the authors.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Shuai Li: Conceptualization, Data curation, Funding acquisition, Validation, Writing – review & editing. **Lin Gao:** Data curation, Formal analysis, Software, Visualization, Writing – original draft, Writing –

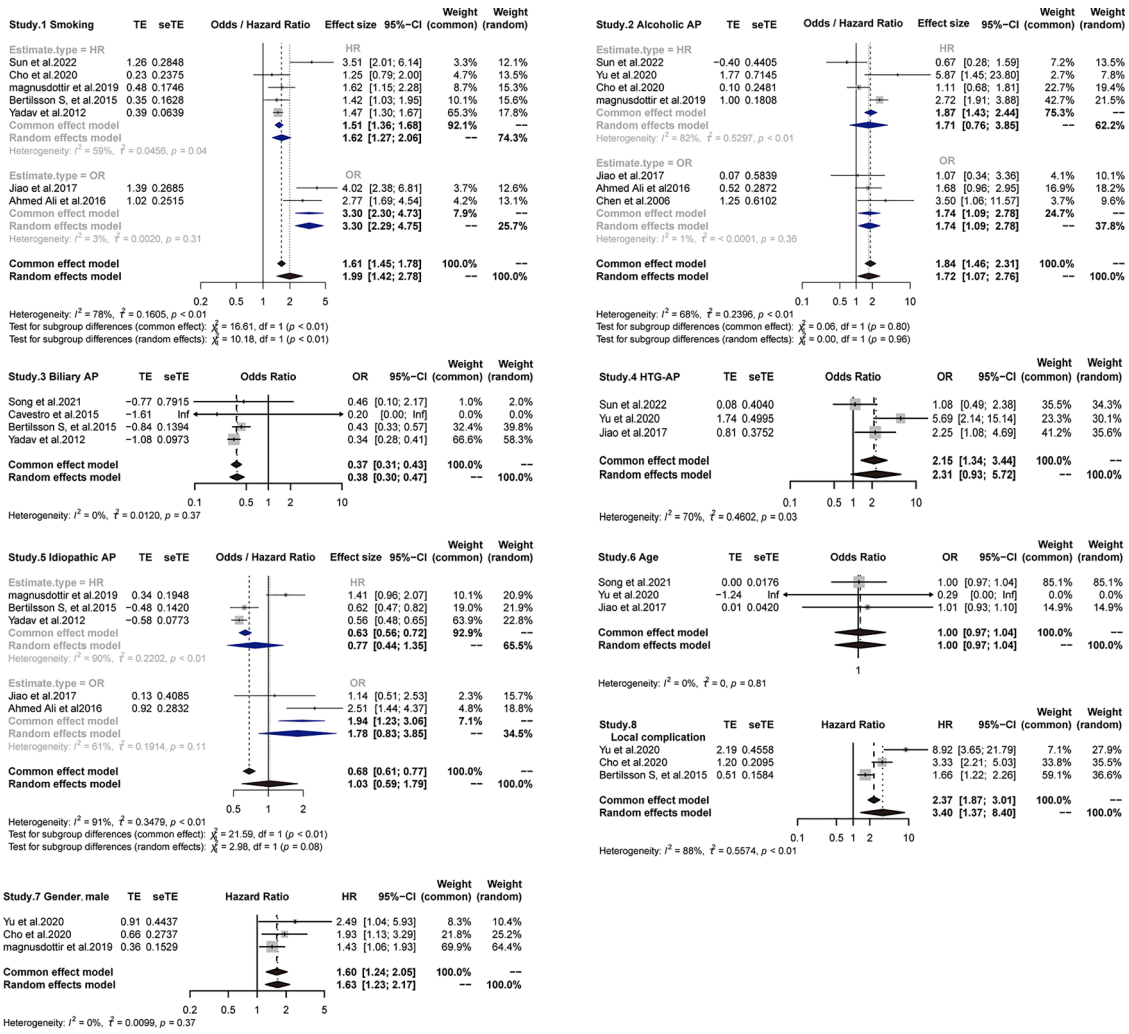

Fig. 4. Forest plots of association between risk factors and RAP. AP: acute pancreatitis; HTG-AP: hypertriglyceridemia-induced acute pancreatitis; OR: odds ratio; HR: hazard ratio; TE: estimate of treatment effect; seTE: standard error of treatment estimate.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.06.006.

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