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SYSTEMATIC REVIEW

The risk of recurrent pancreatitis after first episode of acute pancreatitis in relation to etiology and severity of disease: A systematic review, meta-analysis and meta-regression analysis

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Abstract

Background and Aim: The study aims to determine and quantify the stratified risk of recurrent pancreatitis (RP) after the first episode of acute pancreatitis in relation to etiology and severity of disease.
Methods: A systematic review and meta-analysis in compliance with PRISMA statement standards was conducted. A search of electronic information sources was conducted to identify all studies investigating the risk of RP after the first episode of acute pancreatitis. Proportion meta-analysis models using random effects were constructed to calculate the weighted summary risks of RP. Meta-regression was performed to evaluate the effect of different variables on the pooled outcomes.
Results: Analysis of 57,815 patients from 42 studies showed that the risk of RP after first episode was 19.8% (95% confidence interval [CI] 17.5–22.1%). The risk of RP was 11.9% (10.2–13.5%) after gallstone pancreatitis, 28.7% (23.5–33.9%) after alcohol-induced pancreatitis, 30.3% (15.5–45.0%) after hyperlipidemia-induced pancreatitis, 38.1% (28.9–47.3%) after autoimmune pancreatitis, 15.1% (11.6–18.6%) after idiopathic pancreatitis, 22.0% (16.9–27.1%) after mild pancreatitis, 23.9% (12.9–34.8%) after moderate pancreatitis, 21.6% (14.6–28.7%) after severe pancreatitis, and 6.6% (4.1–9.2%) after cholecystectomy following gallstone pancreatitis. Meta-regression confirmed that the results were not affected by the year of study (P = 0.541), sample size (P = 0.064), length of follow-up (P = 0.348), and age of patients (P = 0.138) in the included studies.
Conclusions: The risk of RP after the first episode of acute pancreatitis seems to be affected by the etiology of pancreatitis but not the severity of disease. The risks seem to be higher in patients with autoimmune pancreatitis, hyperlipidemia-induced pancreatitis, and alcohol-induced pancreatitis and lower in patients with gallstone pancreatitis and idiopathic pancreatitis.

Introduction

Acute pancreatitis, which is one of the most common critical gastrointestinal conditions, is associated with significant morbidity, mortality, and hospitalization costs.[1–3] Acute pancreatitis can be caused by gallstones, alcohol use, hypertriglyceridemia, hypercalcemia, drugs, autoimmune conditions, procedures such as endoscopic retrograde cholangiopancreatography (ERCP), trauma, infections, and congenital factors, or it can be idiopathic.[4] Despite improvements in mortality, an episode of acute pancreatitis can have significant impact on quality of life.[5,6] Although most patients with acute pancreatitis recover completely after successful conservative management, the risk of recurrence after the first attack of pancreatitis remains a potential concern.

The risk of recurrent pancreatitis can be reduced by addressing the factors causing acute pancreatitis. For example, early cholecystectomy, no alcohol intake, and good control of triglyceride levels may reduce the risk of recurrent pancreatitis in patients with gallstone-induced, alcohol-induced, and hyperlipidemia-induced pancreatitis, respectively.[7,8] Recurrent attack of pancreatitis can not only cause morbidity and even mortality but can also negatively affect the quality of life of the patient.[6] Recurrent pancreatitis may increase the risk of developing chronic pancreatitis or even pancreatic cancer.[9]

There is currently no comprehensive systematic review in the literature quantifying the risk of recurrent pancreatitis after the first episode of acute pancreatitis in relation to etiology and severity of disease. The risk of recurrent pancreatitis after the first attack of acute pancreatitis has been evaluated by a large number of studies, providing a robust basis for a comprehensive systematic review and meta-analysis. We aimed to determine and quantify the stratified risk of recurrent pancreatitis after the first episode of acute pancreatitis in relation to etiology and severity of disease.

Objectives

This study has the following objectives:

1. To determine and quantify the stratified risk of recurrent pancreatitis after the first episode of acute pancreatitis in relation to etiology and severity of disease
2. To evaluate the effect of variations in different covariates among the individual studies on overall pooled risk of recurrent pancreatitis using meta-regression analysis model.
3. To evaluate the certainty of the available evidence using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system.[10]

Methods

The predefined protocol and design of this study were compliant with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement standards.[11] The predefined protocol for this study was prospectively registered in PROSPERO, which is a publicly available international prospective register of systematic reviews (Registration Number: CRD42022377399). Considering that this study was a systematic review with meta-analysis of outcomes which did not include research directly involving human or animal participation, Institutional Review Board (IRB) approval and ethical approval were not required.

Eligibility criteria

Study design. All randomized controlled trials, cohort studies, case–control studies, and case series reporting the risk of recurrent pancreatitis after first episode of acute pancreatitis were considered to be of interest for inclusion. Randomized controlled trials of therapeutic interventions for patients with first episode of acute pancreatitis that reported the risk of recurrent pancreatitis in their study arms were considered for inclusion.

Population. All adult patients with first episode of acute pancreatitis of any cause (gallstone-induced, alcohol-induced, hyperlipidemia-induced, hypercalcemia-induced, drug-induced, autoimmune, iatrogenic, traumatic, infective, or idiopathic) and any severity (mild, moderately severe, or severe) were considered eligible. Definitions for severity of acute pancreatitis should have been consistent with definitions suggested by Banks *et al.*[12]: mild (absence of organ failure and the absence of local or systemic complications), moderately severe (presence of transient organ failure or local or systemic complications in the absence of persistent organ failure), and severe (persistent organ failure).

Outcome. The risk of recurrent pancreatitis was the outcome of interest. It was defined as confirmed diagnosis of acute pancreatitis any time after the first episode of acute pancreatitis.

Search methods. The detail of search strategy and electronic sources used are provided in Data S1. The search strategy was developed and incorporated independently by two authors with expertise in evidence synthesis. The last search was applied on August 1, 2022, without any language restrictions.

Selection of studies and data extraction. Two independent authors screened the title and abstract of the articles obtained via the aforementioned search strategy. We evaluated the full texts of potentially eligible articles and included the eligible studies. This was followed by creation of a data extraction sheet using pilot-testing technique. We extracted information on bibliographic data, design of each study, sample size of each study, included population description, duration of follow-up, cause of first episode of acute pancreatitis, severity of first episode of acute pancreatitis, patients who had cholecystectomy or ERCP, patient's age, gender, body mass index, history of hypertension, diabetes or ischemic heart disease, smoking status, and risk of recurrence. Any disagreements during study selection and data extraction were discussed between the first two independent authors, and a third independent author was consulted when required.

Risk of bias assessment. The methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal tool which evaluates the methodological quality in terms of eligibility criteria, measurement of condition/exposure/factor of interest, consecutiveness and completion of recruitment process, demographics and clinical characteristics of the included population, outcome measures, and statistical analyses.[13] The methodological quality assessment was conducted by two independent reviewers. Any disagreements during this process were discussed between the first two independent authors, and a third independent author was consulted when required.

Data analysis. We integrated the quantitative risk of recurrent pancreatitis from individual studies and calculated numerical estimates of the overall effect. The DerSimonian–Laird random-effects method with 95% confidence level and correction factor of 0.5 was used to calculate the weighted pooled risk of recurrent pancreatitis. The statistical heterogeneity was measured as I^2 using Cochran Q test (χ^2), and it was classified as low heterogeneity when I^2 was 0–25%, moderate heterogeneity when I^2 was 25–75%, and high heterogeneity when I^2 was 75–100%. Meta-regression models were constructed to assess the effect of differences in the year of study, sample size, length of follow-up, and age of patients among the individual studies on overall pooled risk of recurrent pancreatitis. OpenMeta[Analyst] software was used for proportion meta-analysis model.

Additional analyses. We performed subgroup analyses based on cause of first episode of acute pancreatitis, severity of first episode of acute pancreatitis, and patients with first episode of gallstone pancreatitis who underwent cholecystectomy. Moreover, we performed the following sensitivity analyses in order to evaluate the consistency and robustness of the results: (a) Leave-one-out analysis to investigate the effect of each study on the pooled risk of recurrent pancreatitis; (b) separate analysis of studies with low overall risk of bias.

Summary of findings table. We evaluated the certainty of evidence based on the recommended standards and domains by the GRADE system, and a summary of findings table was produced.[11]

Results

Results of the search. The search of electronic databases resulted in 459 articles of which 393 articles were excluded directly because they were not relevant to the subject of this study. After reviewing the full text of the remaining 66 articles, 24 more articles were excluded (22 articles included patients who had more than one previous episodes of pancreatitis; two studies included the same population as one of the eligible studies). Consequently, 42 studies[8,9,14–53] (32 retrospective cohort, 8 prospective cohort, and 2 randomized controlled trials) including a total of 57 815 patients were eligible for inclusion. The study flow chart is shown in Figure 1. Among the included studies, 10 studies included only patients with gallstone pancreatitis, 5 studies included only patients with alcohol-induced pancreatitis, 4 studies included only patients with autoimmune pancreatitis, 3 studies included only patients with idiopathic pancreatitis, and 20 studies included all patients with acute pancreatitis of any cause. The mean duration of follow-up was 47 months (95% confidence interval [CI] 40–53). The baseline characteristics of the included studies and population are shown in Tables 1 and 2, respectively.

Risk of bias in included studies. Table S1 highlights the outcomes of methodological quality assessment based on the JBI assessment tool.

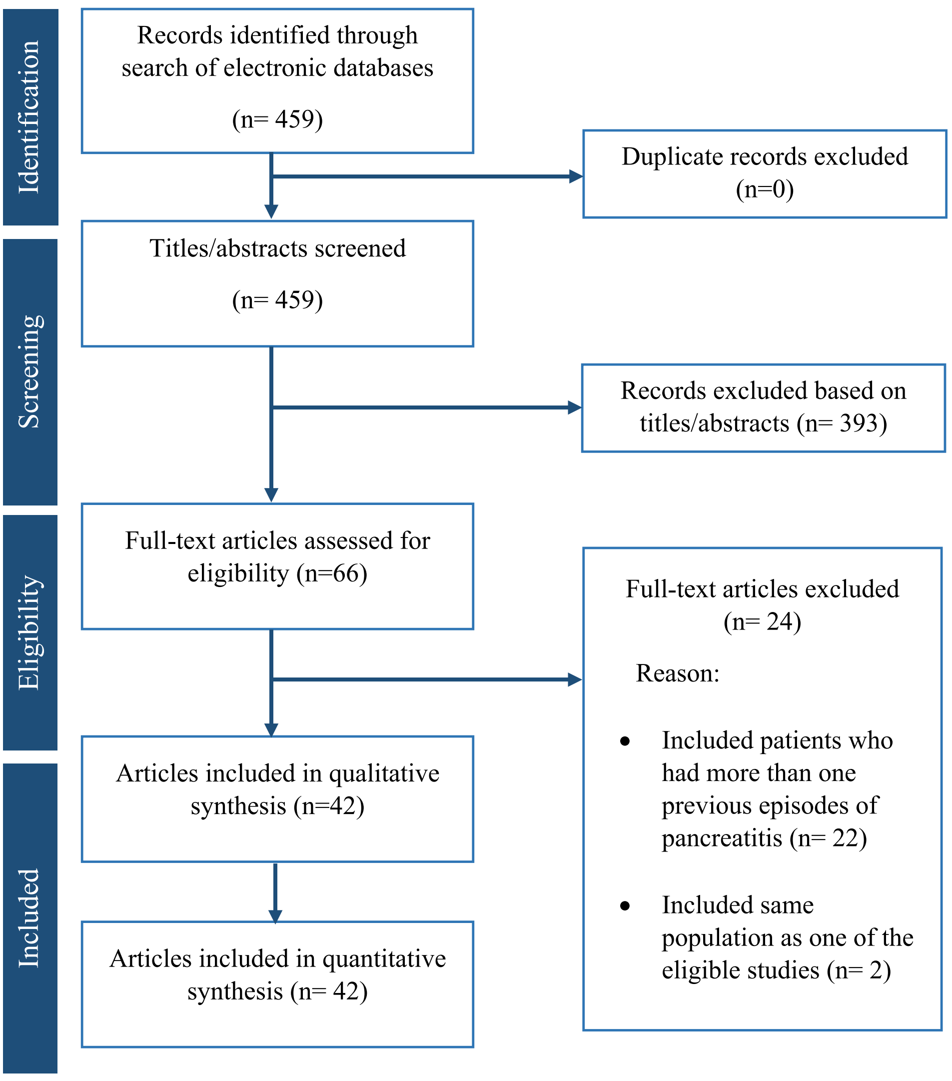


Figure 1 PRISMA flow chart.

Table 1 Baseline characteristics of the included studies

First Author	Year	Country	Journal	Study design	Follow-up length (months)	Description of Included population	Cause of pancreatitis	Total sample size
Sun	2022	China	*International Journal of General Medicine*	Retrospective observational	25	Adult patients with a first attack of acute pancreatitis	Any	592
Patra	2021	India	*Journal of Gastroenterology and Hepatology*	Retrospective observational	60	Adult patients with a first attack of acute pancreatitis	Any	100
Yu	2020	China	*Pancreatology*	Retrospective observational	36	Adult patients with a first attack of acute pancreatitis	Any	522
Paredes	2020	Spain	*Pancreatology*	Retrospective observational	72	Patients with inflammatory bowel disease with first attack of acute pancreatitis	Any	185
Kim	2020	Korea	*Medicine*	Retrospective observational	35	Adult patients with a first attack of acute pancreatitis	Any	437
Chen	2019	China	*European Radiology*	Retrospective observational	63	Adult patients with a first attack of acute pancreatitis	Any	389
Cho	2019	New Zealand	*Clinical Pharmacology and Therapeutics*	Retrospective observational	83	Adult patients with a first attack of acute pancreatitis	Any	10 190
Cho (2)	2019	Republic of Korea	*Scandinavian Journal of Gastroenterology*	Retrospective observational	38	Adult patients with a first attack of acute pancreatitis	Any	617
Hallensleben	2019	Netherlands	*United European Gastroenterology Journal*	Prospective observational	48	Adult patients with a first attack of acute idiopathic pancreatitis	Idiopathic	191
Ishii	2019	Japan	*Scandinavian Journal of Gastroenterology*	Retrospective observational	39	Adult patients with a first attack of acute autoimmune pancreatitis	Autoimmune	76
Magnusdottir	2019	Iceland	*Scandinavian Journal of Gastroenterology*	Retrospective observational	48	Adult patients with a first attack of acute pancreatitis	Any	1102
Molina	2019	Spain	*Digestive and Liver Disease*	Retrospective observational	14	Adult patients with a first attack of acute gallstone pancreatitis not fit for cholecystectomy	Gallstone	247
Lee	2018	South Korea	*Journal of Gastroenterology*	Retrospective observational	60	Adult patients with a first attack of acute autoimmune pancreatitis	Autoimmune	138
Wu	2018	America	*Digestive Diseases and Sciences*	Retrospective observational	36	Adult patients with a first attack of acute pancreatitis	Any	151
Stigliano	2017	Italy	*Digestive and Liver Disease*	Prospective observational	42	Adult patients with a first attack of acute pancreatitis	Any	266
Nikkola	2017	Finland	*Alcohol and Alcoholism*	Retrospective observational	50	Adult patients with a first attack of acute alcohol-induced pancreatitis	Alcohol	74
Ahmed Ali	2016	Netherlands	*Clinical Gastroenterology and Hepatology*	Prospective observational	57	Adult patients with a first attack of acute pancreatitis	Any	669
Ragnarsson	2016	Sweden	*Scandinavian Journal of Gastroenterology*	Retrospective observational	NR	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	254
Kamal	2016	USA	*American Journal of Gastroenterology*	Retrospective observational	NR	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	17 010
Hayashi	2016	Japan	*World Journal of Gastroenterology*	Retrospective observational	NR	Adult patients with a first attack of acute pancreatitis	Any	73
Bertillson	2015	Sweden	*Clinical Gastroenterology and Hepatology*	Retrospective observational	55	Adult patients with a first attack of acute pancreatitis	Any	1457
Raty	2015	Finland	*Annals of Surgery*	Randomized controlled trial	36	Adult patients with a first attack of acute idiopathic pancreatitis	Idiopathic	85
Albulushi	2014	Oman	*Oman Medical Journal*	Retrospective observational	NR	Adult patients with a first attack of acute pancreatitis	Any	174
Deng	2014	China	*Journal of digestive diseases*	Retrospective observational	NR	Adult patients with a first attack of acute pancreatitis	Any	1894
Mustafa	2014	England	*Surgical endoscopy*	Retrospective observational	60	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	4682
Johnstone	2013	UK	*The Surgeon*	Retrospective observational	NR	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	523
Yadav	2012	America	*American Journey of Gastroenterology*	Retrospective observational	40	Adult patients with a first attack of acute pancreatitis	Any	7456

(Continues)

Table 1 (Continued)

First Author	Year	Country	Journal	Study design	Follow-up length (months)	Description of Included population	Cause of pancreatitis	Total sample size
El-Dhuwaib	2012	UK	*Annals of Royal College of Surgeons England*	Retrospective observational	18	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	5454
Hart	2012	USA	*Gut*	Retrospective observational	47	Adult patients with a first attack of acute autoimmune pancreatitis	Autoimmune	116
Maire	2011	France	*American Journey of Gastroenterology*	Retrospective observational	41	Adult patients with a first attack of acute autoimmune pancreatitis	Autoimmune	44
Lankisch	2009	Germany	*American Journal of Gastroenterology*	Prospective observational	94	Adult patients with a first attack of acute pancreatitis	Any	532
Nordback	2009	Finland	*Gastroenterology*	Randomized controlled trial	24	Adult patients with a first attack of acute alcohol-induced pancreatitis	Alcohol	120
Pelli	2008	Finland	*Scandinavian Journal of Gastroenterology*	Prospective observational	38	Adult patients with a first attack of acute alcohol-induced pancreatitis	Alcohol	68
Pelli (2)	2007	Finland	*Pancreatology*	Prospective observational	47	Adult patients with a first attack of acute alcohol-induced pancreatitis	Alcohol	54
Lund	2006	Denmark	*Scandinavian Journal of Gastroenterology*	Retrospective observational	72	Adult patients with a first attack of acute pancreatitis	Any	155
Hernandez	2004	Spain	*American Journal of Gastroenterology*	Prospective observational	NR	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	233
Alimoglu	2003	Turkey	*World Journal of Surgery*	Retrospective observational	NR	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	43
McCullough	2003	Canada	*HPB*	Retrospective observational	60	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	164
Billi	2003	Italy	*Digestive and Liver Disease*	Prospective observational	12	Adult patients with a first attack of acute gallstone pancreatitis	Gallstone	47
Pelli (3)	2000	Finland	*Scandinavian Journal of Gastroenterology*	Retrospective observational	48	Adult patients with a first attack of acute alcohol-induced pancreatitis	Alcohol	562
Ballinger	1996	UK	*Gut*	Retrospective observational	36	Adult patients with a first attack of acute idiopathic pancreatitis	Idiopathic	31
Corfield	1985	UK	*Gut*	Retrospective observational	NR	Adult patients with a first attack of acute pancreatitis	Any	638

NR, not reported.

Risk of recurrent pancreatitis

All patients. A total of 57 495 patients from 42 studies were analyzed. Among 57 ,495 patients with first episode of acute pancreatitis, 7045 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 19.8% (95% CI 17.5–22.1%). The level of heterogeneity between the studies was high (I^2 = 98%, $P < 0.001$) (Fig. 2a). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2). The median time from the first episode to recurrence was 7 months (95% CI 4–11).

Patients with gallstone pancreatitis. A total of 37 578 patients from 29 studies were analyzed. Among 37 578 patients with first episode of acute gallstone pancreatitis, 3025 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 11.9% (95% CI 10.2–13.5%). The level of heterogeneity between the studies was high (I^2 = 95%, $P < 0.001$) (Fig. 2b). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2).

Patients with gallstone pancreatitis who had cholecystectomy. A total of 6283 patients from 11 studies were analyzed. Among 6283 patients with first episode of acute gallstone pancreatitis who had cholecystectomy, 406 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 6.6% (95% CI 4.1–9.2%). The level of heterogeneity between the studies was high (I^2 = 95%, $P < 0.001$) (Fig. 2c). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2).

Patients with alcohol-induced pancreatitis. A total of 4283 patients from 22 studies were analyzed. Among 4283 patients with first episode of acute alcohol-induced pancreatitis, 1451 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 28.7% (95% CI 23.5–33.9%). The level of heterogeneity between the studies was high (I^2 = 92%, $P < 0.001$) (Fig. 2d). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2).

Patients with hyperlipidemia-induced pancreatitis. A total of 638 patients from 8 studies were analyzed. Among 638 patients

Table 2 Baseline characteristics of the included population

First Author	Year	Cause of acute pancreatitis							Cholecystectomy	ERCP
		Gallstone	Alcohol	Hyperlipidemia	Autoimmune	Idiopathic	Drug	Other		
Sun	2022	289/592	68/592	157/592	NR	NR	NR	78/592	NR	NR
Patra	2021	31/100	21/100	0/100	0/100	35/100	0/100	11/100	NR	NR
Yu	2020	326/522	34/522	116/522	NR	NR	NR	46/522	169/326	119/522
Paredes	2020	34/185	2/185	0/185	0/185	38/185	109/185	2/185	NR	NR
Kim	2020	71/439	166/437	8/437	NR	67/437	1/437	NR	10/71.	NR
Chen	2019	112/389	97/389	68/389	NR	81/389	NR	31/389	NR	NR
Cho	2019	2860/10190	NR	NR	NR	NR	NR	NR	NR	NR
Cho (2)	2019	304/617	182/617	NR	NR	56/617	NR	75/617	164/304	NR
Hallensleben	2019	0/191	0/191	0/191	0/191	191/191	0/191	0/191	41/191	15/191
Ishii	2019	0/76	0/76	0/76	76/76	0/76	0/76	0/76	NR	NR
Magnusdottir	2019	450/1102	227/1102	NR	NR	283/1102	NR	142/1102	141/450	NR
Molina	2019	247/247	0/247	0/247	0/247	0/247	0/247	0/247	0/247	57/247
Lee	2018	0/138	0/138	0/138	138/138	0/138	0/138	0/138	NR	109/138
Wu	2018	7/151	42/151	NR	NR	NR	NR	102/151	NR	NR
Stigliano	2017	125/266	41/266	8/266	NR	38/266	12/266	NR	70/125	37/125
Nikkola	2017	0/74	74/74	0/74	0/74	0/74	0/74	0/74	NR	NR
Ahmed Ali	2016	384/669	153/669	NR	NR	108/669	NR	24/669	NR	NR
Ragnarsson	2016	254/254	0/254	0/254	0/254	0/254	0/254	0/254	137/254	35/254
Kamal	2016	17,010/17010	0/17010	0/17010	0/17010	0/17010	0/17010	0/17010	13,305/17010	1248/17010
Hayashi	2016	19/73	14/73	3/73.	4/73.	10/73.	1/73.	22/73	NR	NR
Bertillson	2015	704/1457	249/1457	NR	NR	431/1457	NR	72/1457	426/704	107/1457
Raty	2015	0/85	0/85	0/85	0/85	85/85	0/85	0/85	39/85	0/85
Albulushi	2014	61/174	56/174	6/174	1/174	36/174	3/174	11/174	NR	NR
Deng	2014	670/1894	306/1894	272/1894	NR	432/1894	NR	214/1894	NR	NR
Mustafa	2014	4682/4682	0/4682	0/4682	0/4682	0/4682	0/4682	0/4682	3085/4682	419/4682
Johnstone	2013	523/523	0/523	0/523	0/523	0/523	0/523	0/523	363/523	164/421
Yadav	2012	2047/7456	1427/7456	NR	NR	2681/7456	NR	1113/7456	1451/2047	NR
El-Dhuwaib	2012	5454/5454	0/5454	0/5454	0/5454	0/5454	0/5454	0/5454	3392/5454	1399/5454
Hart	2012	0/116	0/116	0/116	116/116	0/116	0/116	0/116	NR	NR
Maire	2011	0/44	0/44	0/44	44/44	0/44	0/44	0/44	NR	11/44.
Lankisch	2009	224/532	158/532	NR	NR	106/532	NR	44/532	111/224	NR
Nordback	2009	0/120	120/120	0/120	0/120	0/120	0/120	0/120	NR	NR
Pelli	2008	0/68	68/68	0/68	0/68	0/68	0/68	0/68	0/68	0/68
Pelli (2)	2007	0/54	54/54	0/54	0/54	0/54	0/54	0/54	0/54	0/54
Lund	2006	50/155	69/155	0/155	0/155	15/155	0/155	0/155	NR	NR
Hernandez	2004	233/233	0/233	0/233	0/233	0/233	0/233	0/233	61/233	NR
Alimoglu	2003	43/43	0/43	0/43	0/43	0/43	0/43	0/43	27/43	31/43
McCullough	2003	164/164	0/164	0/164	0/164	0/164	0/164	0/164	164/164	103/164
Billi	2003	47/47	0/47	0/47	0/47	0/47	0/47	0/47	0/47	47/47
Pelli (3)	2000	0/562	562/562	0/562	0/562	0/562	0/562	0/562	0/562	0/562
Ballinger	1996	0/31	0/31	0/31	0/31	31/31	0/31	0/31	0/31	20/31
Corfield	1985	319/638	51/638	NR	NR	148/638	NR	120/638	NR	NR

with first episode of acute hyperlipidemia-induced pancreatitis, 149 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 30.3% (95% CI 15.5–45.0%). The level of heterogeneity between the studies was high (I^2 = 94%, P < 0.001) (Fig. 2e). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2).

Patients with autoimmune pancreatitis. A total of 379 patients from 6 studies were analyzed. Among 379 patients with first episode of acute autoimmune pancreatitis, 154 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 38.1% (95% CI 28.9–47.3%). The level of heterogeneity between the studies was moderate (I^2 = 62%, P = 0.024) (Fig. 2f). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2).

Patients with idiopathic pancreatitis. A total of 4754 patients from 17 studies were analyzed. Among 4754 patients with first episode of acute idiopathic pancreatitis, 293 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 15.1% (95% CI 11.6–18.6%). The level of heterogeneity between the studies was high (I^2 = 96%, P < 0.001) (Fig. 2g). The certainty

Table 2 (Continued)

First Author	Severity of acute pancreatitis			Age	Male gender	BMI	Hypertension	Ischemic heart disease	Diabetes	Smoking
	Mild	Moderate	Severe							
Sun	368/592	151/592	73/592	49 ± 26	383/592	25.4 ± 4.6	NR	NR	72/592	133/592
Patra	59/100	23/100	18/100	42 ± 18.5	64/100	NR	NR	NR	NR	NR
Yu	201/522	250/522	71/522	52.9 ± 16.2	305/522	22.3 ± 3.0	87/522	NR	56/522	61/522
Paredes	170/185	13/185	2/185	41.8 ± 17.3	98/185	NR	NR	NR	4/185	74/185
Kim	163/437	148/437	2/437	50 ± 15	209/437	NR	96/437	NR	80/437	NR
Chen	122/389	205/389	62/389	49.2 ± 15.44	238/389	NR	NR	NR	NR	145/389
Cho	9000/10190	0/10190	1190/10190	56.3 ± 19.2	4966/10190	NR	NR	NR	1335/10190	4972/10190
Cho (2)	NR	NR	NR	60.6 ± 16.8	380/617	NR	NR	NR	NR	NR
Hallensleben	NR	NR	NR	61 ± 5	102/191	27 ± 1.25	NR	NR	26/191	40/141
Ishii	NR	NR	NR	66.9 ± 10.0	67/76	NR	NR	NR	32/76	NR
Magnusdottir	769/1102	270/1102	63/1102	56 ± 19	593/1102	NR	NR	NR	NR	441/1102
Molina	178/247	38/247	31/247	80 ± 12	101/247	NR	171/247	43/247	51/247	NR
Lee	NR	NR	NR	59.9 ± 10	112/138	NR	NR	NR	39/138	NR
Wu	NR	NR	NR	40.8 ± 9.67	98/151	31.4 ± 5.53	NR	NR	50/151	47/151
Stigliano	172/266	39/266	55/266	58 ± 17	158/266	NR	NR	NR	NR	NR
Nikkola	48/74	22/74	4//74	48 ± 12.5	70/74	NR	NR	NR	NR	36/74
Ahmed Ali	NR	NR	147/669	57 ± 7	366/669	27.5 ± 5.6	NR	NR	136/669	158/585
Ragnarsson	172/254	82/254	0/254	67.6	129/254	NR	NR	NR	NR	NR
Kamal	NR	NR	0/17010	NR	6309/17010	NR	NR	NR	NR	NR
Hayashi	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bertillson	NR	NR	144/1457	61 ± 19	772/1457	NR	NR	NR	NR	NR
Raty	84/85	0/85	1/85.	56.5	52/85	NR	NR	NR	NR	NR
Albulushi	131/174	29/174	14/174	44 ± 11	93/174	NR	NR	NR	NR	NR
Deng	1532/1894	0/1894	362/1894	43.3 ± 16.5	1146/1894	NR	NR	NR	NR	NR
Mustafa	NR	NR	NR	62 ± 24	NR	NR	NR	NR	NR	NR
Johnstone	NR	NR	NR	58 ± 7	NR	NR	NR	NR	NR	NR
Yadav	NR	NR	NR	58 ± 8	3318/7456	NR	NR	NR	NR	1342/7456
El-Dhuwaib	NR	NR	NR	63 ± 8	1998/5454	NR	NR	NR	NR	NR
Hart	NR	NR	NR	66.2 ± 18	93/116	NR	NR	NR	NR	NR
Maire	NR	NR	NR	37.5 ± 14	22/45.	NR	NR	NR	NR	NR
Lankisch	437/532	84/532	11/532	56 ± 18	289/532	NR	NR	NR	NR	NR
Nordback	NR	NR	33/120	46.5	101/120	27.1	NR	NR	NR	67/120
Pelli	NR	NR	18/68	46 ± 12	59/68	27.6 ± 0.4	NR	NR	10//68	41//68
Pelli (2)	41/54	0/54	13/54	49 ± 12	47/54	NR	NR	NR	8//54	NR
Lund	NR	NR	NR	48 ± 19	99/155	NR	NR	NR	NR	NR
Hernandez	NR	NR	63/233	66.24 ± 16.5	106/233	29.04 ± 5.8	NR	NR	NR	NR
Alimoglu	NR	NR	NR	NR	14/43	NR	NR	NR	NR	NR
McCullough	164/164	0/164	0/164	53	NR	NR	NR	NR	NR	NR
Billi	36/47	0/47	11/47.	70.6 ± 12.5	15/37	NR	18/42	34/42	7/47.	NR
Pelli (3)	NR	NR	NR	41 ± 11	503/562	NR	NR	NR	NR	NR
Ballinger	NR	NR	NR	61.7 ± 17	15/31	NR	NR	NR	NR	NR
Corfield	NR	NR	NR	60 ± 23	311/638	NR	NR	NR	NR	NR

BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; NR, not reported.

of available evidence was judged to be moderate based on GRADE system (Table S2).

Patients with mild pancreatitis. A total of 11 901 patients from 10 studies were analyzed. Among 11 901 patients with first episode of mild acute pancreatitis, 1707 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 15.1% (95% CI 11.6–18.6%). The level of heterogeneity between the studies was high ($I^2 = 97\%$, $P < 0.001$) (Fig. 2h). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2).

Patients with moderately severe pancreatitis. A total of 822 patients from 6 studies were analyzed. Among 822 patients with first episode of moderately severe acute pancreatitis, 183 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 23.9% (95% CI 12.9–34.8%). The level of heterogeneity between the studies was high (I^2 = 94%,

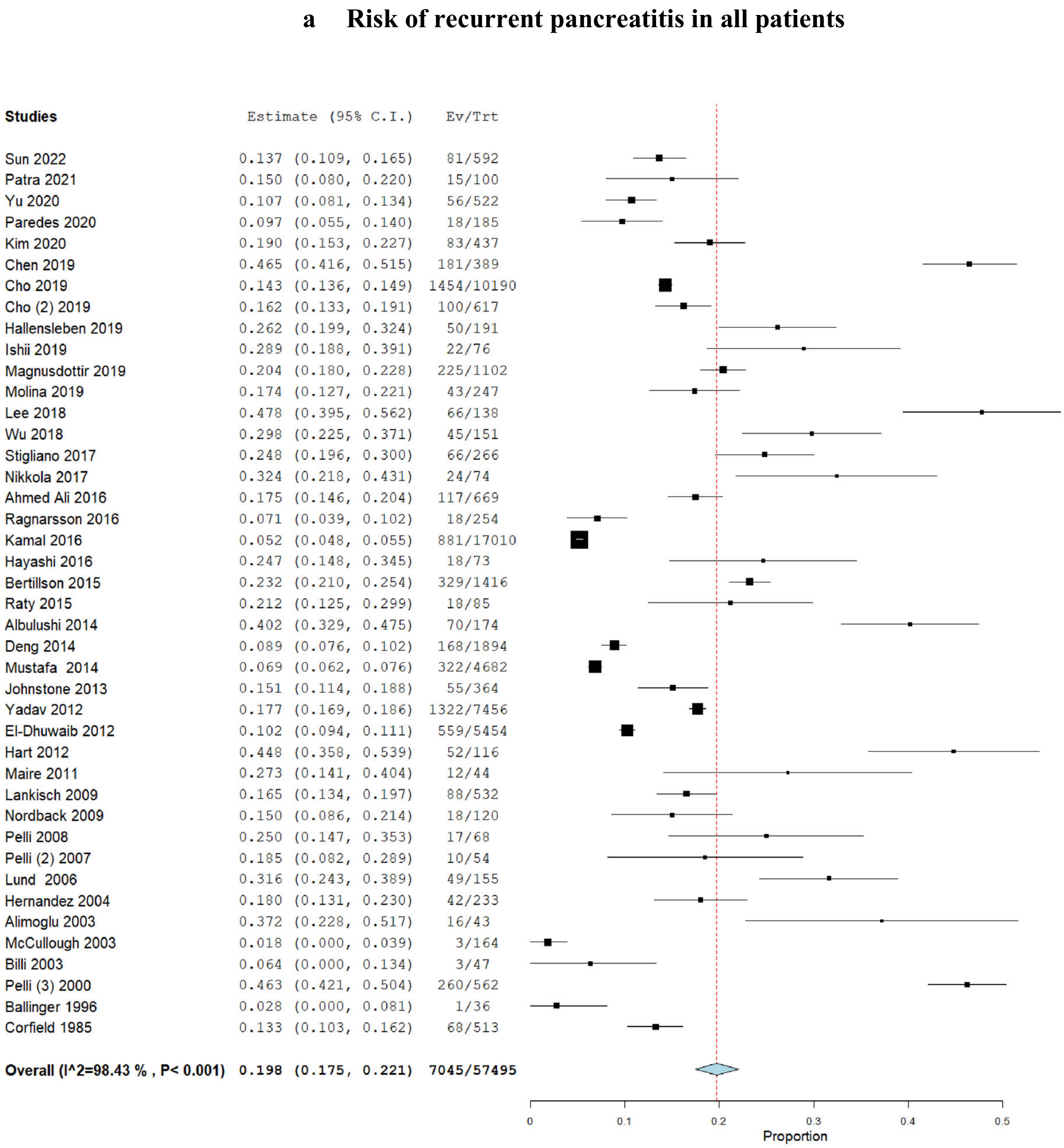


Figure 2 The forest plots for the risk of recurrent pancreatitis in (a) all patients; (b) patients with gallstone pancreatitis; (c) patients with gallstone pancreatitis who had cholecystectomy; (d) patients with alcohol-induced pancreatitis; (e) patients with hyperlipidemia-induced pancreatitis; (f) patients with autoimmune pancreatitis; (g) patients with idiopathic pancreatitis; (h) patients with mild pancreatitis; (i) patients with moderately severe pancreatitis; (j) patients with severe pancreatitis.

$P < 0.001$) (Fig. 2i). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2).

Patients with severe pancreatitis. A total of 1976 patients from 9 studies were analyzed. Among 1976 patients with first episode of severe acute pancreatitis, 330 patients developed recurrent pancreatitis. The pooled risk of recurrent pancreatitis was 21.6% (95% CI 14.6–28.7%). The level of heterogeneity between the studies was high (I^2 = 94%, $P < 0.001$) (Fig. 2j). The certainty of available evidence was judged to be moderate based on GRADE system (Table S2).

Meta-regression analyses. Meta-regression confirmed that the pooled risk of recurrent pancreatitis was not affected by the year of study (coefficient: 0.001, P = 0.541),

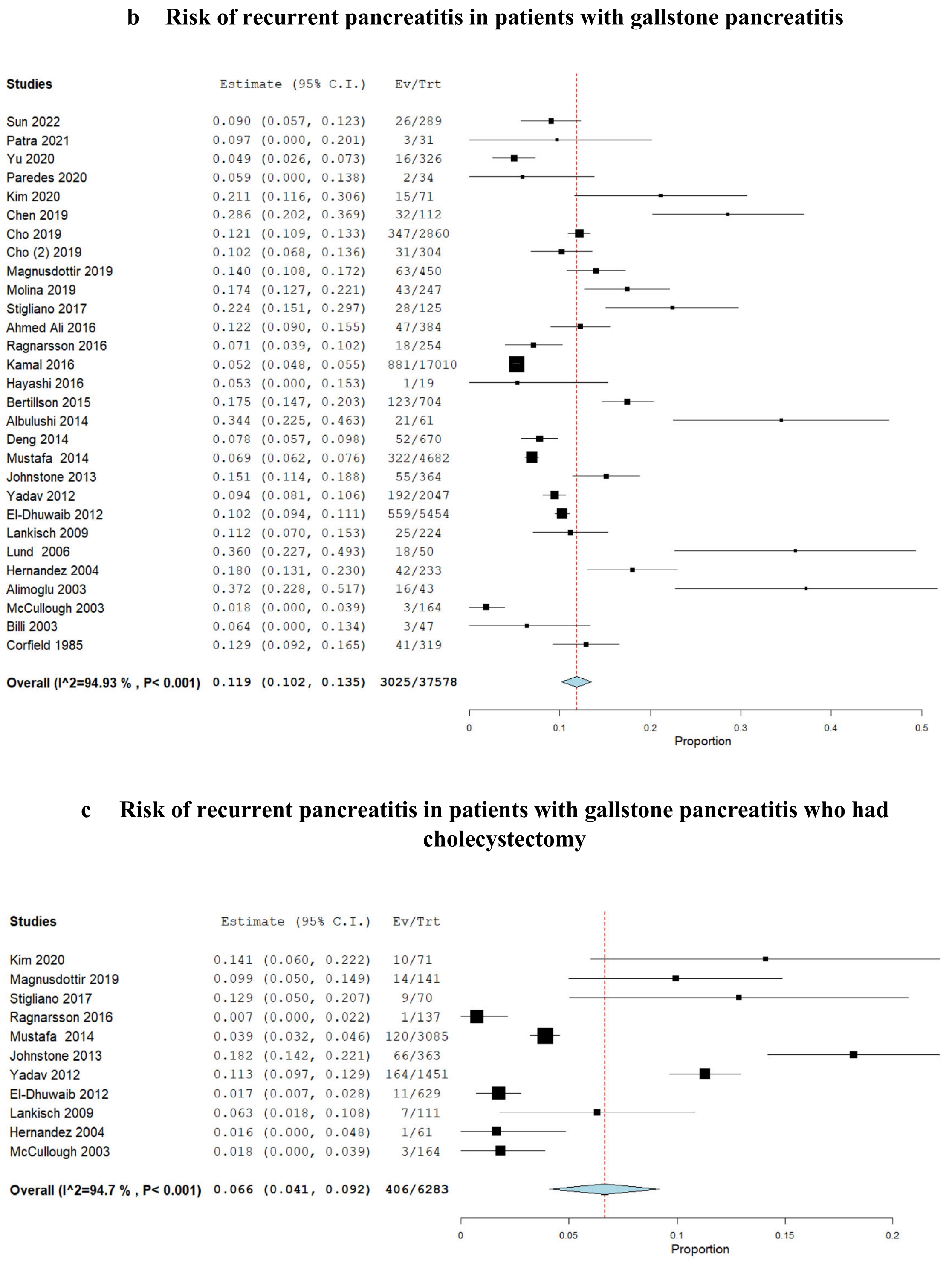
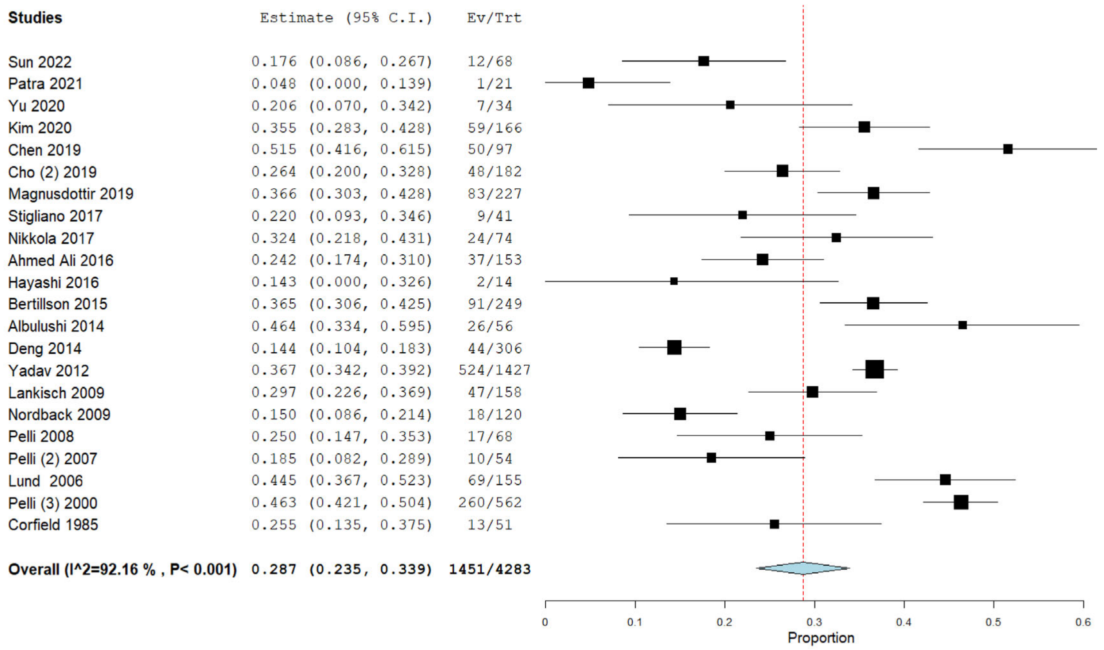


Figure 2 (continued)

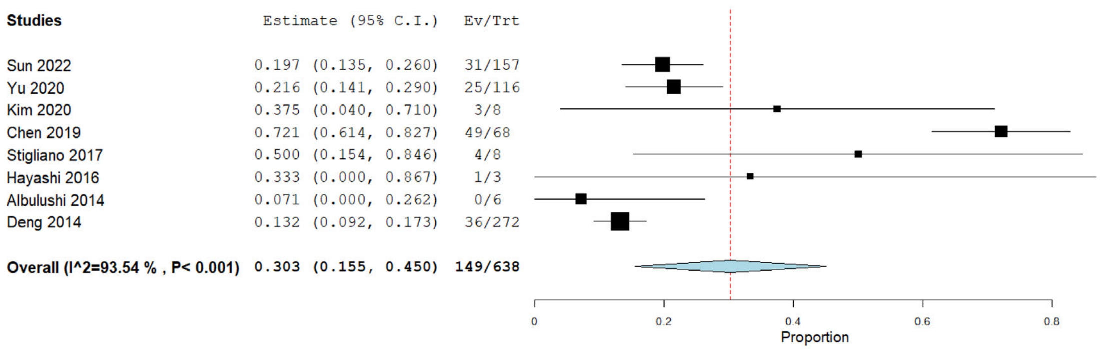
sample size (coefficient: −0.000001, P = 0.064), length of follow-up (coefficient: 0.001, P = 0.348), and age of patients (coefficient: −0.003, P = 0.138) in the included studies (Fig. 3).

Sensitivity analyses. Sensitivity analyses confirmed consistency of the results (Fig. S1). Leave-one-out analysis showed that removal of one study at a time did not affect the pooled risk of recurrent pancreatitis. Moreover, separate analysis of studies with

d Risk of recurrent pancreatitis in patients with alcohol-induced pancreatitis



e Risk of recurrent pancreatitis in patients with hyperlipidaemia-induced pancreatitis



f Risk of recurrent pancreatitis in patients with autoimmune pancreatitis

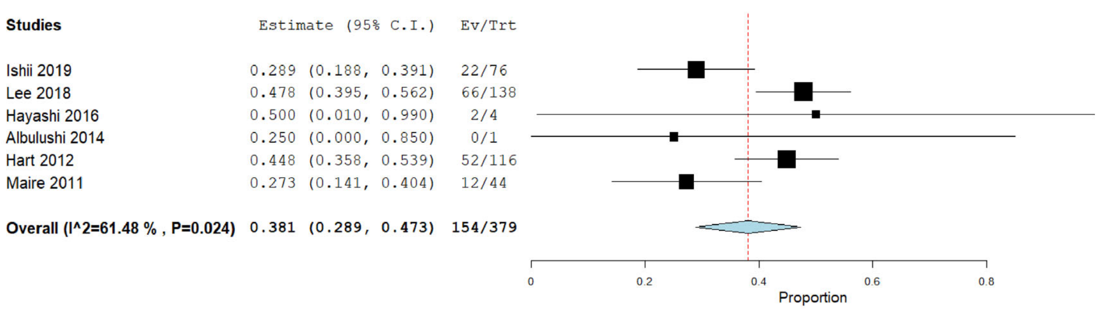


Figure 2 (continued)

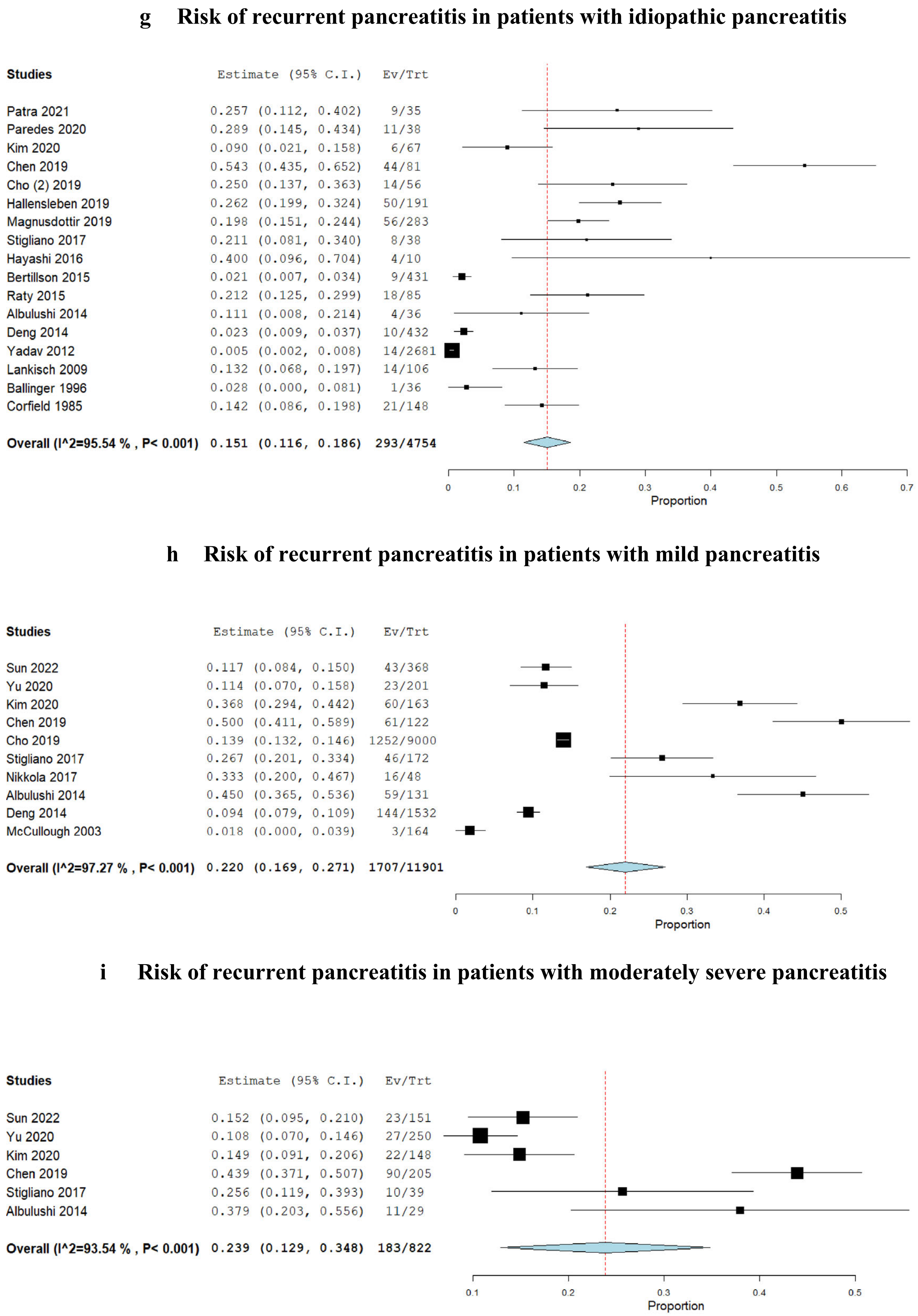


Figure 2 (continued)

j Risk of recurrent pancreatitis in patients with severe pancreatitis

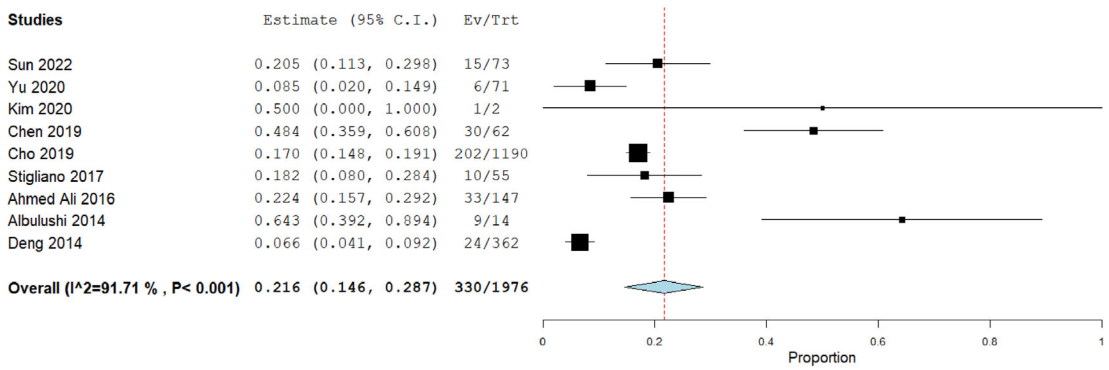


Figure 2 (continued)

low overall risk of bias did not affect the pooled risk of recurrent pancreatitis.

Discussion

We conducted a systematic review and meta-analysis to determine the risk of recurrent pancreatitis after the first episode of acute pancreatitis in relation to etiology and severity of disease. Analysis of 57 815 patients from 42 studies showed that the risk of recurrent pancreatitis after first episode of pancreatitis of any cause was 19.8% (95% CI 17.5–22.1%). Subgroup analyses based on etiology of first episode showed that the risk of recurrent pancreatitis was 11.9% (95% CI 10.2–13.5%) after gallstone pancreatitis, 28.7% (95% CI 23.5–33.9%) after alcohol-induced pancreatitis, 30.3% (95% CI 15.5–45.0%) after hyperlipidemia-induced pancreatitis, 38.1% (95% CI 28.9–47.3%) after autoimmune pancreatitis, and 15.1% (95% CI 11.6–18.6%) after idiopathic pancreatitis. Subgroup analyses based on severity of first episode showed that the risk of recurrence was 22.0% (95% CI 16.9–27.1%) after mild pancreatitis, 23.9% (95% CI 12.9–34.8%) after moderate pancreatitis, 21.6% (95% CI 14.6–28.7%) after severe pancreatitis. The risk of recurrence in patients with gallstone pancreatitis who had cholecystectomy was 6.6% (95% CI 4.1–9.2%). Meta-regression confirmed that the results were not affected by the year of study, sample size, length of follow-up, and age of patients in the included studies. Sensitivity analyses confirmed consistency of the results. The quality and GRADE certainty of available evidence were moderate.

The current study is the first meta-analysis that quantifies the risk of recurrent pancreatitis after the first episode of acute pancreatitis in relation to etiology and severity of disease. In fact, the focus of previous meta-analyses in the literature has mainly been on etiology and incidence of acute pancreatitis but not the risk of recurrence after the first episode. The present synthesis is therefore novel. Although there is no similar meta-analysis to compare our results with, other prognostic aspects of first episode of acute pancreatitis have been evaluated by other authors. Sankaran *et al.*[54] analyzed 8492 patients with acute pancreatitis from 14 studies and concluded that 10% of patients with a first episode of acute pancreatitis and 36% of patients with recurrent acute pancreatitis develop chronic pancreatitis. Unfortunately, that study did not stratify the risk of recurrence after first attack by the etiology of acute pancreatitis.

Our results suggested that the risk of recurrence seems to be higher in patients with autoimmune pancreatitis, hyperlipidemia-induced pancreatitis, and alcohol-induced pancreatitis and lower in patients with gallstone pancreatitis and idiopathic pancreatitis. These findings can be explained based on the available evidence in the literature. Although autoimmune pancreatitis responds very well to initial oral corticosteroids therapy,[55] the recurrence rate remains high because there is a tendency to discontinue steroid therapy after successful induction of remission due to concerns about the side effects of long-term corticosteroids therapy.[22] Although maintenance steroid therapy has been shown to be effective in preventing recurrent attacks, there is no consensus on the appropriate duration of maintenance therapy.[22,25] Interestingly, the recurrent attacks can occur even during maintenance therapy.[22,25] All of these would explain high risk of recurrence in patients with autoimmune pancreatitis.

The high risks of recurrent attacks after first episode of hyperlipidemia-induced pancreatitis and alcohol-induced pancreatitis may be explained by poor compliance of patients with appropriate treatment strategies. Healthy diet, appropriate medical therapy, and avoiding aggravating factors are crucial for preventing recurrent attacks of hyperlipidemia-induced pancreatitis.[56] However, it has been shown that adherence to treatment strategies for hyperlipidemia is challenging due to patient-related, physician-related, and healthcare-related factors.[57] The patient-related factors (inadequate health literacy, attitudes regarding the effectiveness of the treatment, lack of knowledge about the disease being treated, psychological problems, and negative previous experience) have been recognized as the strongest reason for poor compliance.[57] Similarly, abstinence from alcohol after the first attack of alcohol-induced pancreatitis is crucial for preventing the recurrent attacks. Although many hospitalized patients with alcohol-induced pancreatitis are motivated to stop or reduce drinking, most of them continue drinking which results in development of recurrent attacks.[27]

Consistent with findings of previous studies, our results highlighted that performing cholecystectomy significantly reduced the risk of recurrent pancreatitis after first attack of gallstone

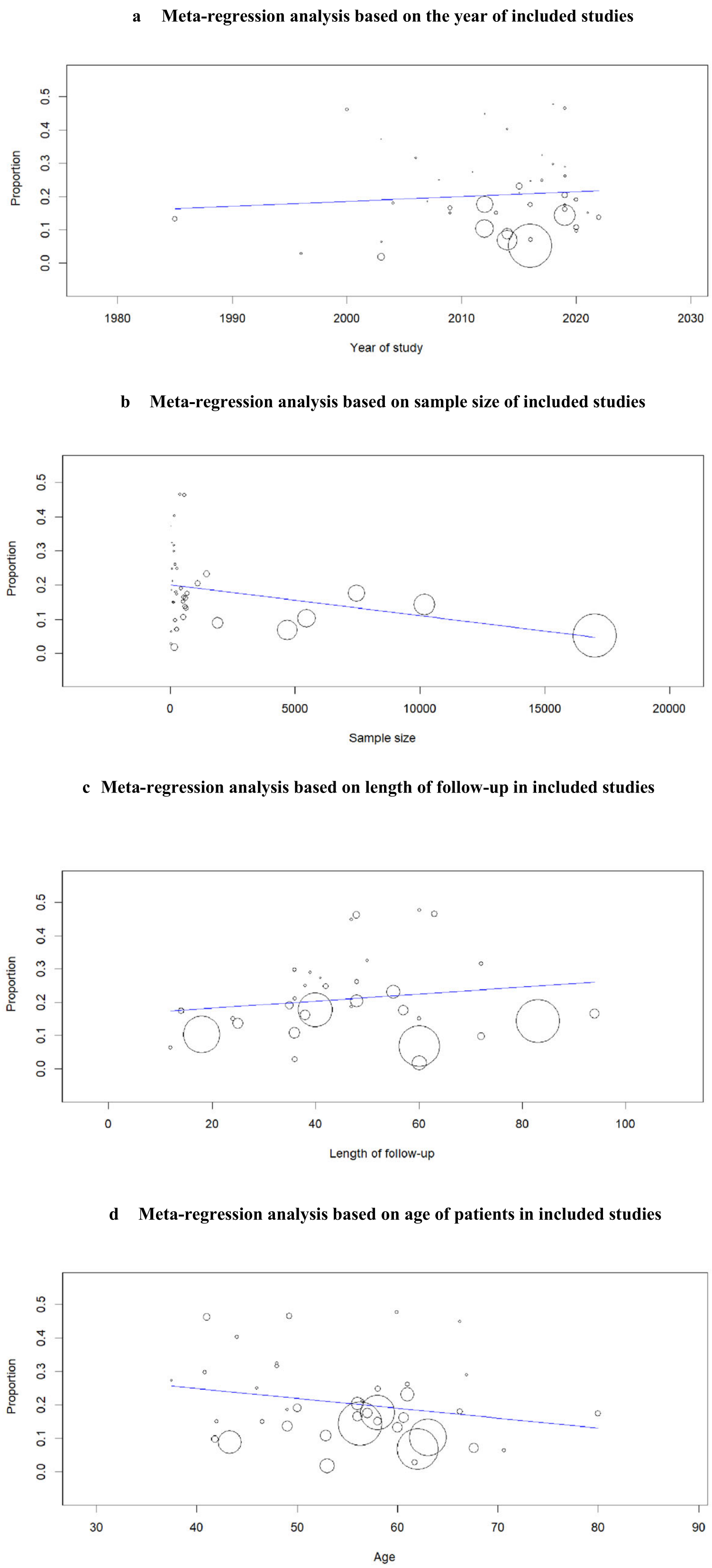


Figure 3 Results of meta-regression analyses based on (a) year of included studies; (b) sample size of the included studies; (c) length of follow-up in included studies; (d) age of patients in included studies.

pancreatitis. Prasanth *et al*.[58] conducted a meta-analysis of 11 randomized controlled trials and concluded that early cholecystectomy has definite advantages in terms of reducing recurrent pancreaticobiliary events and length of hospital stay after gallstone pancreatitis.[58] A recent meta-analysis conducted by Umans *et al*.[59] showed that cholecystectomy after idiopathic acute pancreatitis may also reduce the risk of recurrent pancreatitis and argued that current diagnostics are insufficient to exclude a biliary cause in this setting.[59] The available data from the included studies in our review were not adequate to perform subgroup analyses for patients with idiopathic acute pancreatitis who underwent cholecystectomy; hence, we cannot make any conclusions against or in favor of the findings by Umans *et al*.[59]

It was very interesting to see that the risk of recurrent pancreatitis after the first episode of pancreatitis did not significantly differ among patients with mild, moderate, and severe pancreatitis. The available data were not adequate to investigate whether this finding remains consistent among the patients with different etiology of pancreatitis. However, the above findings suggest that regardless of the severity of the first attack of acute pancreatitis, treatment of underlying cause and avoiding aggravating factors are the key steps for reducing the risk of recurrent attacks.

The results of current study should be interpreted taking into account the following strengths and limitations. The strengths of the current study include the following: (1) use of objective and systematic approach in evidence synthesis compliant with PRISMA standards; (2) large sample size in terms of the number of included studies and patients; (3) conducting subgroup analyses based on etiology and severity of acute pancreatitis; (4) low clinical between-study heterogeneity; (5) evaluation of effect of different covariates on the results using meta-regression technique; (6) use of GRADE system to evaluate certainty of available evidence. The limitations for the current study include (1) the retrospective nature of most of the included studies and inevitable risk of selection bias; (2) high statistical between-study heterogeneity; (3) inadequate data on risk of recurrence after other causes of pancreatitis (drug-induced, iatrogenic, traumatic, or infective); (4) inadequate data about baseline comorbidities of the included population in most of the included studies.

Conclusions

The risk of recurrent pancreatitis after first episode of acute pancreatitis seems to be affected by the etiology of pancreatitis but not the severity of disease. The risks seem to be higher in patients with autoimmune pancreatitis, hyperlipidemia-induced pancreatitis, and alcohol-induced pancreatitis, and lower in patients with gallstone pancreatitis and idiopathic pancreatitis.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Supporting Information.

Table S1. The outcomes of methodological quality assessment of the studies included in the proportion meta-analysis model using the Joanna Briggs Institute Critical Appraisal tool.

Table S2. Summary of findings table for the proportion meta-analysis model.