SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3438.

GAGYI ENDRE BOTOND

Transzlációs és klinikai farmakológia

című program

Programvezető: Dr. Ferdinandy Péter, egyetemi tanár

Témavezető: Dr. Erőss Bálint, egyetemi adjunktus

THE DISEASE CONTINUUM FROM ACUTE TO RECURRENT AND CHRONIC PANCREATITIS: PROGRESSION PATTERNS IN CHILDREN AND ADULTS

Ph.D. Thesis

Gagyi Endre Botond, M.D.

SEMMELWEIS UNIVERSITY

Translational Medicine Program

Pharmaceutical Sciences and Health Technologies Division

Supervisor:	Bálint Erőss, M.D., Ph.D., FRCP
Official reviewers:	Dr. Vasile Drug, M.D., Ph.D. Dr. Alexandra Mikó, M.D., Ph.D.
Head of the Complex Examination Committee:	Prof. Gábor Varga, M.D., Ph.D.
Members of the Complex Examination Committee:	Prof. Karl J. Oldhafer, M.D., Ph.D.
	Roland Molontay, Ph.D.
	Áron Vincze, M.D., Ph.D.
	Zoltán Zádori, Ph.D.

Budapest

2026

“Shoot for the moon. Even if you miss, you'll land among the stars.”

— *Norman Vincent Peale*

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

ANC	Acute necrotic collection
AP	Acute pancreatitis
APFC	Acute peripancreatic fluid collection
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CoCoPop	Condition–Context–Population
CP	Chronic pancreatitis
CRP	C-reactive protein
EMBASE	Excerpta Medica database
EPI	Exocrine pancreatic insufficiency
ICD	International Classification of Diseases
I^2	Higgins and Thompson's I-squared statistic (measure of heterogeneity)
INSPPIRE	International Study Group of Pediatric Pancreatitis: In Search for a Cure
IR	Incidence rate
JBI	Joanna Briggs Institute
MD	Mean difference
MEDLINE	Medical Literature Analysis and Retrieval System Online
OR	Odds ratio
P	P-value
PECO	Population, Exposure, Comparator, Outcome
PI	Prediction interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QUIPS	Quality In Prognostic Studies
RAP	Recurrent acute pancreatitis
SD	Standard deviation
SAPE	Sentinel acute pancreatitis event (model)
WBC	White blood cell count

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to deepen scientific understanding of pancreatitis progression and improve early identification of patients at risk for recurrent or chronic disease. My mission is to highlight the clinical importance of the transition from acute pancreatitis to RAP and CP by providing high-quality evidence that supports more accurate patient counselling and follow-up. My specific goal is to generate robust, clinically applicable data on progression rates and risk factors, enabling better recommendations and earlier recognition of evolving chronic pancreatitis.

2.2. Scientometrics

Number of all publications:	8
Cumulative IF:	31.6
Av IF/publication:	3.6
Ranking (SCImago):	D1:5, Q1:3
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7
Av IF/publication:	3.5
Ranking (Sci Mago):	D1:1, Q1:1,
Number of citations on Google Scholar:	40
Number of citations on MTMT (independent):	33
H-index:	4

The detailed bibliography of the student can be found on pages 75-78.

2.3. Future plans

Looking ahead, I intend to continue expanding the scientific work initiated during my doctoral studies. My immediate aim is to complete a third meta-analysis focusing exclusively on the risk factors that drive the progression of pancreatitis in adult populations, thereby complementing the two completed analyses on disease progression.

I am also planning to analyze data from the gastrointestinal bleeding registry, as I believe these real-world clinical datasets can provide important insights that directly benefit patient care.

Beyond research, an equally important priority for me is to finish my radiology residency training and grow into a confident and competent radiologist. I would like to carry the research-oriented mindset I developed during my PhD into my future clinical work. My long-term aim is to combine careful imaging-based assessment with evidence-based medicine, so that I can support my patients with thoughtful, data-driven decisions and contribute meaningfully to their care as a practising physician.

3. SUMMARY OF THE THESIS

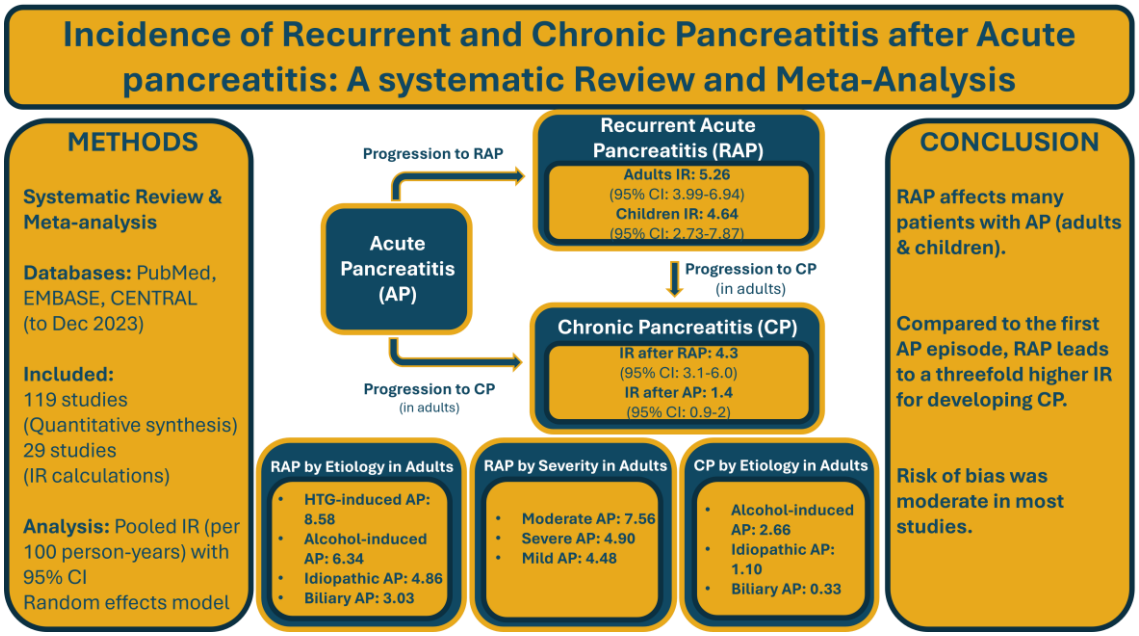
In this thesis, we conducted two complementary systematic reviews and meta-analyses to characterize progression from AP to RAP and CP across the lifespan and to identify key factors associated with this transition. In the first study, focusing on adults, we quantified the incidence rates of RAP and CP after AP, as well as CP after RAP, explicitly accounting for the time-dependent nature of disease progression. By applying person-time–based measures, we addressed variability in follow-up across studies and complemented these analyses with proportion-based syntheses. In the second study, we synthesized the pediatric literature on AP progression, evaluating both progression rates and associated risk factors, predominantly using INSPPIRE-based diagnostic frameworks.

Across both studies, recurrence after AP emerged as a frequent outcome, and progression to CP became substantially more likely once RAP developed, underscoring RAP as a pivotal stage in the disease course. Persistent metabolic or exposure-related drivers, such as hypertriglyceridemia in both age groups and alcohol-related disease in adults, were consistently associated with higher recurrence. In contrast, etiologies reflecting a single, self-limited insult, such as trauma-, drug-, and virus-induced AP in children, were associated with lower recurrence.

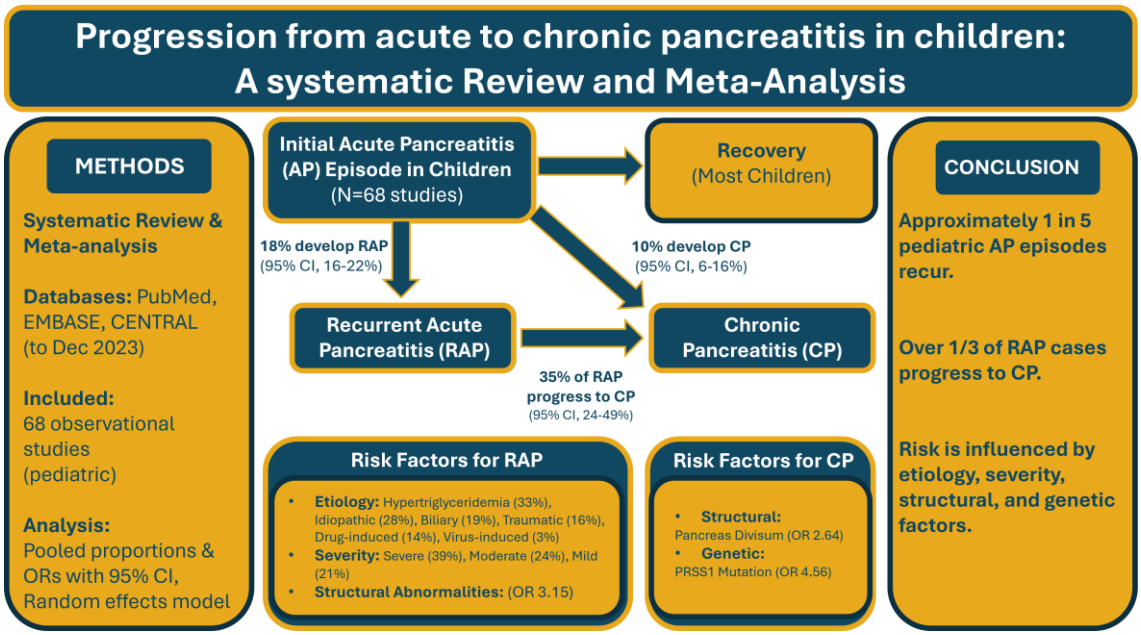
In adults, recurrence and progression were strongly influenced by modifiable exposures and care pathways, particularly alcohol consumption and smoking. In children, progression was driven mainly by predisposition, with genetic mutations, especially PRSS1 and anatomical abnormalities such as pancreas divisum, showing strong associations with RAP and CP. Follow-up duration was explicitly considered in both studies. In adults, progression was treated as a time-dependent process using person-time–based measures. In children, analyses did not identify a meaningful association between follow-up length and AP-RAP progression, consistent with early recurrence in at-risk patients. Overall, this thesis provides standardized, age- and etiology-specific evidence on progression across the pancreatitis continuum.

4. GRAPHICAL ABSTRACT

4.1. Study 1



4.2. Study 2



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases, with an incidence of 13 – 45 per 100,000 persons per year, while chronic pancreatitis (CP) occurs in 5 – 12 per 100,000 persons per year (1). AP is linked to considerable morbidity, mortality, and extended hospital stays (2), while CP represents a chronic, progressive, and irreversible disease that profoundly compromises quality of life and shortens life expectancy (3). Evidence increasingly supports that AP, RAP, and CP form a disease continuum, in which repeated inflammatory episodes may lead to irreversible structural damage and pancreatic dysfunction (4). According to the sentinel acute pancreatitis event (SAPE) model, RAP represents an intermediate stage between AP and CP (5, 6). RAP is clinically relevant both because it can only be diagnosed after multiple AP episodes and because it represents the most powerful predictor of progression to CP (6, 7). AP in children, once considered rare, now approaches adult incidence rates, affecting 3 – 13 per 100,000 persons annually, while pediatric CP develops at approximately 2 per 100,000 persons (8-10). Although many children recover fully after a single AP episode, a substantial subset progress to RAP and even CP (2). Importantly, etiology and disease mechanisms in children differ markedly from adults: whereas alcohol use and smoking are major drivers in adults, pediatric disease is more often related to genetic, structural, or metabolic factors (11-13).

5.1.2. What is the problem to solve?

Despite the recognition of an AP - RAP - CP continuum, several key gaps remain. Incidence and progression estimates vary widely due to heterogeneity in follow-up duration, study design, and diagnostic criteria. Etiology and severity specific risks are not well quantified in adults, and existing studies report inconsistent findings. In children, risk factors differ fundamentally from adults, making it inappropriate to extrapolate adult data to pediatric populations (13). There is no comprehensive synthesis integrating both adult and pediatric progression patterns using standardized methodological approaches. These gaps limit clinicians' ability to identify high-risk individuals, anticipate disease evolution, and intervene early to prevent progression.

5.1.3. What is the importance of the topic?

AP, RAP, and CP represent a major clinical and socioeconomic burden. AP requires hospitalization and causes significant morbidity and mortality (2). RAP leads to repeated admissions, increased healthcare costs, and cumulative pancreatic injury (6, 7). CP causes chronic pain, exocrine and endocrine insufficiency, significant psychological distress, and reduced life expectancy (3, 6, 14). In children, RAP and CP result in persistent abdominal pain and impaired quality of life (15, 16). Understanding who progresses, why, and how quickly is crucial because CP remains incurable, and only early identification of at-risk individuals offers the chance to prevent irreversible pancreatic damage.

5.1.4. What would be the impact of our research results?

Our findings provide standardized, etiology and age specific (adults - children) estimates of progression from AP to RAP and CP, supporting more accurate identification of high-risk patients. By clarifying key predictors in both adults and children, the results support more personalized follow-up and earlier intervention to prevent irreversible pancreatic damage. These insights may also inform future clinical guidelines and improve long-term outcomes.

6. OBJECTIVES

6.1. Study I.

In the first study, we aimed to characterize the progression of acute pancreatitis to recurrent and chronic pancreatitis by evaluating incidence rates, cumulative incidence, recurrence patterns, and progression rates, taking into account the time-dependent nature of disease evolution and stratifying our analysis by the etiology and severity of the initial episode.

6.2. Study II.

In the second study, we aimed to synthesize current evidence on how acute pancreatitis progresses to recurrent and chronic pancreatitis in children and to identify the key risk factors that contribute to this progression.

7. METHODS

7.1. Study I.

7.1.1. Methodology and protocol

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement (17). The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021283252), and all methods were implemented strictly as prespecified in the protocol.

7.1.2. Search strategy

A comprehensive systematic search was conducted in three major medical databases: MEDLINE (via PubMed), the Cochrane Library (CENTRAL), and EMBASE on December 19, 2023. Eligible studies were restricted to those published after 1992, and the search strategy applied the terms: acute AND (chronic OR recurrent) AND pancreatitis.

7.1.3. Eligibility criteria

To ensure comprehensive identification of relevant literature, study selection was guided by the condition–context–population (CoCoPop) framework (18). Eligible studies were required to meet both of the following conditions. First, they had to include patients with acute pancreatitis (AP) diagnosed according to the Atlanta Classification (19), which defines AP by at least two of three criteria: typical abdominal pain, serum amylase or lipase levels exceeding three times the upper limit of normal, or characteristic findings on imaging (19). Second, studies needed to report outcomes related to disease progression, specifically the proportion of patients developing RAP or CP after a single or repeated AP episode. The primary endpoints of the analysis were the estimated incidence rates (IRs) of RAP and CP following an initial AP episode, and the estimated IR of CP among patients with RAP. Secondary endpoints included cumulative incidence estimates, the proportions of RAP and CP after a first AP event, and the proportion of CP occurring after RAP. For analyses focusing on RAP, only studies that enrolled consecutive patients experiencing their first episode of AP were included. To calculate CP, we included two types of studies and analyzed them separately: those with

consecutive patients after a first AP episode and those involving consecutive patients with RAP. Throughout the manuscript, the term “AP” always refers to patients experiencing their first episode of acute pancreatitis. We applied no restrictions regarding minimum follow-up duration, and studies were eligible with a sample size of at least 10 participants. Conference abstracts, review articles, case reports, as well as in vitro and animal studies were excluded from the analysis.

7.1.4. Study selection and data extraction

Study selection and data extraction were conducted in accordance with the guidance of the Cochrane Handbook (20). Reference management and record screening were performed using EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). As the Atlanta Classification was first introduced in 1992 (19), the literature search was limited to studies published from January 1st, 1992 onward. Following duplicate removal, two reviewers (EBG and DP) independently screened studies in a two-step process, initially assessing titles and abstracts, followed by full-text evaluation. To assess agreement at each stage, we calculated Cohen’s Kappa coefficient (21). Any discrepancies were resolved by a third reviewer (BT). Data extraction was carried out independently by two investigators (EBG and DP) using a predefined and standardized Excel data sheet (Office 365, Microsoft, Redmond, WA, USA). Any discrepancies were resolved through discussion with a third reviewer (BT). Collected data encompassed study identifiers and characteristics, including first author, geographic region, year of publication, study period, study design, and number of centers, as well as patient-related information such as age, sex distribution, sample size, average follow-up time, and reported proportions of RAP and CP, both overall and stratified by etiology and disease severity. In cases where multiple publications originated from overlapping study populations, we included only the article with the larger sample size. When necessary, we contacted study authors to obtain missing information.

7.1.5. Risk of bias

The methodological quality of the included studies was independently assessed by two reviewers (EBG and DP) using the Joanna Briggs Institute Prevalence Critical Appraisal Tool (JBI) (22). Any disagreements were resolved in consultation with a third reviewer (BT). The appraisal consisted of nine predefined domains, each rated as “yes,” “no,”

"unclear," or "not applicable," yielding a maximum possible score of nine points. Higher scores indicated a lower risk of bias.

7.1.6. Data synthesis

All statistical analyses were conducted using R software (R Core Team 2021, version 4.1.1) (23), with analyses implemented through the meta (24) and dmetar (25) packages. Outcomes reported by at least three studies were visualized using forest plots. For the effect size, we applied the incidence rate (IR) with a 95% confidence interval (CI). Although IRs are conventionally derived from the number of new events per person-time based on individual follow-up data, such detailed information was unavailable in the included studies. Consequently, IRs were estimated using the total sample size, the number of patients experiencing the event of interest, and the reported mean follow-up duration. Because substantial heterogeneity across studies was expected, we used a random effects model for data synthesis, and we quantified heterogeneity with the Higgins and Thompson I^2 statistic (26). Publication bias was evaluated with funnel plots and Egger's tests (27) when at least ten studies were available for a given outcome. Leave-one-out analyses were conducted for outcomes with a minimum of eight studies to determine whether any single study disproportionately influenced the pooled IR or the degree of heterogeneity. Following the recommendations by Inthout et al. (28), prediction intervals were reported where applicable. To examine whether age, sex, or disease severity had a confounding effect on the pooled IR, we performed random effects meta-regression for outcomes reported by at least ten studies. To facilitate interpretation, we estimated 5-year cumulative incidences using the formula described by Rothman et al. ($CI = 1 - e^{(-IR \times T)}$, where 'e' = 2.71828; T, 5 years; IR, incidence rate; e, Euler number) (29). To further characterize disease progression from AP to RAP and CP, recurrence and progression rates were also synthesized using proportional meta-analysis. In these analyses, the effect measure was the pooled proportion with corresponding 95% confidence intervals, derived from the total number of patients and the number of individuals experiencing the event in each study.

7.2. Study II.

7.2.1. Methodology and protocol

The present systematic review and meta-analysis adhered to the standards set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (17). Prior to study initiation, the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251086520), and the review was subsequently conducted in full compliance with the predefined protocol.

7.2.2. Eligibility criteria

We selected studies according to predefined eligibility criteria structured using both the CoCoPop (Condition, Context, Population) (18) and PECO (Population, Exposure, Comparator, Outcome) (30) frameworks, enabling us to evaluate progression rates as well as associated risk factors. Eligible studies involved pediatric patients (under 18 years) diagnosed with AP, RAP, or CP. We included prospective and retrospective observational studies and case series that either reported progression rates from AP to RAP, AP to CP, or RAP to CP over time, or provided comparative data between disease groups relevant to potential risk factors such as age, sex, etiology, or disease severity. Studies were excluded if they focused exclusively on adults, lacked extractable data for the outcomes of interest, or were published as case reports, reviews, editorials, abstracts, or in vitro or animal studies. To ensure methodological consistency, we used the diagnostic definitions exactly as they were reported in the original studies. Among the 68 included studies, 76% applied the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) criteria (31), while the remaining 24% relied on alternative definitions, including institutional criteria, ICD-based codes, or combinations of multiple frameworks. Based on the INSPPIRE criteria, a diagnosis of AP requires the presence of at least two of the following three features: abdominal pain typical of AP, serum amylase and/or lipase levels elevated to at least three times the upper limit of normal, or imaging findings consistent with AP. RAP is defined as two or more clearly separated AP episodes, with complete resolution of symptoms for a minimum of one month or normalization of pancreatic enzyme levels between attacks (31). Chronic pancreatitis (CP) is diagnosed when any one of the following is present: characteristic pancreatic pain accompanied by typical imaging findings, exocrine pancreatic insufficiency with

supportive imaging, or endocrine insufficiency together with imaging evidence of CP (31). Severity of AP was classified using the 2012 Revised Atlanta Classification, whereby mild AP is characterized by the absence of organ failure and local or systemic complications, moderately severe AP includes transient organ failure lasting less than 48 hours and/or local complications, and severe AP is defined by persistent organ failure exceeding 48 hours. (32). No minimum follow-up duration was required for inclusion, allowing us to capture the full range of available evidence on disease progression in pediatric pancreatitis.

7.2.3. Information sources and search strategy

A comprehensive literature search was undertaken across major medical databases MEDLINE (via Pubmed), the Cochrane Library (CENTRAL), and EMBASE on December 21, 2024. The search included studies published from 1992 onward and used the following terms: acute AND (chronic OR recurrent) AND pancreatitis. To maintain methodological rigor, we followed the Cochrane Handbook recommendations for both study selection and data extraction (20). Although the INSPPIRE criteria (31) are now widely applied in pediatric populations, they were developed in 2012 and are diagnostically grounded in the original Atlanta Classification introduced in 1992 (19). Because the foundational diagnostic framework for AP (the 2-out-of-3 rule) was first formalized in the 1992 Atlanta criteria, we restricted our search to articles published on or after January 1, 1992 to ensure consistency in diagnostic standards across studies.

7.2.4. Study selection and data extraction

All retrieved references were imported into EndNote 21 (Clarivate Analytics, Philadelphia, PA, USA), where duplicate records were identified and eliminated before the screening process commenced. Two independent authors (EBG and ET) evaluated the studies in a two-step process, first by title and abstract and subsequently by full-text review. Any disagreements were resolved by a third author (MO). Inter-rater agreement after each screening stage was quantified using Cohen's Kappa coefficient (21). The same two authors (EBG and ET) independently extracted data, with inconsistencies again resolved by the third author (MO). Extracted variables included the first author, year of publication, sample size, study location, proportion of male participants, study period, design, number of centers, age distribution, follow-up duration, and the proportion of

patients progressing to RAP and CP, including breakdowns by etiology and severity. When available in at least three studies, we also collected group-level comparative data (for example: comorbidities, laboratory parameters, and clinical characteristics) across AP, RAP, and CP subgroups. If multiple publications reported on populations with possible overlap, only the study with the largest sample size was retained for analysis. When data were missing or unclear, we contacted the original study authors for confirmation or clarification.

7.2.5. Risk of bias

The risk of bias of the included studies was independently assessed by two reviewers (EBG and ET) using the Joanna Briggs Institute Prevalence Critical Appraisal Tool (JBI) (22) or, where appropriate, the Quality In Prognostic Studies (QUIPS) tool (33), depending on the study design. The JBI tool was applied to studies reporting disease progression outcomes, such as recurrence or progression to CP, whereas the QUIPS tool was used for studies comparing diagnostic groups (e.g., AP, RAP, and CP) across clinical, demographic, or laboratory parameters. Any disagreements between the two authors were resolved by a third author (MO).

7.2.6. Data synthesis

All statistical analyses were conducted using R software (version 4.2.1; R Foundation, Vienna, Austria) (23), employing the meta (24) and dmetar (25) packages. Given the expected variability across studies, we applied a random-effects model for all meta-analyses. Between-study heterogeneity was quantified using the I^2 statistic described by Higgins and Thompson (26), and prediction intervals (PI) were reported when applicable, in accordance with the recommendations of Inthout et al. (28). For proportion-based outcomes, we extracted the number of events and the total sample size from each study and calculated pooled proportions with 95% confidence intervals (CIs). For dichotomous comparisons, odds ratios (ORs) with 95% CIs were derived from extracted event counts and group sizes. For continuous variables, the mean difference (MD) was used as the effect size, based on reported sample sizes, means, and standard deviations (SDs). Forest plots were generated to present pooled effect estimates for outcomes reported in at least three studies. Publication bias was assessed using funnel plots and Peter's tests, restricted to outcomes informed by at least ten studies (34). Leave-one-out sensitivity analyses were

also performed to evaluate the impact of individual studies on pooled estimates and heterogeneity. A two-sided P value of <0.05 was considered statistically significant.

8. RESULTS

8.1. Study I: The incidence of recurrent and chronic pancreatitis after acute pancreatitis: a systematic review and meta-analysis

8.1.1. Study search and selection

Our search initially identified 18,483 records. After screening titles, abstracts, and full texts, 119 studies were included in both the qualitative and quantitative syntheses. All 119 contributed to the proportion analyses, while 29 studies (2, 9, 11, 35-60) reported mean follow-up durations suitable for incidence rate calculations. Among these, 24 were adult cohort studies, comprising 9 prospective and 15 retrospective designs. While most were single-center investigations, 3 were multicenter cohorts. The studies were geographically diverse, originating from Europe (11 studies), Asia (9 studies), and North America (4 studies). Follow-up durations showed considerable variation, ranging from 19 to 120 months. The selection process is detailed in Figure 1, and the study and patient baseline characteristics for the IR analyses are presented in Tables 1 and 2 (2, 9, 11, 35-60).

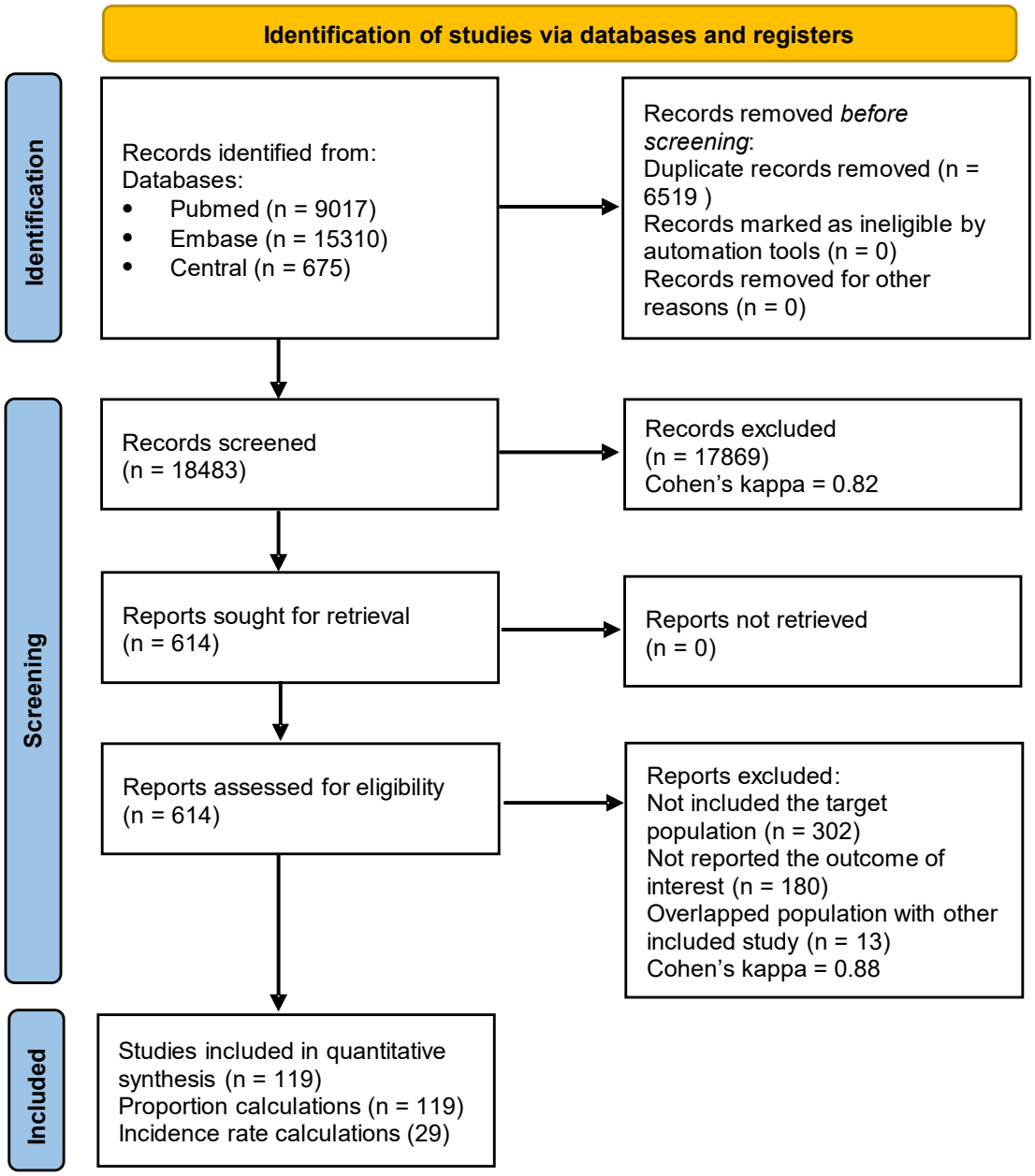


Figure 1. PRISMA flowchart of the included studies in the meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews, and Meta-Analyses.

Table 1. Characteristics of included studies

First Author	Country	Study Design	Centers (N)	Study period	Mean Follow-up Time (month)	Number of AP patients	Number of patients progressed to RAP	Number of patients progressed to CP
Adult population with acute pancreatitis								
Ahmed et al. 2016[35]	The Netherlands	prospective cohort	15	2003-2007	57.2	669	117	51
Bang et al. 2015[36]	South Korea	retrospective cohort	1	2005-2010	41.5	119	15	NR
Bertilsson et al. 2015[37]	Sweden	retrospective cohort	1	2003-2012	56.2	1457	329	79
Blanco et al. 2020[38]	Italy	prospective cohort	1	2016-2018	28	127	48	NR
Castoldi et al. 2013[39]	Italy	prospective cohort	56	NR	51.7	631	80	NR
Cavestro et al. 2014[40]	Italy	prospective cohort	1	2002-2011	52.5	196	40	13
Halonen et al. 2003[41]	Finland	retrospective cohort	1	1989-1997	66	145	39	NR
Hu et al. 2021[42]	China	retrospective cohort	1	2014-2016	40.1	923	173	NR

Hui et al. 2004[43]	Hong Kong	retrospective cohort	1	1996-2000	56.3	139	12	NR
Kaw et al. 2002[44]	USA	prospective cohort	1	1995-1999	33.5	117	3	NR
Kim, S et al. 2016[45]	South Korea	retrospective cohort	1	2004-2016	22.2	290	35	NR
Kim, Y et al. 2020[46]	South Korea	retrospective cohort	1	2010-2016	35.1	313	83	15
Lee et al. 2016[47]	South Korea	retrospective cohort	1	2003-2014	58	171	24	NR
Magnusdottir et al. 2019[2]	Iceland	retrospective cohort	2	2006-2015	52	1102	225	40
Nikkola et al. 2016[48]	Finland	prospective cohort	1	2001-2005	120	77	27	9
Ridtitid et al. 2018[60]	Thailand	retrospective cohort	1	2006-2016	45.7	130	13	NR
Ruiz et al. 2023[53]	Spain	retrospective cohort	1	2014-2020	67.63	561	106	NR
Sargen et al. 2001[49]	United Kingdom	prospective cohort	1	NR	19.4	76	7	NR
Stigliano et al. 2017[50]	Italy	prospective cohort	1	2007-2015	42.0	266	66	22
Valverde et al. 2020[51]	Spain	retrospective cohort	1	2010-2017	54.2	78	13	NR

Vipperla et al. 2016[52]	USA	retrospective cohort	1	2001-2013	50.2	76	15	NR
Wang et al. 2017[54]	USA	retrospective cohort	1	2000-2015	25.2	140	24	NR
Yoon et al. 2015[55]	South Korea	prospective cohort	1	2005-2012	24.2	92	2	NR
Yu et al. 2020[56]	China	retrospective cohort	1	2016-2016	36	522	56	NR
Pediatric population with acute pancreatitis								
Al Hindi et al. 2021[57]	Bahrein	retrospective cohort	1	2006-2017	39.4	56	6	NR
Poddar et al. 2016[58]	India	retrospective cohort	1	2003-2014	21.1	160	8	24
Sag et al. 2017[11]	Turkey	retrospective cohort	1	2005-2016	68.1	63	10	1
Zhong et al. 2021[59]	China	retrospective cohort	1	2013-2019	34.2	130	19	NR
Volkan et al. 2023[9]	Turkey	retrospective cohort	4	2010-2017	31.2	165	51	21

AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; NR, not reported; USA, United States of America; N, number

Table 2. Baseline characteristics of included patients

First Author	Total sample size (N)	Sex (male% of total)	Mean age (years)	Severe first AP episode (%)	Cause of acute pancreatitis (N and (%))					
					Alcohol	Biliary	Idiopathic	HTG	Viral infection	Trauma
Adult population with acute pancreatitis										
Ahmed et al. 2016[35]	669	55	57m (42-70)i	22	153 (23%)	384 (58%)	108 (15%)	NR	NR	NR
Bang et al. 2015[36]	119	53.8	62±16.5	NR	0	119 (100%)	0	0	0	0
Bertilsson et al. 2015[37]	1457	53	61±19	9.9	249 (17%)	705 (48%)	431 (29.6%)	NR	NR	NR
Blanco et al. 2020[38]	127	62.9	57 (18-89)r	NR	23 (18%)	60 (47.2%)	35 (28%)	NR	NR	NR
Castoldi et al. 2013[39]	631	49.6	60.6±18.5	11.6	36 (5.7%)	439 (69.6%)	107 (17%)	NR	NR	NR
Cavestro et al. 2014[40]	196	25.5	58.8±16.9	25.5	16 (8.2%)	122 (62.6%)	49 (25.5%)	NR	NR	NR
Halonen et al. 2003[41]	145	82.8	44 (20–78)r	100	113 (77.9%)	NR	NR	NR	NR	NR
Hu et al. 2021[42]	923	49.6	52.6	NR	159 (17.2%)	215 (23.2%)	NR	48 (5.2%)	NR	NR

Hui et al. 2004[43]	139	46	62.6	17.2	0	139 (100%)	0	0	0	0
Kaw et al. 2002[44]	117	31.6	53	NR	0	117 (100%)	0	0	0	0
Kim, S et al. 2016[45]	290	47.9	66.8±16	NR	0	290 (100%)	0	0	0	0
Kim, Y et al. 2020[46]	313	66.7	NR	0.6	166 (53%)	71 (22.6%)	67 (21.4%)	8 (2.6%)	NR	NR
Lee et al. 2016[47]	171	58.4	59.3±14.7	9.4	0	171 (100%)	0	0	0	0
Magnusdottir et al. 2019[2]	1102	53.8	56±19	6	227 (20.6%)	451 (40.8%)	283 (25.7%)	NR	NR	NR
Nikkola et al. 2016[48]	77	90.0	48m (25-71)r	5	77 (100%)	0	0	0	0	0
Ridtitid et al. 2018[60]	130	40.0	NR	0	0	130 (100%)	0	0	0	0
Ruiz et al. 2023[53]	561	44.2	NR	NR	38 (6.8%)	367 (65.4%)	113 (20.1%)	NR	NR	NR
Sargen et al. 2001[49]	76	NR	59.6 (18-93)r	19.7	0	76 (100%)	0	0	0	0
Stigliano et al. 2017[50]	266	59.0	58.6±17	20	41 (15.4%)	125 (47%)	38 (14.3%)	8 (3%)	NR	NR
Valverde et al. 2020[51]	78	51.3	57±17.2	NR	0	0	78 (100%)	0	0	0
Vipperla et al. 2016[52]	76	67.0	45.9±13.5	33	0	0	0	76 (100%)	0	0
Wang et al. 2017[54]	140	76.4	39.6 (20-63)r	NR	0	0	0	140 (100%)	0	0

Yoon et al. 2015[55]	92	61.3	54.5±14.7	31.5	0	92 (100%)	NR	0	0	0
Yu et al. 2020[56]	522	58.4	52.9±16.2	13.6	34 (6.5%)	326 (62.5%)	NR	116 (22.2%)	NR	NR
Pediatric population with acute pancreatitis										
Al Hindi et al. 2021[57]	56	58.9	8 (5-11)i	NR	NR	23 (41.1%)	13 (23.2%)	NR	20 (35.1%)	NR
Poddar et al. 2016[58]	160	70.6	11.3±3.9	69	NR	16 (10%)	84 (52.5%)	NR	11 (7%)	34 (21%)
Sag et al. 2017[11]	63	49.2	9.6±4.8	17.4	NR	6 (9.6%)	16 (25.4%)	NR	2 (3.2%)	7 (11.1%)
Zhong et al. 2021[59]	130	55.3	NR	3	NR	41 (31.5%)	37 (28.5%)	12 (9.3%)	13 (10%)	21 (16.1%)
Volkan et al. 2023[9]	165	44.8	9.6±4.5	NR	NR	33 (20%)	65 (39.4%)	NR	NR	NR

AP, acute pancreatitis; HTG, hypertriglyceridemia; NR, not reported; ±SD, standard deviation; m, median; i, interquartile range; r, range; N, number

8.1.2. Overall incidence rates of RAP and CP

We first examined the overall incidence rates (IRs) of RAP and CP following an initial episode of AP. After a first AP episode, the IR of RAP was 5.26 per 100 person-years (95% CI 3.99–6.94; I^2 = 93%) in adults and 4.64 per 100 person-years (95% CI 2.73–7.87; I^2 = 88%) in children, with no significant difference between groups (p = 0.671) (Figure 2.1). As expected, adults had a substantially higher IR of CP after RAP (4.31 per 100 person-years; 95% CI 3.10–5.99; I^2 = 76%) compared with the IR of CP after a first AP episode (1.38 per 100 person-years; 95% CI 0.97–1.96; I^2 = 75%) (Figure 2.2).

8.1.3. Incidence rates of RAP and CP by etiology and severity in adults

To better delineate patterns of disease progression, we analyzed the IRs of RAP and CP stratified by etiology and severity of the initial AP episode. With respect to RAP, etiology-specific IRs after the first AP event (Figure 2.3) were highest in hypertriglyceridemia-related AP (8.58 per 100 person-years; 95% CI 6.86–10.72; I^2 = 16%), followed by alcohol-related AP (6.34 per 100 person-years; 95% CI 4.80–8.37; I^2 = 79%). Lower IRs were observed in idiopathic AP (4.86 per 100 person-years; 95% CI 4.19–5.64; I^2 = 33%), while biliary AP was associated with the lowest recurrence rate (3.03 per 100 person-years; 95% CI 2.40–3.81; I^2 = 77%). A comparable etiology-dependent trend was noted for CP development (Figure 2.4). The highest IR of CP was seen following alcohol-induced AP (2.66 per 100 person-years; 95% CI 1.58–4.48; I^2 = 66%), followed by idiopathic AP (1.10 per 100 person-years; 95% CI 0.80–1.51; I^2 = 0%), whereas biliary AP showed the lowest rate of progression to CP (0.33 per 100 person-years; 95% CI 0.13–0.80; I^2 = 81%). When stratified by severity of the index AP episode (Figure 2.5), RAP incidence was highest in moderately severe AP (7.56 per 100 person-years; 95% CI 4.63–12.34; I^2 = 88%), compared with mild AP (4.48 per 100 person-years; 95% CI 3.13–6.43; I^2 = 90%) and severe AP (4.90 per 100 person-years; 95% CI 3.66–6.55; I^2 = 0%). Due to limited available data, CP incidence could not be evaluated according to disease severity.

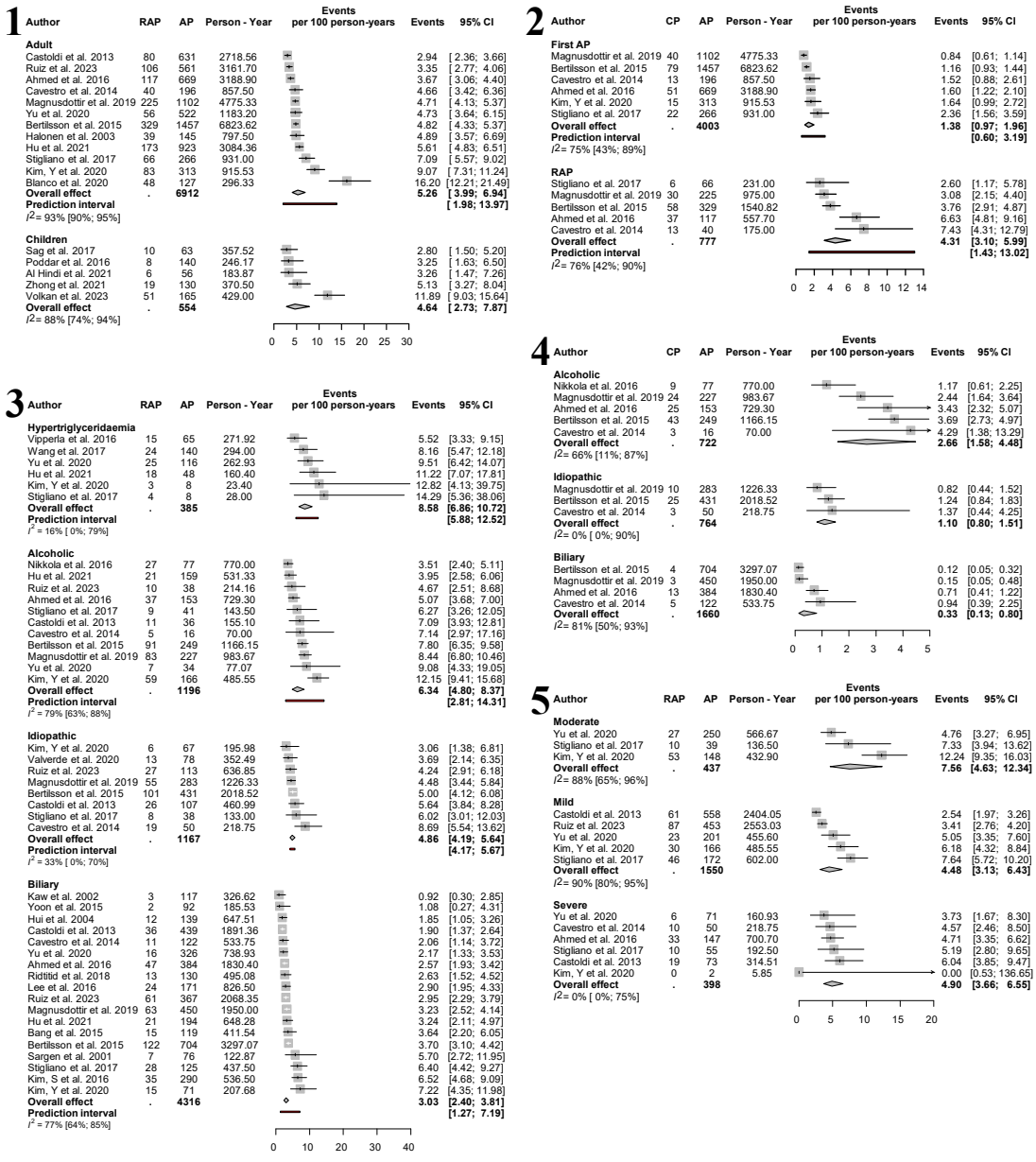


Figure 2. Forest plots showing: 1) the IRs of recurrent acute pancreatitis in adults and children after an episode of acute pancreatitis; 2) the IRs of chronic pancreatitis after acute pancreatitis and recurrent acute pancreatitis in adults; 3) the IRs of recurrent acute pancreatitis in adults by etiology after an episode of acute pancreaittis; 4) the IRs of chronic pancreatitis in adults by etiology; 5) the IRs of recurrent acute pancreatitis in adults by severity; RAP, recurrent acute pancreatitis; AP, acute pancreatitis; CP, chronic pancreatitis; CI, confidence interval; I2, Higgins, and Thompson I2 statistics;

8.1.4. Proportions calculations

Proportional meta-analyses were conducted using data from 119 studies, with the main findings presented in Figure 4. Overall, AP recurred in 20% of adult patients and 23% of pediatric patients, with no significant difference between age groups ($p = 0.227$). When stratified by etiology, recurrence rates in adults versus children were 21% and 28% for idiopathic AP ($p = 0.125$), and 8% and 15% for biliary AP ($p = 0.055$), respectively. Across all populations, progression to CP occurred in 8% of patients following an initial AP episode and increased to 24% after RAP. In adults, etiology-specific recurrence rates were highest in hypertriglyceridemia-associated AP (28%), followed by alcohol-related AP (24%), idiopathic AP (21%), and biliary AP (8%). A similar distribution was observed for progression to CP in adults, with the highest rates seen after alcohol-induced AP (18%), followed by idiopathic AP (7%) and biliary AP (2%). When recurrence was analyzed according to the severity of the index AP episode, rates were comparable between moderate (21%) and mild AP (20%), while a lower recurrence rate was observed after severe AP (13%).

Condition	Groups	Outcome	Population	Geographic area	Studies	Total Sample Size (n)	Effect size measure	Events per 100 person-years	95% CI	I^2	5 year Cumulative indicence
AP	All etiologies	RAP	Adult	Worldwide	12	6912	IR	5.26	[3.99; 6.94]	0.93	23.1%
AP	All etiologies	RAP	Children	Worldwide	5	554	IR	4.64	[2.73; 7.87]	0.88	20.7%
AP	All etiologies	CP	Adult	Worldwide	6	4003	IR	1.38	[0.97; 1.96]	0.75	6.7%
RAP	All etiologies	CP	Adult	Worldwide	5	777	IR	4.31	[3.10; 5.99]	0.76	19.4%
AP	Alcoholic	RAP	Adult	Worldwide	11	1196	IR	6.34	[4.80; 8.37]	0.79	27.2%
AP	Idiopathic	RAP	Adult	Worldwide	8	1167	IR	4.86	[4.19; 5.64]	0.33	21.6%
AP	HTG	RAP	Adult	Worldwide	6	385	IR	8.58	[6.86; 10.72]	0.16	34.9%
AP	Biliary	RAP	Adult	Worldwide	18	4316	IR	3.03	[2.40; 3.81]	0.77	14.0%
AP	Severe	RAP	Adult	Worldwide	6	398	IR	4.90	[3.66; 6.55]	0.00	21.7%
AP	Moderate	RAP	Adult	Worldwide	3	437	IR	7.56	[4.63; 12.34]	0.88	31.5%
AP	Mild	RAP	Adult	Worldwide	5	1550	IR	4.48	[3.13; 6.43]	0.90	20.1%
AP	Alcoholic	CP	Adult	Worldwide	5	722	IR	2.66	[1.58; 4.48]	0.66	12.4%
AP	Biliary	CP	Adult	Worldwide	4	1660	IR	0.33	[0.13; 0.80]	0.81	1.6%
AP	Idiopathic	CP	Adult	Worldwide	3	764	IR	1.10	[0.80; 1.51]	0.00	5.3%
Condition	**Groups**	**Outcome**	**Population**	**Geographic area**	**Studies**	**Total Sample Size (n)**	**Effect size measure**	**Proportion**	**95% CI**	**I^2**	**Proportion in percentage**
AP	All etiologies	RAP	Adult	Worldwide	40	29955	Proportion	0.20	[0.18; 0.22]	0.95	20%
AP	All etiologies	RAP	Children	Worldwide	17	1602	Proportion	0.23	[0.18; 0.28]	0.76	23%
AP	All etiologies	RAP	Adult	Asia	21	17693	Proportion	0.18	[0.16; 0.21]	0.95	18%
AP	All etiologies	RAP	Adult	Europe	16	11592	Proportion	0.23	[0.19; 0.26]	0.94	23%
AP	Alcoholic	RAP	Adult	Worldwide	25	3366	Proportion	0.24	[0.20; 0.29]	0.85	24%
AP	Alcoholic	RAP	Adult	Asia	14	2247	Proportion	0.21	[0.16; 0.27]	0.85	21%
AP	Alcoholic	RAP	Adult	Europe	11	1119	Proportion	0.29	[0.23; 0.36]	0.74	29%
AP	Idiopathic	RAP	Adult	Worldwide	23	2899	Proportion	0.21	[0.17; 0.24]	0.69	21%
AP	Idiopathic	RAP	Children	Worldwide	7	286	Proportion	0.28	[0.17; 0.43]	0.70	28%
AP	Idiopathic	RAP	Adult	Asia	10	1219	Proportion	0.18	[0.13; 0.24]	0.72	18%
AP	Idiopathic	RAP	Adult	Europe	12	1600	Proportion	0.23	[0.20; 0.27]	0.53	23%
AP	HTG	RAP	Adult	Worldwide	21	2767	Proportion	0.28	[0.23; 0.35]	0.86	28%
AP	Biliary	RAP	Adult	Worldwide	57	12743	Proportion	0.08	[0.07; 0.10]	0.82	8%
AP	Biliary	RAP	Children	Worldwide	7	427	Proportion	0.15	[0.07; 0.28]	0.81	15%
AP	Biliary	RAP	Adult	Asia	31	7016	Proportion	0.09	[0.07; 0.11]	0.83	9%
AP	Biliary	RAP	Adult	Europe	22	5391	Proportion	0.08	[0.05; 0.11]	0.82	8%
AP	Drug induced	RAP	Adult	Worldwide	6	112	Proportion	0.07	[0.03; 0.16]	0.00	7%
AP	Mild	RAP	Adult	Worldwide	10	2993	Proportion	0.20	[0.14; 0.27]	0.90	20%
AP	Mild	RAP	Children	Worldwide	5	327	Proportion	0.20	[0.11; 0.34]	0.73	20%
AP	Moderate	RAP	Adult	Worldwide	7	1386	Proportion	0.21	[0.14; 0.30]	0.90	21%
AP	Moderate	RAP	Children	Worldwide	4	148	Proportion	0.22	[0.13; 0.34]	0.00	22%
AP	Severe	RAP	Adult	Worldwide	11	1131	Proportion	0.13	[0.08; 0.22]	0.82	13%
AP	Severe	RAP	Children	Worldwide	4	39	Proportion	0.61	[0.15; 0.93]	0.63	61%
AP	All etiologies	CP	Adult	Worldwide	7	3822	Proportion	0.08	[0.05; 0.12]	0.87	8%
AP	All etiologies	CP	Children	Worldwide	4	527	Proportion	0.08	[0.02; 0.25]	0.78	8%
AP	Alcoholic	CP	Adult	Worldwide	7	760	Proportion	0.18	[0.11; 0.29]	0.72	18%
AP	Biliary	CP	Adult	Worldwide	5	1685	Proportion	0.02	[0.01; 0.07]	0.82	2%
AP	Idiopathic	CP	Adult	Worldwide	6	918	Proportion	0.07	[0.03; 0.16]	0.81	7%
RAP	All etiologies	CP	Adult	Worldwide	8	779	Proportion	0.24	[0.11; 0.45]	0.93	24%
RAP	Idiopathic	CP	Adult	Worldwide	6	387	Proportion	0.30	[0.12; 0.57]	0.91	30%
RAP	Alcoholic	CP	Adult	Worldwide	3	58	Proportion	0.22	[0.02; 0.84]	0.73	22%

Figure 3. Summary forest plot presenting all incidence rate (IR) and proportion estimates related to the recurrence of acute pancreatitis and its progression to chronic pancreatitis. Abbreviations: AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; HTG, hypertriglyceridemia; CI, confidence interval; I^2, Higgins and Thompson heterogeneity statistic. Each row corresponds to an individual forest plot. Values shown in the cumulative incidence column were derived from the incidence rate calculations (see Methods).

8.1.5. Factors associated with the incidence rates of RAP and CP in adults

We also evaluated several potential risk factors that could contribute to higher RAP incidence rates (Figure 4). Alcohol consumption was associated with a significantly elevated IR of RAP (6.87 per 100 person-years in the “yes” group vs. 4.22 in the “no” group, $p < 0.01$), as was smoking (6.76 vs. 4.23, $p = 0.02$). In biliary AP, the absence of cholecystectomy markedly increased recurrence risk (3.92 vs. 1.67, $p = 0.038$). Smaller study populations were also linked to higher RAP incidence rates, with an IR of 7.48 in studies enrolling fewer than 500 patients compared with 4.17 in larger cohorts ($p = 0.01$). In contrast, several factors did not show a significant association with RAP incidence. These included study design (retrospective vs. prospective: 5.07 vs. 5.55, $p = 0.73$), geographical region (Europe vs. Asia: 4.98 vs. 6.20, $p = 0.46$), and the number of centers involved (unicentric vs. multicentric: 5.93 vs. 3.71, $p = 0.09$). Differences in CP diagnostic criteria, however, were associated with variability in CP incidence after AP, with higher rates observed in studies applying the M-ANNHEIM classification (1.75 vs. 1.06 per 100 person-years, $p = 0.03$). These analyses were conducted in adult cohorts including all etiologies of AP, except for the cholecystectomy comparison, which was restricted to biliary AP. All results are expressed as events per 100 person-years.

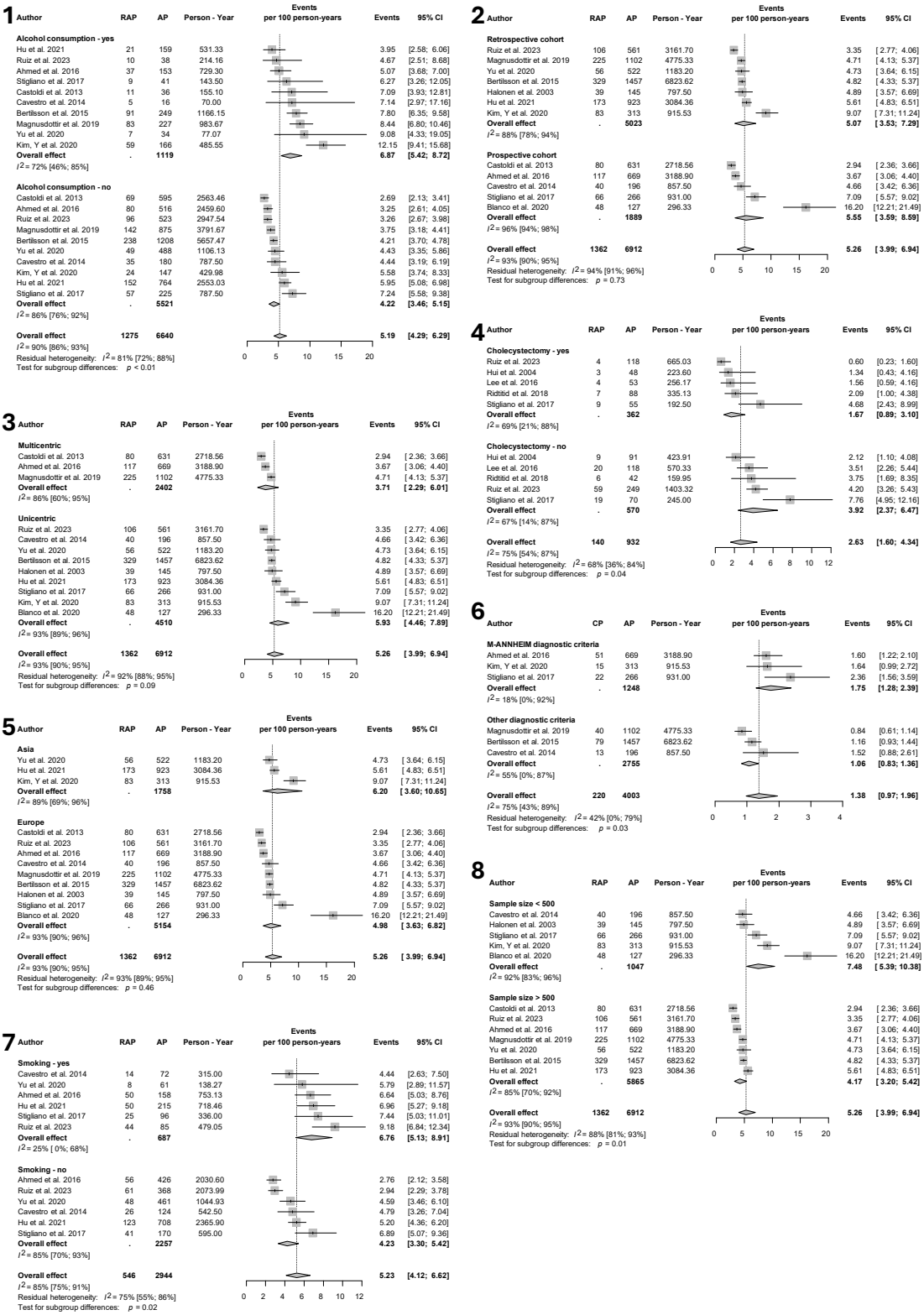


Figure 4. Forest plots illustrating the associations between various factors and the incidence rates (IRs) of RAP or CP following an episode of acute pancreatitis (AP). The investigated factors include: (1) alcohol consumption; (2) study design; (3) number of

centers; (4) cholecystectomy; (5) geographical region; (6) CP diagnostic criteria; (7) smoking; and (8) sample size. Abbreviations: AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; IR, incidence rate; CI, confidence interval; I^2, Higgins and Thompson heterogeneity statistic.

8.1.6. Risk of bias assessment and publication bias

The overall risk of bias across outcomes was moderate. Most studies were downgraded due to incomplete follow-up of all participants and limitations in sample size. Publication bias could be assessed for three outcomes, and in all cases the Egger's test yielded p-values greater than 0.01, indicating no statistically significant evidence of publication bias.

8.2. Study II: Progression from acute to chronic pancreatitis in children: a systematic review and meta-analysis

8.2.1. Search and selection

Our systematic search yielded 19,125 records. Following title, abstract, and full-text screening, 68 studies were included in both the qualitative and quantitative syntheses. The study selection process is illustrated in Figure 5.

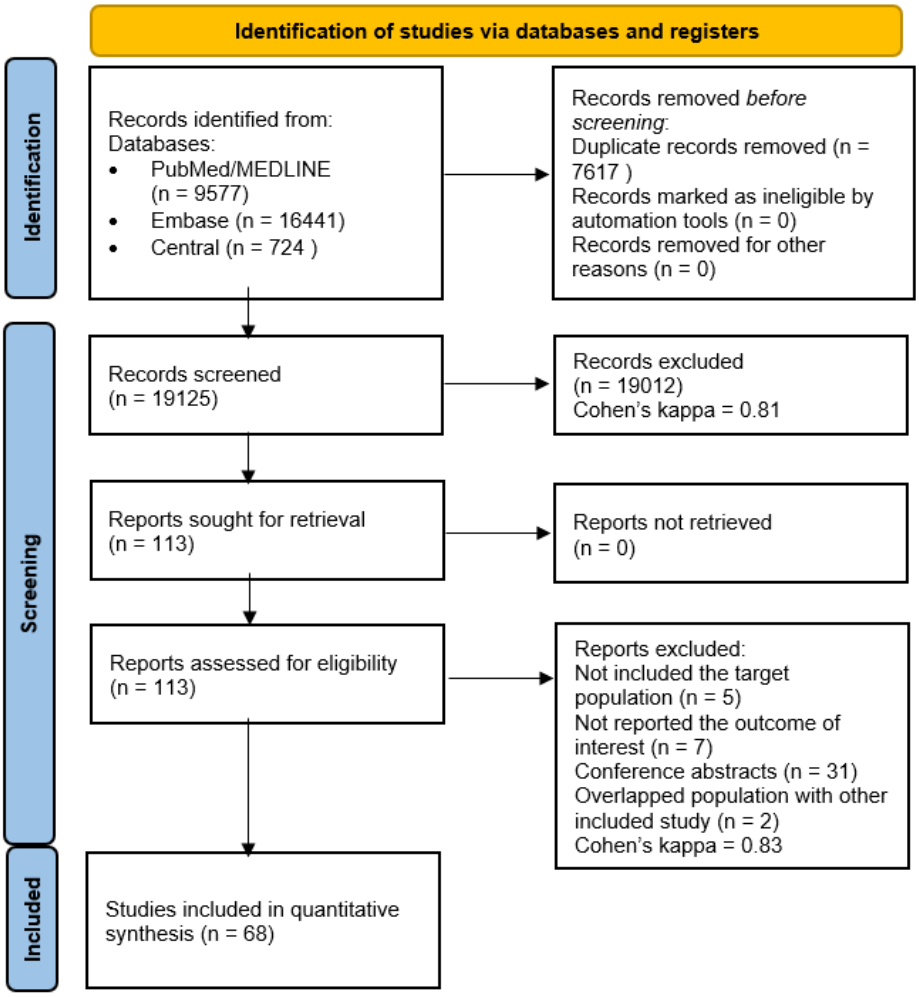


Figure 5. PRISMA flowchart of the article selection process. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

8.2.2. Basic characteristics of included studies

The full review identified 68 studies, of which 44 (9, 12, 57-59, 61-98) (Table 3) examined the progression of acute pancreatitis (AP) to recurrent acute pancreatitis (RAP) or chronic pancreatitis (CP), and 24 compared patient groups with AP, RAP, and CP. Among the 44 studies focusing on the progression of AP, 38 employed a retrospective design and 6 were prospective; 40 were single-center investigations, while four were multicenter. These studies enrolled patients between 1979 and 2022, were published between 1996 and 2024, and together contributed 4,104 pediatric cases to the quantitative synthesis. Geographically, 24 studies (55%) were conducted in Asia, 10 (23%) originated from Europe, 6 (14%) from North America, and 4 (9%) from the Middle East. Sample sizes ranged from 11 to 371 participants: 29 cohorts enrolled fewer than 100 children,

whereas 15 cohorts included 100 or more. Sex distribution was reported in 41 cohorts, with boys representing the majority in 30 of them. Disease severity was documented in 12 cohorts, in which severe AP accounted for approximately 11% of index episodes

Table 3. Characteristics of included studies focusing on the progression of acute pancreatitis

Author	Country	Study design	Centers	Study period	Follow-up time in months (mean or median)	Total cases (followed-up)	AP	RAP	AP to CP	Males	Age	Severe patients
Alabdulkareem et al. 2018[62]	Saudi Arabia	Retrospective	Multicentric	1994 – 2015	NR	50	41	9	NR	26 (52%)	11.6	NR
Anafy et al. 2024[63]	Israel	Retrospective	Unicentric	2005 – 2019	NR	68	44	24	NR	37 (54%)	m15.3 i(12 - 16.8)	NR
Anushree et al. 2022[64]	India	Prospective	Unicentric	2019 – 2021	NR	73	52	21	NR	43 (59%)	8.4±3.2	4 (5.5%)
Appak et al. 2018[65]	Turkey	Retrospective	Unicentric	2014 – 2016	NR	41	32	9	NR	15 (36.6%)	9.3±5.3	NR
Badru et al. 2017[66]	USA	Retrospective	Unicentric	2007 – 2015	NR	48	39	9	NR	11 (22.9%)	m14.4 r(1.7 - 17.8)	NR

Berney et al. 1996[67]	Switzerland	Retrospective	Unicentric	1979 – 1993	NR	21	18	3	NR	9 (42.9%)	10.8±3.5	5 (24%)
Bhanot et al. 2022[68]	UK	Retrospective	Multicentric	2013 – 2014	12	94	60	30	NR	48 (51%)	m11.2 i(7.1 - 14.4)	NR
Bolia et al. 2015[69]	India	Retrospective	Unicentric	2001 – 2011	NR	87	68	19	NR	61 (70.11%)	m12 r(1-18)	NR
Calatayud et al. 2003[70]	Spain	Retrospective	Unicentric	NR	NR	31	25	6	NR	17 (55%)	7.9 r(2-15)	NR
Chlebowczyk et al. 2018[71]	Poland	Retrospective	Unicentric	2004 – 2013	NR	51	39	12	NR	24 (47%)	12.1 r(1.7-18)	NR
Deveci et al. 2023[72]	Turkey	Retrospective	Unicentric	2010 – 2021	NR	108	85	23	8	54 (50%)	10±4.8	NR
Galai et al. 2019[73]	Israel	Retrospective	Unicentric	1995 – 2016	6	59	55	14	NR	34 (57.6%)	m11.3 i(5.9-15.4)	NR
Geetha et al. 2012[74]	India	Prospective	Unicentric	2003 – 2010	NR	73	8	28	37	NR	NR	NR
Getsuwan et al. 2022[75]	Thailand	Retrospective	Unicentric	2000 – 2021	NR	155	134	18	14	NR	NR	NR

Guo et al. 2014[76]	China	Retrospective	Unicentric	2002 – 2012	NR	371	344	27	NR	178 (48%)	NR	NR
Hao et al. 2016[77]	China	Retrospective	Unicentric	2003 – 2015	m55 r(3 - 132)	159	114	45	9	NR	NR	NR
Hindi et al. 2021[57]	Bahrein	Retrospective	Unicentric	2006 – 2017	39 r(4 - 59)	56	50	6	NR	33 (58.9%)	m8	NR
Kandula et al. 2008[78]	United States	Retrospective	Unicentric	1995 – 2004	NR	87	85	2	NR	45 (51.7%)	1.7±0.7	3 (3.4%)
Kim et al. 2023[79]	Korea	Retrospective	Unicentric	2017 – 2022	NR	64	50	14	NR	38 (59.4)	11.9±4.8	NR
Laugel et al. 2005[80]	France	Retrospective	Unicentric	1996 – NR	NR	11	9	2	NR	7 (63.6%)	10.1±3.6	NR
Lopez et al. 2013[81]	Spain	Retrospective	Unicentric	1988 – 2008	NR	27	24	3	NR	18 (66%)	7.2 r(6m-16y)	NR
Majbar et al. 2016[82]	United Kingdom	Prospective	Multicentric	2013 – 2014	NR	94	76	18	NR	48 (51.1%)	11.2±3.4	NR
Mengdi et al. 2022[83]	China	Retrospective	Unicentric	2017 – 2021	33 r(5 - 55)	106	79	27	NR	57 (53.8%)	m7y	NR
Minen et al. 2012[84]	Italy	Retrospective	Unicentric	2007 – 2012	NR	45	34	11	NR	NR	NR	NR

Mirza et al. 2022[85]	India	Retrospective	Unicentric	2017 – 2019	NR	40	27	13	NR	25(62.5%)	9.3r(1-17)	3 (7.5%)
Nasr et al. 2023[86]	USA	Prospective	Unicentric	2013 – 2019	12	74	60	14	NR	40(54%)	NR	6 (8.1%)
Nauka et al. 2018[87]	USA	Retrospective	Unicentric	2011 – 2016	NR	79	63	16	NR	46 (58.2%)	14 (9.5–16)	17 (21.5%)
Ohta et al. 2023[88]	Japan	Retrospective	Unicentric	2005 – 2022	46.5	29	19	10	NR	14(48.3%)	NR	9(31%)
Park et al. 2009[89]	USA	Retrospective	Unicentric	1994 – 2007	NR	215	182	33	NR	86 (40%)	13.1 ±5.6	NR
Pezzilli et al. 2002[90]	Italy	Retrospective	Unicentric	1998 – 1999	NR	50	36	14	NR	25 (50%)	10.5±3.8	NR
Poddar et al. 2016[58]	India	Retrospective	Unicentric	2003 – 2014	21.1 ± 20.9	140	132	8	24	98 (70%)	NR	NR
Poddar et al. 2017[91]	India	Retrospective	Unicentric	2003 – 2015	m25.5 r(8.3–48)	88	NR	51	37	51 (54.8%)	m13 i(10 - 14.5)	NR
Sag et al. 2018[11]	Turkey	Retrospective	Unicentric	2005 – 2016	68.1±24.3	63	53	10	1	31(49%)	9.6±4.8	11(17.4%)
Singh et al. 2017[92]	India	Prospective	Unicentric	2015 – 2016	NR	32	NR	22	10	22 (68.8%)	m14 r(8-18)	2 (6%)

Stringer et al. 2005[93]	United Kingdom	Retrospective	Unicentric	1994 – 2004	NR	33	25	8	NR	19 (57.6%)	12.8±3	NR
Sweeny et al. 2018[12]	Usa	Prospective	Unicentric	2013 – 2016	m21 i(10.2 - 32.7)	115	95	20	NR	60 (52%)	m13.5 i (9.3– 15.9)	14(12.3%)
Tiao et al. 2002[94]	China	Retrospective	Unicentric	1986 – 2000	NR	61	52	9	NR	39 (63.9%)	8.8±4.8	NR
Volkan et al. 2023[9]	Turkey	Retrospective	Multicentric	2010 – 2017	31.2±21.6	165	107	51	21	74 (44.9%)	9.6±4.5	NR
Wang et al. 2022[95]	China	Retrospective	Unicentric	2011 – 2020	NR	275	220	55	NR	140 (50.9%)	m12 i(8 - 16)	28 (10.2%)
Yeung et al. 1996[96]	China	Retrospective	Unicentric	1983 – 1992	NR	43	39	4	NR	23 (53.5%)	m9 r(2-18)	NR
Zeng et al. 2022[61]	China	Retrospective	Unicentric	2014 – 2021	NR	276	NR	140	136	129 (46.7%)	NR	NR
Zheng et al. 2021[97]	China	Retrospective	Unicentric	2017 – 2020	m17.9 i(9.3-25.3)	96	66	30	NR	44 (45.8%)	NR	NR
Zhong et al. 2021[59]	China	Retrospective	Unicentric	2013 – 2019	34.2±20.8	130	111	19	NR	72 (55.4%)	NR	4 (3.1%)

Zhu et al. 2011[98]	China	Retrospective	Unicentric	2003 – 2009	NR	121	116	5	NR	67 (55.4%)	6.8±3.4	NR

AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; NR, not reported; USA, United States of America; N, number; ±SD, standard deviation; m, median; i, interquartile range; r, rang

8.2.3. Acute pancreatitis progression rates based on etiology and severity in children

Using only studies applying the INSPPIRE diagnostic criteria, RAP developed in 21% of children after initial AP (95% CI: 17–24%). When all studies were included, the estimated rate was 18% (95% CI: 16–22%). Direct progression from AP to CP occurred in 10% of children (95% CI: 6–16%). Among those with RAP, 35% progressed to CP (95% CI: 24–49%). Etiology specific differences in RAP progression were statistically significant ($p < 0.001$). Hypertriglyceridemia associated AP showed the highest recurrence rate at 33% (95% CI: 6–79%), followed by idiopathic AP (28%, 95% CI: 18–39%) and biliary AP (19%, 95% CI: 11–32%). Trauma-induced AP had a recurrence rate of 16% (95% CI: 6–36%), drug-induced AP 14% (95% CI: 5–34%), and virus-induced AP 3% (95% CI: 1–12%). Severity related subgroup differences were not statistically significant ($p = 0.272$), although a numerical trend was present. Severe AP progressed to RAP in 39% of children (95% CI: 15–71%), compared with 24% after moderate AP (95% CI: 17–32%) and 21% after mild AP (95% CI: 13–31%). (All details can be seen in Figures 6,7)

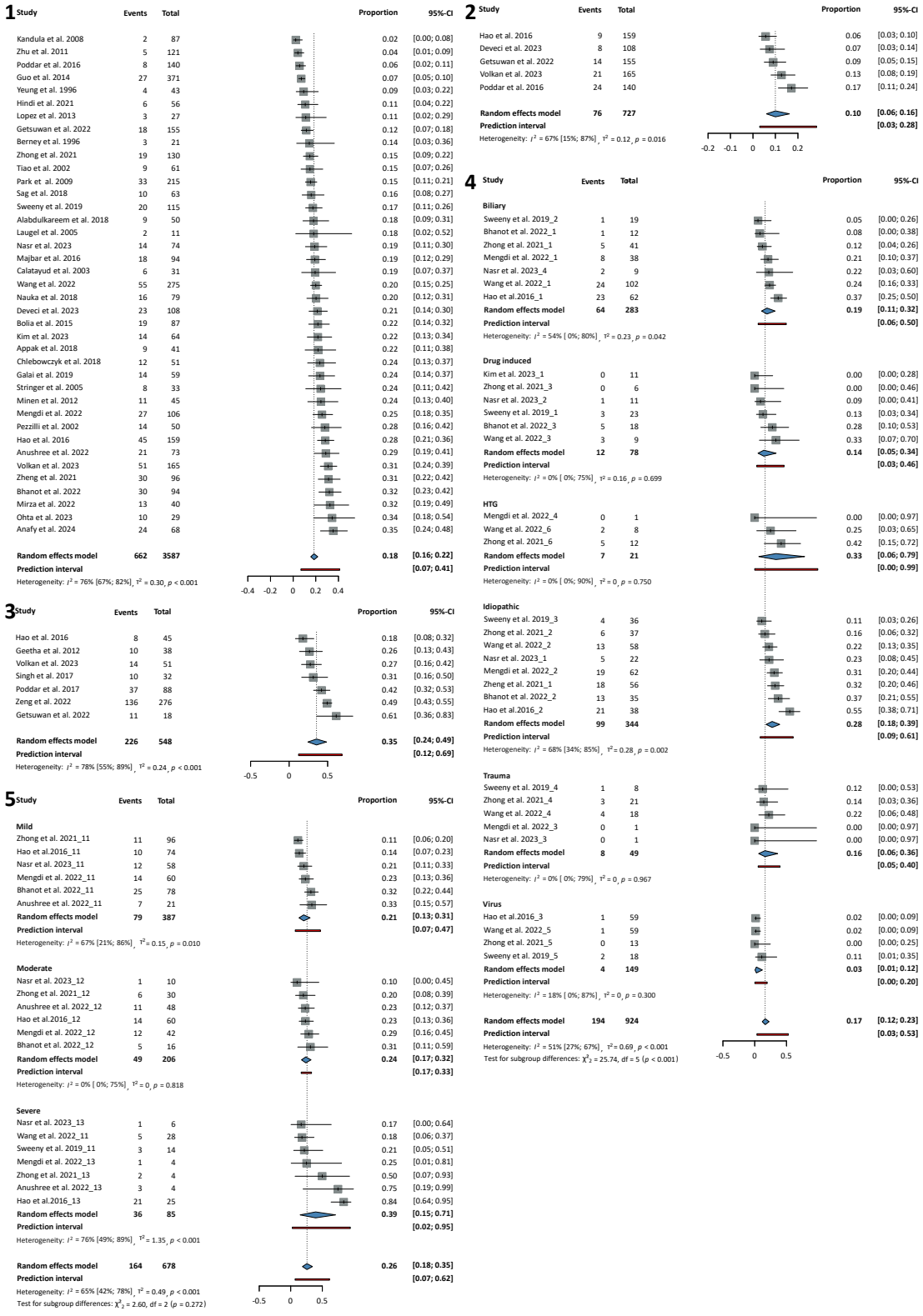


Figure 6. Forest plots showing: 1) the overall proportion of RAP after an episode of AP; 2) the overall proportion of CP after an episode of AP; 3) the overall proportion of CP after RAP; 4) the proportion of RAP after an episode of AP stratified by etiology; 5) the

proportion of RAP after an episode of AP stratified by severity; AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis;

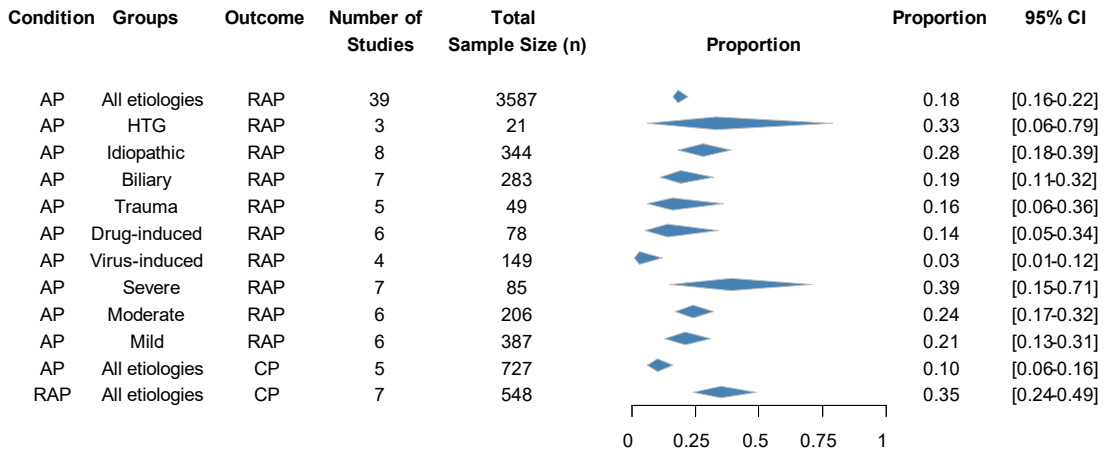


Figure 7. Summary forest plot showing the recurrence rate of AP in overall and stratified by etiology and severity, and the progression rates of AP to CP after a single episode and after RAP. AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; HTG, hypertrigliceridemia; CI, confidence interval

8.2.4. Factors associated with acute pancreatitis progression in children

Anatomical abnormalities showed significant associations with disease progression. General structural anomalies increased the risk of RAP (OR 3.15; 95% CI 1.51–6.56) (Figure 8), while pancreas divisum was associated with CP (OR 2.64; 95% CI 1.51–4.63) (Figure 9). Among genetic factors, PRSS1 mutations showed a strong association with CP (OR 4.56; 95% CI 3.06–6.80) (Figure 9). Male sex, race (white or Hispanic), and family history of AP were not significantly associated with RAP or CP (Figures 8, 9). Age at inclusion and clinical parameters (length of stay, amylase, lipase, WBC, CRP) did not differ between AP and RAP (Figure 10). Other genetic variants (SPINK1, CFTR, CTRC), broader genetic AP categories, and additional anatomical anomalies (choledochal cysts, annular pancreas, maljunction) also showed no significant associations (Figures 8, 9). Medication-related AP was associated with a reduced risk of CP (OR 0.26; 95% CI 0.07–0.91). Exocrine pancreatic insufficiency showed a strong association with CP (OR 22.82; 95% CI 9.26–56.25). Several interventional procedures were linked to increased CP risk, including biliary sphincterotomy (OR 4.16; 95% CI 3.24–5.34), biliary stenting (OR 5.79; 95% CI 4.42–7.60), and pancreatic duct stenting

(OR 12.19; 95% CI 3.16–46.97) (Figure 4). Autoimmune and metabolic AP were not significantly associated with RAP or CP (Figures 3, 4). Diabetes mellitus showed no association with RAP and only a non-significant trend toward increased CP risk (OR 3.77; 95% CI 0.98–14.45) (Figures 3, 4). Systemic lupus erythematosus was not linked to RAP. Clinical complications, including pseudocysts, necrotizing AP, abdominal pain, ICU admission, vomiting, diarrhea, obstructive findings, fever, APFC, and ANC were not predictive of progression (Figures 3, 4).

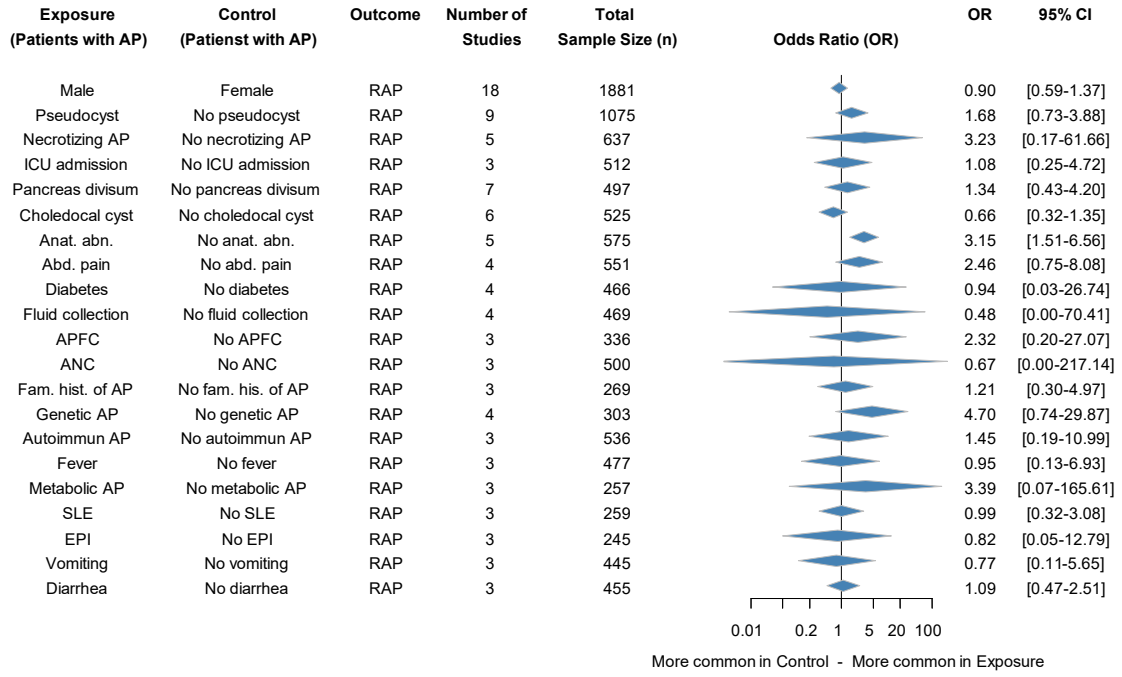


Figure 8. Summary forest plot showing pooled odds ratios for proposed risk factors associated with recurrent acute pancreatitis after an index acute pancreatitis episode in children. AP, acute pancreatitis; RAP, recurrent acute pancreatitis; OR, odds ratio; CI, confidence interval; APFC, acute peripancreatic fluid collection; ANC, acute necrotic collection; EPI, exocrine pancreatic insufficiency; SLE, systemic lupus erythematosus; abd., abdominal; anat. abn., anatomical abnormality; ICU, intensive care unit.

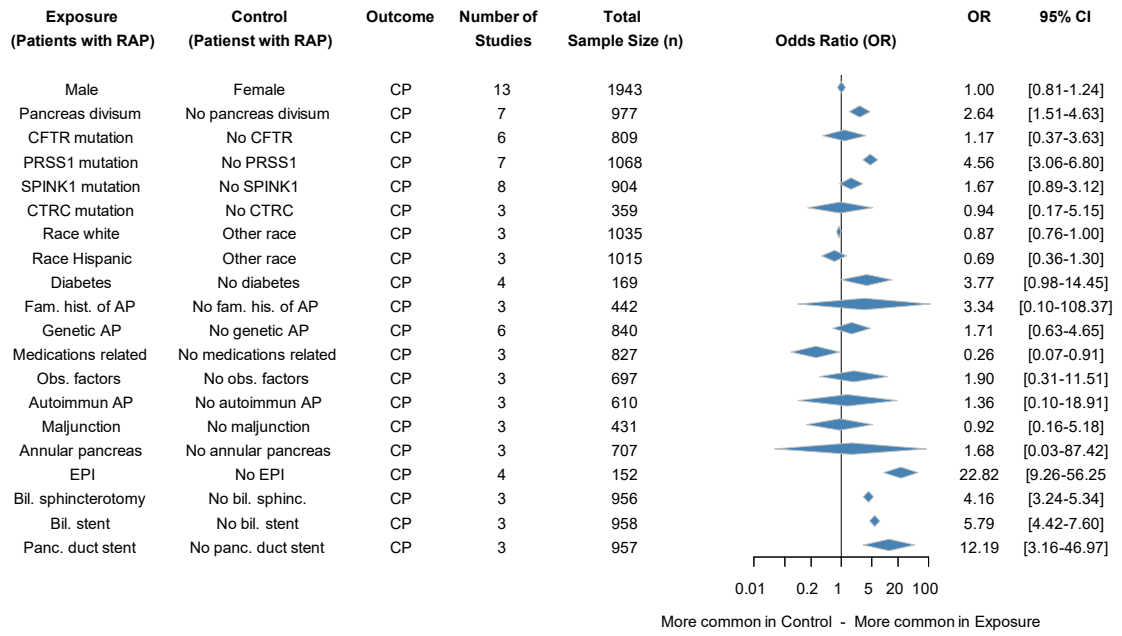


Figure 9. Summary forest plot showing pooled odds ratios for proposed risk factors associated with progression from recurrent acute pancreatitis to chronic pancreatitis in children. OR, odds ratio; CI, confidence interval; AP, acute pancreatitis; EPI, exocrine pancreatic insufficiency; bil., biliary; sphinc., sphincterotomy; panc., pancreatic; fam. hist., family history; obs., obstructive.

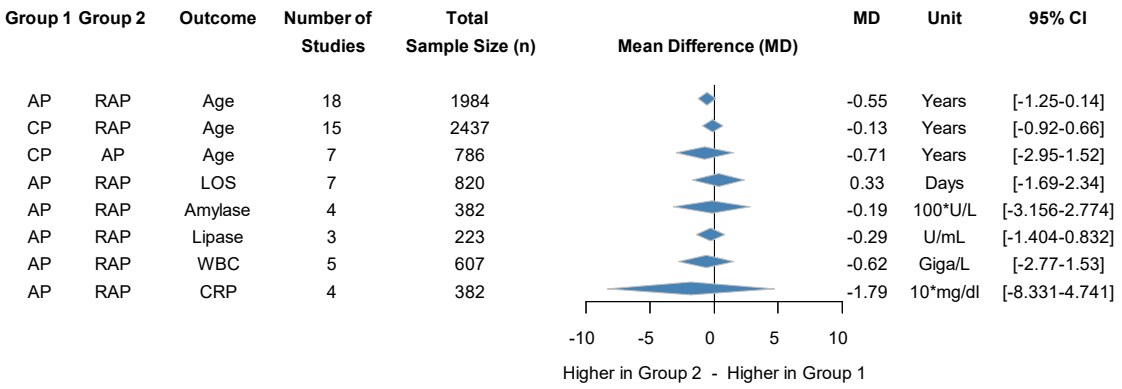


Figure 10. Summary forest plot showing pooled mean differences for continuous clinical variables comparing disease groups in pediatric pancreatitis. AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; LOS, length of hospital stay; WBC, white-blood-cell count; CRP, C-reactive protein; MD, mean difference; CI, confidence interval.

8.2.5. Risk of bias assessment

Study quality was evaluated using the JBI tool for studies assessing AP progression and the QUIPS tool for comparative studies. Overall, most studies were judged to have a moderate risk of bias, largely due to small sample sizes in progression studies and residual confounding in comparison studies. These methodological limitations should be considered when interpreting the findings.

8.2.6. Publication bias and heterogeneity

We evaluated heterogeneity only for the overall progression from AP to RAP, as this was the sole outcome with a sufficient number of studies (≥10) to permit meaningful analysis. Multiple approaches were undertaken. A leave-one-out sensitivity analysis produced only minimal reductions in the substantial heterogeneity observed. To account for diagnostic variability, we performed sensitivity analyses stratified by diagnostic criteria (INSPPIRE vs. non-INSPPIRE) (Figure 11). We further compared studies with reported versus unreported follow-up duration (Figure 11), conducted subgroup analyses based on follow-up length (<12 months, 12–36 months, >36 months; Figure 12), and performed a meta-regression limited to studies with documented follow-up to assess whether follow-up duration influenced RAP progression (Figure 13). Progression rates differed significantly according to diagnostic framework ($p = 0.019$), whereas follow-up reporting status did not significantly affect results ($p = 0.161$). Subgroup comparisons ($p = 0.319$) and meta-regression similarly indicated no association between follow-up length and progression ($p = 0.976$) (Figures 11,12,13). When exploring technical factors that might contribute to heterogeneity, smaller studies (sample size <100) showed significantly higher RAP rates than larger studies (21% vs. 18%, $p = 0.048$). Shorter study periods (<7 years) were also associated with higher RAP proportions compared with longer periods (22% vs. 16%, $p = 0.046$) (Figure 14). In contrast, study design, geographic region, single- versus multicenter setting, and gender distribution did not significantly influence heterogeneity (Figure 15). Assessment of publication bias for the AP - RAP outcome, using both funnel-plot inspection and Peter's test ($p > 0.305$), indicated no evidence of significant publication bias. This assessment was limited to the AP - RAP pathway, as no other progression outcome met the minimum threshold of 10 studies.

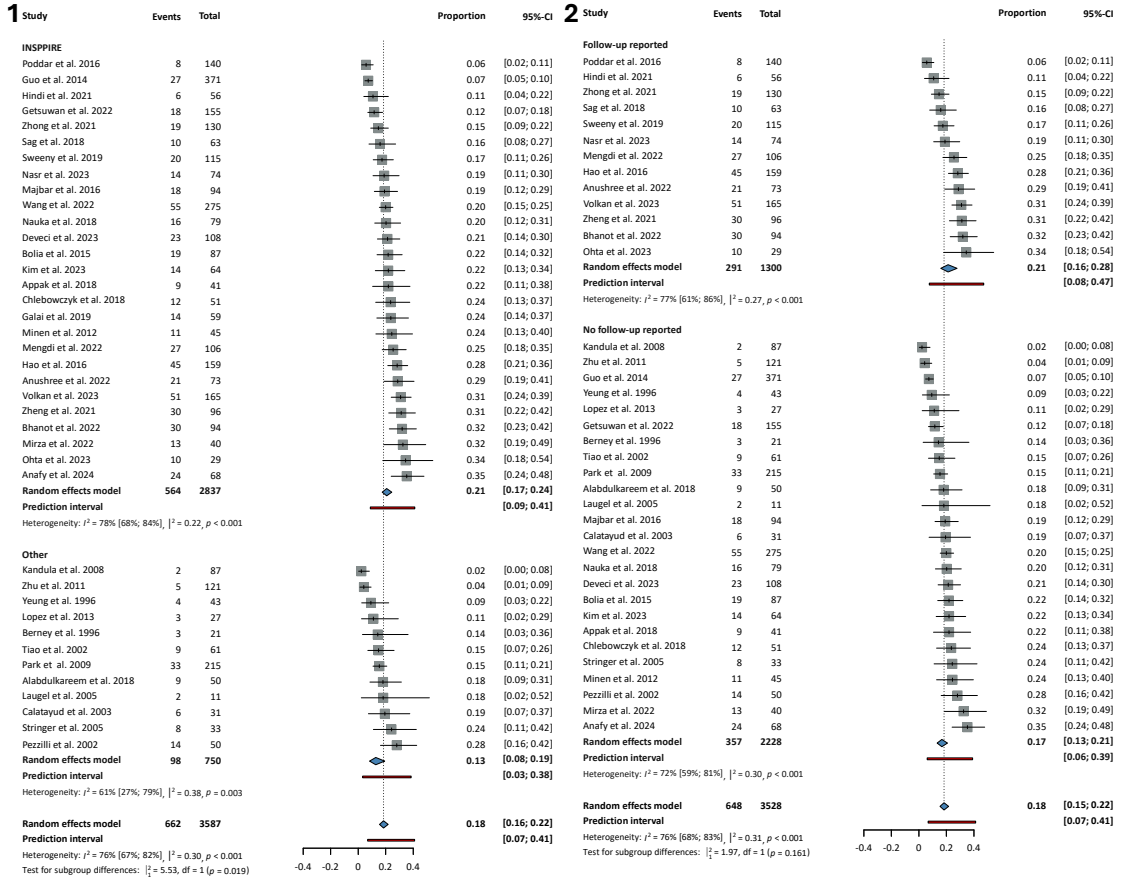


Figure 11. Forest plots showing the relationship between acute pancreatitis (AP) definitions and the reporting of follow-up time in relation to the recurrence of acute pancreatitis. (1): Comparison of studies using INSPPIRE versus other AP definitions. (2): Comparison of studies with reported follow-up duration versus those without reported follow-up.

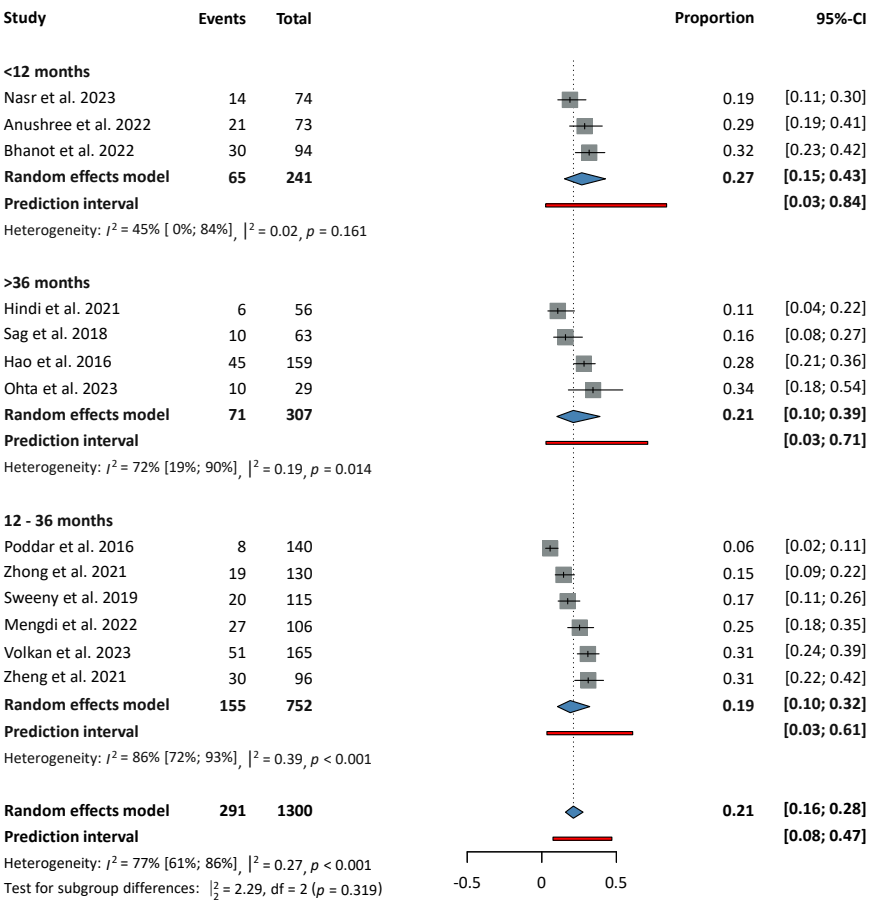


Figure 12. Subgroup analysis of recurrence rates of acute pancreatitis (AP to RAP) stratified by follow-up duration (<12 months, 12–36 months, and >36 months). Each square represents an individual study estimate with its 95% confidence interval (CI); the diamond indicates the pooled proportion within each subgroup using a random-effects model. Horizontal red lines show the 95% prediction intervals. Recurrence rates were 27% (<12 months), 21% (>36 months), and 15% (12–36 months). Subgroup differences were not statistically significant (p=0.319).

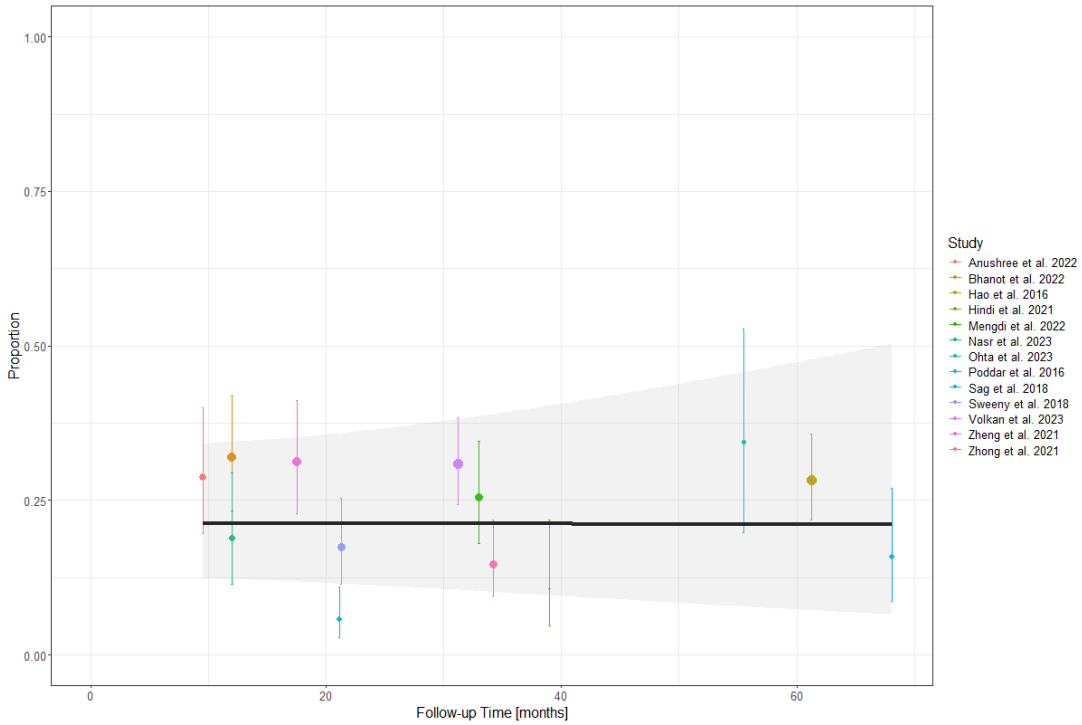


Figure 13. Meta-regression of follow-up duration and recurrence of acute pancreatitis. Each point represents a study with 95% CI, and the solid line with grey band shows the fitted regression. No significant association was observed between follow-up length and RAP progression (p = 0.976).

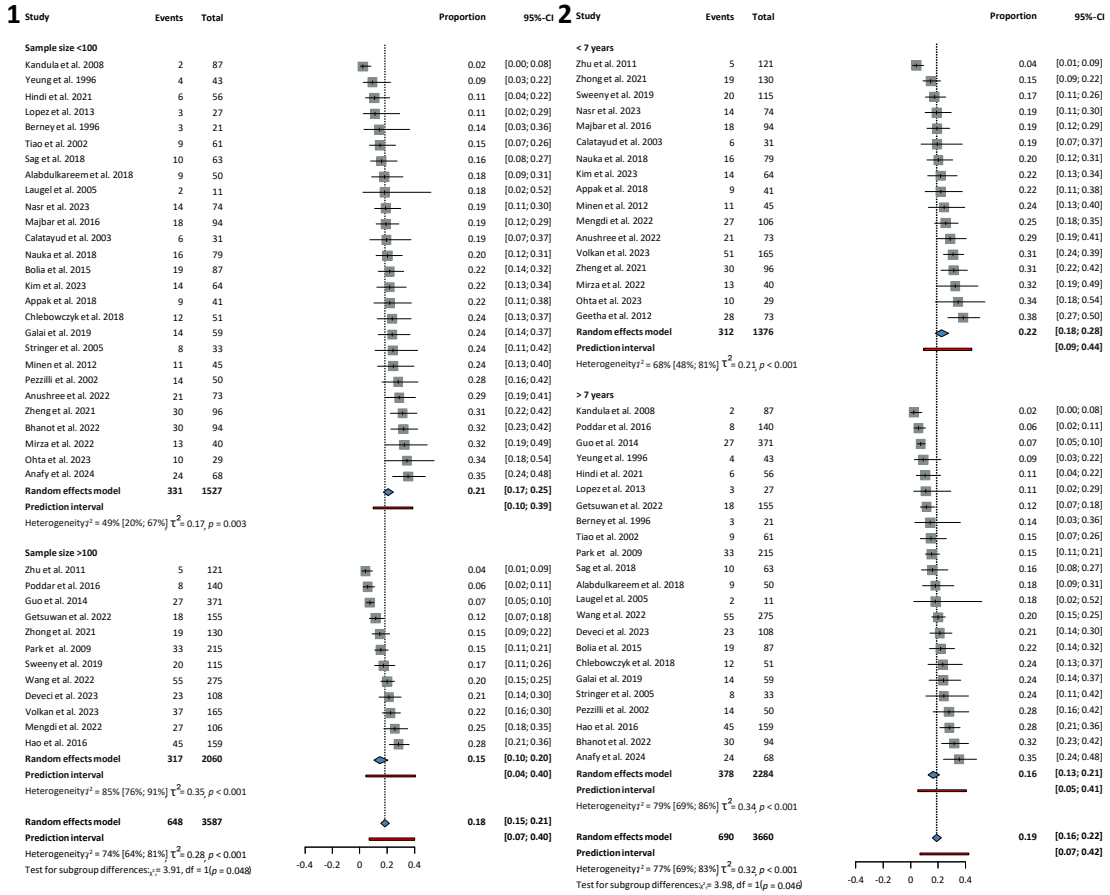


Figure 14. Forest plots showing the relationship between sample size and study period in relation to the recurrence of acute pancreatitis. (1): comparing studies with sample sizes of less than or more than 100 patients. (2): comparing studies with a study period of less than or more than 7 years.

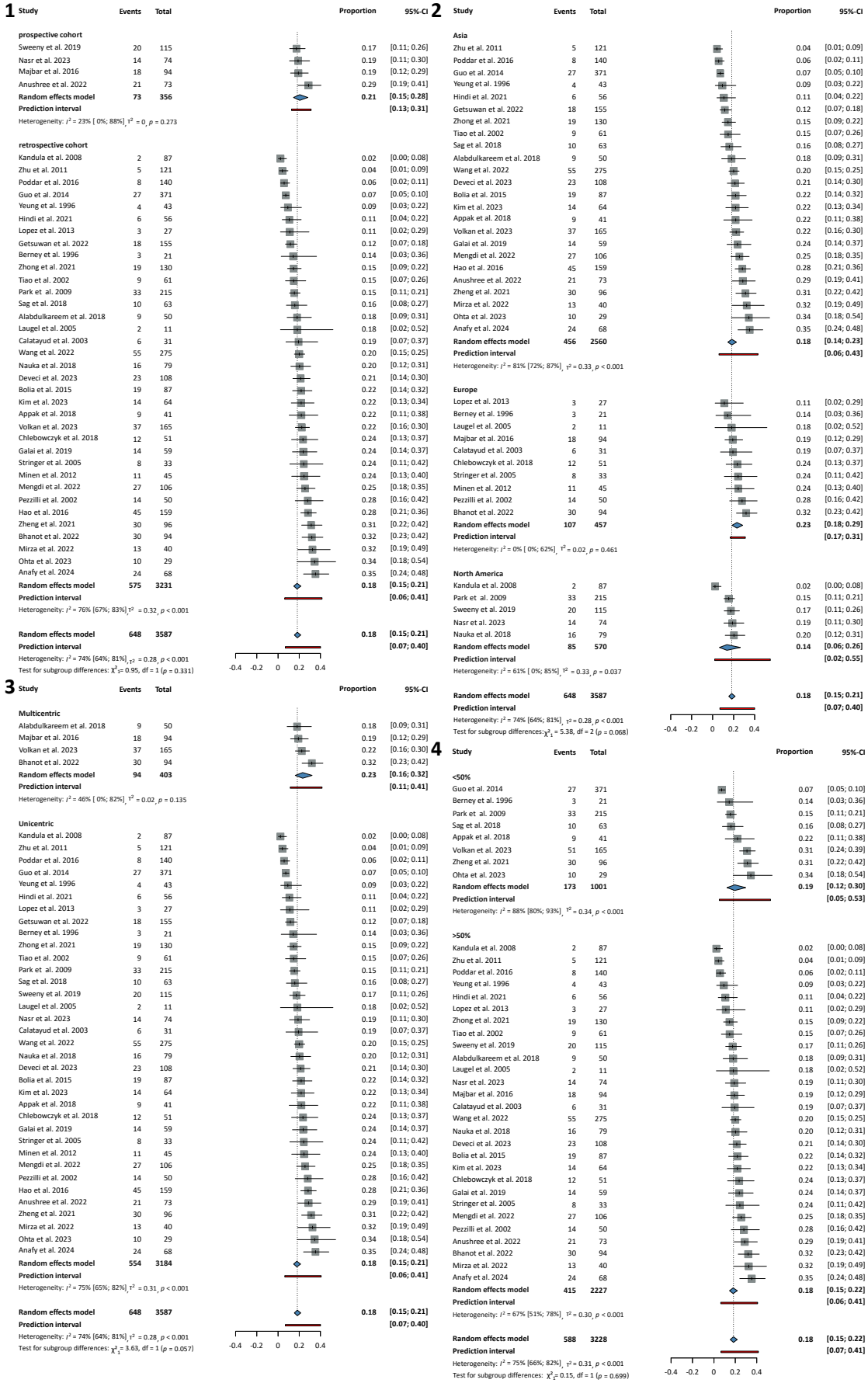

1
Study Events Total Proportion 95%-CI
prospective cohort
Sweeny et al. 2019 20 115 0.17 [0.11; 0.26]
Nasr et al. 2023 14 74 0.19 [0.11; 0.30]
Majbar et al. 2016 18 94 0.19 [0.12; 0.29]
Anushree et al. 2022 21 73 0.29 [0.19; 0.41]
Random effects model 73 356 0.21 [0.15; 0.28]
Prediction interval [0.13; 0.31]
Heterogeneity: I^2 = 23% [0%; 88%], τ^2 = 0, p = 0.273
retrospective cohort
Kandula et al. 2008 2 87 0.02 [0.00; 0.08]
Zhu et al. 2011 5 121 0.04 [0.01; 0.09]
Poddar et al. 2016 8 140 0.06 [0.02; 0.11]
Guo et al. 2014 27 371 0.07 [0.05; 0.10]
Yeung et al. 1996 4 43 0.09 [0.03; 0.22]
Hindi et al. 2021 6 56 0.11 [0.04; 0.22]
Lopez et al. 2013 3 27 0.11 [0.02; 0.29]
Getsuwan et al. 2022 18 155 0.12 [0.07; 0.18]
Berney et al. 1996 3 21 0.14 [0.03; 0.36]
Zhong et al. 2021 19 130 0.15 [0.09; 0.22]
Tiao et al. 2002 9 61 0.15 [0.07; 0.26]
Park et al. 2009 33 215 0.15 [0.11; 0.21]
Sag et al. 2018 10 63 0.16 [0.08; 0.27]
Alabdulkareem et al. 2018 9 50 0.18 [0.09; 0.31]
Laugel et al. 2005 2 11 0.18 [0.02; 0.52]
Calatayud et al. 2003 6 31 0.19 [0.07; 0.37]
Wang et al. 2022 55 275 0.20 [0.15; 0.25]
Nauka et al. 2018 16 79 0.20 [0.12; 0.31]
Deveci et al. 2023 23 108 0.21 [0.14; 0.30]
Bolia et al. 2015 19 87 0.22 [0.14; 0.32]
Kim et al. 2023 14 64 0.22 [0.13; 0.34]
Appak et al. 2018 9 41 0.22 [0.11; 0.38]
Volkan et al. 2023 37 165 0.22 [0.16; 0.30]
Chlebowczyk et al. 2018 12 51 0.24 [0.13; 0.37]
Galai et al. 2019 14 59 0.24 [0.14; 0.37]
Stringer et al. 2005 8 33 0.24 [0.11; 0.42]
Minen et al. 2012 11 45 0.24 [0.13; 0.40]
Mengdi et al. 2022 27 106 0.25 [0.18; 0.35]
Pezzilli et al. 2002 14 50 0.28 [0.16; 0.42]
Hao et al. 2016 45 159 0.28 [0.21; 0.36]
Zheng et al. 2021 30 96 0.31 [0.22; 0.42]
Bhanot et al. 2022 30 94 0.32 [0.23; 0.42]
Mirza et al. 2022 13 40 0.32 [0.19; 0.49]
Ohta et al. 2023 10 29 0.34 [0.18; 0.54]
Anafy et al. 2024 24 68 0.35 [0.24; 0.48]
Random effects model 575 3231 0.18 [0.15; 0.21]
Prediction interval [0.06; 0.41]
Heterogeneity: I^2 = 76% [67%; 83%], τ^2 = 0.32, p < 0.001
Random effects model 648 3587 0.18 [0.15; 0.21]
Prediction interval [0.07; 0.40]
Heterogeneity: I^2 = 74% [64%; 81%], τ^2 = 0.28, p < 0.001
Test for subgroup differences: χ^2_1 = 0.95, df = 1 (p = 0.331)
-0.4 -0.2 0 0.2 0.4
2
Study Events Total Proportion 95%-CI
Asia
Zhu et al. 2011 5 121 0.04 [0.01; 0.09]
Poddar et al. 2016 8 140 0.06 [0.02; 0.11]
Guo et al. 2014 27 371 0.07 [0.05; 0.10]
Yeung et al. 1996 4 43 0.09 [0.03; 0.22]
Hindi et al. 2021 6 56 0.11 [0.04; 0.22]
Getsuwan et al. 2022 18 155 0.12 [0.07; 0.18]
Zhong et al. 2021 19 130 0.15 [0.09; 0.22]
Tiao et al. 2002 9 61 0.15 [0.07; 0.26]
Sag et al. 2018 10 63 0.16 [0.08; 0.27]
Alabdulkareem et al. 2018 9 50 0.18 [0.09; 0.31]
Wang et al. 2022 55 275 0.20 [0.15; 0.25]
Deveci et al. 2023 23 108 0.21 [0.14; 0.30]
Bolia et al. 2015 19 87 0.22 [0.14; 0.32]
Kim et al. 2023 14 64 0.22 [0.13; 0.34]
Appak et al. 2018 9 41 0.22 [0.11; 0.38]
Volkan et al. 2023 37 165 0.22 [0.16; 0.30]
Galai et al. 2019 14 59 0.24 [0.14; 0.37]
Mengdi et al. 2022 27 106 0.25 [0.18; 0.35]
Hao et al. 2016 45 159 0.28 [0.21; 0.36]
Anushree et al. 2022 21 73 0.29 [0.19; 0.41]
Zheng et al. 2021 30 96 0.31 [0.22; 0.42]
Mirza et al. 2022 13 40 0.32 [0.19; 0.49]
Ohta et al. 2023 10 29 0.34 [0.18; 0.54]
Anafy et al. 2024 24 68 0.35 [0.24; 0.48]
Random effects model 456 2560 0.18 [0.14; 0.23]
Prediction interval [0.06; 0.43]
Heterogeneity: I^2 = 81% [72%; 87%], τ^2 = 0.33, p < 0.001
Europe
Lopez et al. 2013 3 27 0.11 [0.02; 0.29]
Berney et al. 1996 3 21 0.14 [0.03; 0.36]
Laugel et al. 2005 2 11 0.18 [0.02; 0.52]
Majbar et al. 2016 18 94 0.19 [0.12; 0.29]
Calatayud et al. 2003 6 31 0.19 [0.07; 0.37]
Chlebowczyk et al. 2018 12 51 0.24 [0.13; 0.37]
Stringer et al. 2005 8 33 0.24 [0.11; 0.42]
Minen et al. 2012 11 45 0.24 [0.13; 0.40]
Pezzilli et al. 2002 14 50 0.28 [0.16; 0.42]
Bhanot et al. 2022 30 94 0.32 [0.23; 0.42]
Random effects model 107 457 0.23 [0.18; 0.29]
Prediction interval [0.17; 0.31]
Heterogeneity: I^2 = 0% [0%; 62%], τ^2 = 0.02, p = 0.461
North America
Kandula et al. 2008 2 87 0.02 [0.00; 0.08]
Park et al. 2009 33 215 0.15 [0.11; 0.21]
Sweeny et al. 2019 20 115 0.17 [0.11; 0.26]
Nasr et al. 2023 14 74 0.19 [0.11; 0.30]
Nauka et al. 2018 16 79 0.20 [0.12; 0.31]
Random effects model 85 570 0.14 [0.06; 0.26]
Prediction interval [0.02; 0.55]
Heterogeneity: I^2 = 61% [0%; 85%], τ^2 = 0.33, p = 0.037
Random effects model 648 3587 0.18 [0.15; 0.21]
Prediction interval [0.07; 0.40]
Heterogeneity: I^2 = 74% [64%; 81%], τ^2 = 0.28, p < 0.001
Test for subgroup differences: χ^2_1 = 5.38, df = 2 (p = 0.068)
-0.4 -0.2 0 0.2 0.4
3
Study Events Total Proportion 95%-CI
Multicentric
Alabdulkareem et al. 2018 9 50 0.18 [0.09; 0.31]
Majbar et al. 2016 18 94 0.19 [0.12; 0.29]
Volkan et al. 2023 37 165 0.22 [0.16; 0.30]
Bhanot et al. 2022 30 94 0.32 [0.23; 0.42]
Random effects model 94 403 0.23 [0.16; 0.32]
Prediction interval [0.11; 0.41]
Heterogeneity: I^2 = 46% [0%; 82%], τ^2 = 0.02, p = 0.135
Unicentric
Kandula et al. 2008 2 87 0.02 [0.00; 0.08]
Zhu et al. 2011 5 121 0.04 [0.01; 0.09]
Poddar et al. 2016 8 140 0.06 [0.02; 0.11]
Guo et al. 2014 27 371 0.07 [0.05; 0.10]
Yeung et al. 1996 4 43 0.09 [0.03; 0.22]
Hindi et al. 2021 6 56 0.11 [0.04; 0.22]
Lopez et al. 2013 3 27 0.11 [0.02; 0.29]
Getsuwan et al. 2022 18 155 0.12 [0.07; 0.18]
Berney et al. 1996 3 21 0.14 [0.03; 0.36]
Zhong et al. 2021 19 130 0.15 [0.09; 0.22]
Tiao et al. 2002 9 61 0.15 [0.07; 0.26]
Park et al. 2009 33 215 0.15 [0.11; 0.21]
Sag et al. 2018 10 63 0.16 [0.08; 0.27]
Sweeny et al. 2019 20 115 0.17 [0.11; 0.26]
Laugel et al. 2005 2 11 0.18 [0.02; 0.52]
Nasr et al. 2023 14 74 0.19 [0.11; 0.30]
Calatayud et al. 2003 6 31 0.19 [0.07; 0.37]
Wang et al. 2022 55 275 0.20 [0.15; 0.25]
Nauka et al. 2018 16 79 0.20 [0.12; 0.31]
Deveci et al. 2023 23 108 0.21 [0.14; 0.30]
Bolia et al. 2015 19 87 0.22 [0.14; 0.32]
Kim et al. 2023 14 64 0.22 [0.13; 0.34]
Appak et al. 2018 9 41 0.22 [0.11; 0.38]
Chlebowczyk et al. 2018 12 51 0.24 [0.13; 0.37]
Galai et al. 2019 14 59 0.24 [0.14; 0.37]
Stringer et al. 2005 8 33 0.24 [0.11; 0.42]
Minen et al. 2012 11 45 0.24 [0.13; 0.40]
Mengdi et al. 2022 27 106 0.25 [0.18; 0.35]
Pezzilli et al. 2002 14 50 0.28 [0.16; 0.42]
Hao et al. 2016 45 159 0.28 [0.21; 0.36]
Anushree et al. 2022 21 73 0.29 [0.19; 0.41]
Zheng et al. 2021 30 96 0.31 [0.22; 0.42]
Mirza et al. 2022 13 40 0.32 [0.19; 0.49]
Ohta et al. 2023 10 29 0.34 [0.18; 0.54]
Anafy et al. 2024 24 68 0.35 [0.24; 0.48]
Random effects model 554 3184 0.18 [0.15; 0.21]
Prediction interval [0.06; 0.41]
Heterogeneity: I^2 = 75% [65%; 82%], τ^2 = 0.31, p < 0.001
Random effects model 648 3587 0.18 [0.15; 0.21]
Prediction interval [0.07; 0.40]
Heterogeneity: I^2 = 74% [64%; 81%], τ^2 = 0.28, p < 0.001
Test for subgroup differences: χ^2_1 = 3.63, df = 1 (p = 0.057)
-0.4 -0.2 0 0.2 0.4
4
Study Events Total Proportion 95%-CI
<50%
Guo et al. 2014 27 371 0.07 [0.05; 0.10]
Berney et al. 1996 3 21 0.14 [0.03; 0.36]
Park et al. 2009 33 215 0.15 [0.11; 0.21]
Sag et al. 2018 10 63 0.16 [0.08; 0.27]
Appak et al. 2018 9 41 0.22 [0.11; 0.38]
Volkan et al. 2023 51 165 0.31 [0.24; 0.39]
Zheng et al. 2021 30 96 0.31 [0.22; 0.42]
Ohta et al. 2023 10 29 0.34 [0.18; 0.54]
Random effects model 173 1001 0.19 [0.12; 0.30]
Prediction interval [0.05; 0.53]
Heterogeneity: I^2 = 88% [80%; 93%], τ^2 = 0.34, p < 0.001
>50%
Kandula et al. 2008 2 87 0.02 [0.00; 0.08]
Zhu et al. 2011 5 121 0.04 [0.01; 0.09]
Poddar et al. 2016 8 140 0.06 [0.02; 0.11]
Yeung et al. 1996 4 43 0.09 [0.03; 0.22]
Hindi et al. 2021 6 56 0.11 [0.04; 0.22]
Lopez et al. 2013 3 27 0.11 [0.02; 0.29]
Zhong et al. 2021 19 130 0.15 [0.09; 0.22]
Tiao et al. 2002 9 61 0.15 [0.07; 0.26]
Sweeny et al. 2019 20 115 0.17 [0.11; 0.26]
Alabdulkareem et al. 2018 9 50 0.18 [0.09; 0.31]
Laugel et al. 2005 2 11 0.18 [0.02; 0.52]
Nasr et al. 2023 14 74 0.19 [0.11; 0.30]
Majbar et al. 2016 18 94 0.19 [0.12; 0.29]
Calatayud et al. 2003 6 31 0.19 [0.07; 0.37]
Wang et al. 2022 55 275 0.20 [0.15; 0.25]
Nauka et al. 2018 16 79 0.20 [0.12; 0.31]
Deveci et al. 2023 23 108 0.21 [0.14; 0.30]
Bolia et al. 2015 19 87 0.22 [0.14; 0.32]
Kim et al. 2023 14 64 0.22 [0.13; 0.34]
Chlebowczyk et al. 2018 12 51 0.24 [0.13; 0.37]
Galai et al. 2019 14 59 0.24 [0.14; 0.37]
Stringer et al. 2005 8 33 0.24 [0.11; 0.42]
Mengdi et al. 2022 27 106 0.25 [0.18; 0.35]
Pezzilli et al. 2002 14 50 0.28 [0.16; 0.42]
Anushree et al. 2022 21 73 0.29 [0.19; 0.41]
Bhanot et al. 2022 30 94 0.32 [0.23; 0.42]
Mirza et al. 2022 13 40 0.32 [0.19; 0.49]
Anafy et al. 2024 24 68 0.35 [0.24; 0.48]
Random effects model 415 2227 0.18 [0.15; 0.22]
Prediction interval [0.06; 0.41]
Heterogeneity: I^2 = 67% [51%; 78%], τ^2 = 0.30, p < 0.001
Random effects model 588 3228 0.18 [0.15; 0.22]
Prediction interval [0.07; 0.41]
Heterogeneity: I^2 = 75% [66%; 82%], τ^2 = 0.31, p < 0.001
Test for subgroup differences: χ^2_1 = 0.15, df = 1 (p = 0.699)
-0.4 -0.2 0 0.2 0.4

Figure 15. Forest plots showing the pooled proportion of pediatric patients developing recurrent acute pancreatitis (RAP) after an initial acute pancreatitis (AP) episode, stratified by study characteristics. (1) Study design and RAP. (2) Geographic region and RAP. (3) Number of centers and RAP. (4) Proportion of males.

9. DISCUSSION

9.1. Summary of findings, international comparisons (including all studies)

In this thesis, we conducted two complementary systematic reviews and meta-analyses to characterize the progression of AP to RAP and CP in adults and children, and to identify the major risk factors contributing to this transition. Our first study is the first meta-analysis to evaluate IRs of RAP and CP after AP, thereby addressing the time dependency of progression. By using IRs, we overcame differences in follow-up durations and obtained a more accurate representation of the transition from AP to RAP and CP. For completeness, proportions were also analyzed without time correction. Our second is the first meta-analysis focused specifically on pediatric AP progression, providing complementary evidence for patterns observed in adults.

Across age groups, recurrence occurs frequently, and chronicity becomes substantially more likely once recurrence has developed, supporting the concept that repeated inflammatory episodes contribute to ongoing injury and fibrosis and can promote irreversible disease transition (99). Both in our analysis, CP occurs substantially more often after RAP than after a first AP episode, supporting the clinical view that RAP is a major inflection point in the disease course (99).

A clear etiologic pattern emerges in both populations. Etiologies linked to persistent metabolic or exposure related risk (such as hypertriglyceridemia in both populations or alcohol-related disease in adults) are consistently associated with higher recurrence and, in adults, with a higher burden of CP (48, 100, 101). In contrast, etiologies that typically reflect a single, self-limited insult show lower recurrence in children, including trauma-, drug-, and virus-induced AP, reinforcing the idea that ongoing or recurrent drivers, rather than the index event alone, shape long-term risk. Medication-related (not drug-induced) AP is also linked to a lower risk of CP.

Idiopathic AP remains a clinically important high-risk category in both adults and children. A substantial part of this risk likely reflects missed or under-recognized etiologies. Endoscopic ultrasonography can uncover diagnostic information in a large proportion of idiopathic cases, frequently identifying biliary tract disease (102). Accordingly, deeper etiologic investigation in “idiopathic” presentations can enable

targeted treatment and reduce preventable recurrence and downstream progression (51, 102). In pediatric cohorts, comprehensive evaluation in apparently idiopathic cases remains essential, including genetics and advanced imaging, and endoscopic ultrasound can meaningfully contribute to etiologic clarification (103, 104).

Biliary AP generally shows a more favorable long-term course when definitive treatment is performed. In adults, lower recurrence in biliary disease aligns with the effect of cholecystectomy and/or endoscopic management after the first episode. In children, biliary recurrence remains possible but appears mitigated by definitive therapy, while retained stones, microlithiasis, or sphincter dysfunction may explain residual risk (105). In our first study in the adult population, among patients with biliary AP, the absence of cholecystectomy was associated with higher recurrence, highlighting the role of definitive management in long-term prevention.

Adults and children differ in the dominant architecture of risk. In adults, recurrence and progression are strongly shaped by modifiable exposures; alcohol use and smoking are consistently linked to higher recurrence, in line with evidence that many patients continue drinking despite medical advice (48, 101). In children, major adult exposures are rarely relevant, and progression is more strongly influenced by predisposition, particularly genetic and anatomical factors. PRSS1 and structural abnormalities (including pancreas divisum) are key drivers of RAP and CP (61, 106-108). Several demographic factors (including sex and race) and commonly used clinical laboratory markers have limited utility as stand-alone predictors of long-term progression in pediatric pancreatitis. Clinical complications, such as pseudocysts or necrotizing pancreatitis, are not reliable predictors of progression in our results, challenging the assumption that acute-phase complication severity consistently predicts long-term outcomes.

Strong associations between CP and exocrine pancreatic insufficiency (EPI) and between CP and several endoscopic interventions (including biliary sphincterotomy, biliary stenting, and pancreatic duct stenting) most likely reflect disease stage rather than causality. EPI occurs late after extensive acinar loss (109), and procedures are often performed in more complicated disease, while temporality is not consistently documented (110). Timely endoscopic intervention in select anatomical conditions (such as

symptomatic pancreas divisum) may influence trajectory, although randomized evidence remains limited (108).

Severity of the initial AP episode shows a nuanced association with recurrence in both adults and children. In adults, moderately severe AP tends to have the highest observed recurrence, likely reflecting early mortality and more rapid progression to CP in severe cases. Prior studies report conflicting results, with some suggesting no consistent effect of severity (6), while others link severe AP to increased recurrence and faster CP progression (37). In children, severe AP generally shows a higher recurrence tendency than mild disease, but estimates remain imprecise due to limited data. Overall, these findings are compatible with necrosis-driven fibrogenesis (111), suggesting that severe inflammatory injury may accelerate pancreatic fibrosis across age groups.

Follow-up duration was explicitly considered in both studies to ensure an appropriate interpretation of disease progression over time. In the first study, pancreatitis progression was approached as a time-dependent process, and person-time–based measures were therefore applied to account for variability in follow-up across studies. In the second study, we explored the potential impact of follow-up length using several complementary approaches, including subgroup analyses and meta-regression, and did not identify a meaningful association between follow-up duration and AP - RAP progression. This pattern is compatible with clinical observations suggesting that, in children at risk, recurrence frequently occurs early after the initial episode (11, 12, 59). Taken together, these findings support the importance of incorporating follow-up time into analytical strategies, while also indicating that the temporal distribution of progression events may differ across age groups.

9.2. Strengths (including all studies)

These meta-analyses provide a broad and clinically actionable synthesis of progression after AP across age groups. A key strength of our first study is that we explicitly used incidence rates to capture the time-dependent nature of progression and to reduce bias arising from heterogeneous follow-up durations. We complemented this approach with a large proportions-based synthesis, which allowed us to confirm the direction of the findings and to explore additional clinically relevant subgroups.

A major strength of our second study is its comprehensive scope and its specific focus on pediatric progression rates and risk factors. We included a large number of studies from diverse geographic and clinical settings, prospectively registered the protocol, and performed structured risk-of-bias assessments using validated tools (JBI and QUIPS). We further conducted extensive subgroup, sensitivity, and heterogeneity analyses, which enabled us to identify the most influential sources of variation, particularly diagnostic framework and small-study effects.

9.3. Limitations (including all studies)

Several limitations apply across both studies and should be interpreted in the context of our analytical choices. The available literature is dominated by retrospective, frequently single-center cohorts, and we observed substantial heterogeneity across outcomes. Our progression estimates are influenced by differences in cohort composition, exposure patterns, treatment pathways, follow-up strategies, and diagnostic definitions, particularly for CP. In adults, we were often constrained to calculate person-time using study-level follow-up summaries rather than individual patient data, which limits the precision of our time-dependent inferences. We were also unable to examine the number of RAP episodes or potential dose–response relationships with CP in detail, as episode counts were inconsistently reported.

In children, we relied predominantly on unadjusted risk-factor data, which limits causal interpretation of observed associations. We identified diagnostic heterogeneity as a key contributor to variability in AP - RAP estimates and addressed this through sensitivity and subgroup analyses; however, residual heterogeneity remained. For several clinically important subgroups, including severe AP and rare etiologies, the available evidence was sparse, resulting in wide uncertainty around pooled estimates. Finally, we could assess publication bias only for outcomes supported by a sufficient number of studies; in pediatric analyses this was largely restricted to the AP - RAP pathway. Although formal tests did not indicate major publication bias, statistical power was limited for other progression pathways.

10. CONCLUSIONS

Progression from AP to RAP and CP represents a substantial long-term burden in both adults and children. Recurrence is common, and the transition to CP becomes considerably more likely once RAP develops, supporting the clinical view that preventing recurrence is central to preventing chronic disease. Etiology is a key determinant of risk across age groups, with higher recurrence in settings characterized by persistent drivers (metabolic or exposure-related factors) and lower recurrence when the insult is typically singular and self-limited. Adults and children differ in the dominant mechanisms shaping progression: in adults, modifiable exposures and treatment patterns strongly influence recurrence and chronicity, while in children, genetic and anatomical predispositions are central drivers and should shape diagnostic and follow-up strategies.

11. IMPLICATIONS FOR PRACTICE

These findings support structured risk stratification after a first AP episode in both adults and children, with intensity tailored to etiology, clinical features, and known predispositions. In adults, practice should prioritize prevention through modification of key exposures (especially alcohol use and smoking) and by ensuring definitive management of treatable etiologies, particularly in biliary disease. “Idiopathic” AP should trigger more thorough etiologic work-up to identify hidden causes and enable targeted therapy. Consistent patient education and evidence-based follow-up are essential to reduce recurrence and downstream chronicity. In children, close follow-up is warranted because recurrence often occurs early, and etiologic evaluation should be paired with early assessment for genetic and anatomical factors in unexplained or recurrent cases. Associations involving EPI and procedures should be interpreted primarily as indicators of advanced disease and care pathways rather than isolated causal predictors.

12. IMPLICATIONS FOR RESEARCH

12.1. Methodology and study design

Future studies should improve follow-up design and reporting. Individual follow-up times and event timing should be reported (not only averages), enabling robust time-to-event analyses and clearer evaluation of time-dependence. Studies should also standardize diagnostic definitions for AP, RAP, and especially CP to reduce heterogeneity and improve comparability across cohorts. In adults, future cohorts should report the number of RAP episodes and evaluate dose–response relationships between recurrence burden and CP. In children, multicenter prospective cohorts with adjusted analyses are needed to strengthen causal inference for risk factors, and randomized trials are needed to test whether early targeted interventions in high-risk groups, particularly those defined by anatomical abnormalities, can modify disease trajectory.

12.2. New Areas

Key future directions include improving real-world effectiveness of existing preventive strategies (behavioral and psychological interventions for exposure-related risks), developing better metabolic-risk control approaches in hypertriglyceridemia-associated disease, and refining diagnostic pathways for idiopathic AP using advanced imaging and genetics. In pediatrics, integrated prediction models combining genetics, anatomy, and clinical factors represent an important opportunity for personalized surveillance and early intervention. Larger genetic epidemiology studies are also needed to clarify the role of variants that remain uncertain in current evidence, and to understand how genetic risk interacts with anatomical and environmental factors over time.

13. IMPLICATIONS FOR POLICY MAKERS

Our findings highlight the need for policy frameworks that support early risk stratification and prevention across the pancreatitis disease continuum. Health policies should prioritize timely access to definitive etiologic management, such as cholecystectomy after biliary AP, and structured programs for alcohol and smoking cessation in adult patients. In pediatric care, policies should facilitate access to specialized centers capable of genetic testing, advanced imaging, and multidisciplinary evaluation. Harmonization of diagnostic criteria and standardized reporting requirements across healthcare systems would improve surveillance, benchmarking, and resource allocation. Supporting longitudinal registries and reimbursement models that enable long-term follow-up is essential to reduce progression to chronic, high-burden disease states.

14. FUTURE PERSPECTIVES

Future research should move toward prospective, multicenter studies with standardized diagnostic frameworks and detailed longitudinal follow-up to better characterize time-dependent progression from AP to RAP and CP. Integration of genetic, structural, clinical, and lifestyle data may enable the development of age-specific prediction models to identify high-risk patients early. Advances in imaging, biomarkers, and pancreatic function testing could improve detection of subclinical disease and early fibrosis. Ultimately, translating epidemiologic insights into targeted preventive and therapeutic strategies has the potential to shift care from reactive management toward true disease modification across the lifespan.

15. REFERENCES

1. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144(6):1252-61.
2. Magnusdottir BA, Baldursdottir MB, Kalaitzakis E, Björnsson ES. Risk factors for chronic and recurrent pancreatitis after first attack of acute pancreatitis. Scand J Gastroenterol. 2019;54(1):87-94.
3. Czakó L, Takács T, Hegyi P, Prónai L, Tulassay Z, Lakner L, et al. Quality of life assessment after pancreatic enzyme replacement therapy in chronic pancreatitis. Can J Gastroenterol. 2003;17(10):597-603.
4. Guda NM, Muddana V, Whitcomb DC, Levy P, Garg P, Cote G, et al. Recurrent Acute Pancreatitis: International State-of-the-Science Conference With Recommendations. Pancreas. 2018;47(6):653-66.
5. Testoni PA. Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment. World J Gastroenterol. 2014;20(45):16891-901.
6. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology. 2015;149(6):1490-500.e1.
7. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol. 2012;107(7):1096-103.
8. Mekitarian Filho E, Carvalho WB, Silva FD. Acute pancreatitis in pediatrics: a systematic review of the literature. J Pediatr (Rio J). 2012;88(2):101-14.
9. Volkan B, Akkelle B, Bayrak NA, Tutar E, Kalaycık Şengül Ö, Polat E, et al. Long-Term Follow-Up and Outcome of Pediatric Acute Pancreatitis: A Multicenter Study. Turk Arch Pediatr. 2023;58(4):388-94.
10. Uc A, Husain SZ. Pancreatitis in Children. Gastroenterology. 2019;156(7):1969-78.
11. Sağ E, Kaya G, Bahat-Özdoğan E, Karahan SC, İmamoğlu M, Sarıhan H, et al. Acute pancreatitis in children: A single center experience over ten years. Turk J Pediatr. 2018;60(2):153-8.
12. Sweeny KF, Lin TK, Nathan JD, Denson LA, Husain SZ, Hornung L, et al. Rapid Progression of Acute Pancreatitis to Acute Recurrent Pancreatitis in Children. J Pediatr Gastroenterol Nutr. 2019;68(1):104-9.

13. Kumar S, Ooi CY, Werlin S, Abu-El-Haija M, Barth B, Bellin MD, et al. Risk factors associated with pediatric acute recurrent and chronic pancreatitis: lessons from INSPPIRE. JAMA pediatrics. 2016;170(6):562-9.
14. Machicado JD, Amann ST, Anderson MA, Abberbock J, Sherman S, Conwell DL, et al. Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities. Am J Gastroenterol. 2017;112(4):633-42.
15. Zsoldos F, Párniczky A, Mosztbacher D, Tóth A, Lásztity N, Hegyi P. Pain in the Early Phase of Pediatric Pancreatitis (PINEAPPLE Trial): Pre-Study Protocol of a Multinational Prospective Clinical Trial. Digestion. 2016;93(2):121-6.
16. Suzuki M, Minowa K, Isayama H, Shimizu T. Acute recurrent and chronic pancreatitis in children. Pediatr Int. 2021;63(2):137-49.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372:n71.
18. Munn Z, Stern C, Aromataris E, Lockwood C, Jordan Z. What kind of systematic review should I conduct? A proposed typology and guidance for systematic reviewers in the medical and health sciences. BMC Med Res Methodol. 2018;18(1):5.
19. Bradley EL, 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg. 1993;128(5):586-90.
20. Higgins J. Cochrane handbook for systematic reviews of interventions. Cochrane Collaboration and John Wiley & Sons Ltd. 2008.
21. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-82.
22. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015;13(3):147-53.
23. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2024.
24. Schwarzer G. Meta: General package for meta-analysis. GitHub; 2022.

25. Cuijpers P, Furukawa T, Ebert DD. Dmetar: Companion r Package for the Guide Doing Meta-Analysis in r. 2020.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629-34.
28. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open. 2016;6(7):e010247.
29. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
30. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ Int. 2018;121(Pt 1):1027-31.
31. Morinville VD, Husain SZ, Bai H, Barth B, Alhosh R, Durie PR, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr. 2012;55(3):261-5.
32. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.
33. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.
34. Harbord RM, Harris RJ, Sterne JA. Updated tests for small-study effects in meta-analyses. The Stata Journal. 2009;9(2):197-210.
35. Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clinical Gastroenterology and Hepatology. 2016;14(5):738-46.
36. Bang KB, Kim HJ, Cho YK, Jeon WK. Does Endoscopic Sphincterotomy and/or Cholecystectomy Reduce Recurrence Rate of Acute Biliary Pancreatitis? Korean J Gastroenterol. 2015;65(5):297-305.

37. Bertilsson S, Swärd P, Kalaitzakis E. Factors That Affect Disease Progression After First Attack of Acute Pancreatitis. Clin Gastroenterol Hepatol. 2015;13(9):1662-9.e3.

38. Del Vecchio Blanco G, Gesuale C, Giannarelli D, Varanese M, Fiume D, Monteleone G, et al. Idiopathic acute pancreatitis: a single-center investigation of clinical and biochemical features. Intern Emerg Med. 2021;16(1):93-9.

39. Castoldi L, De Rai P, Zerbi A, Frulloni L, Uomo G, Gabbrielli A, et al. Long term outcome of acute pancreatitis in Italy: results of a multicentre study. Dig Liver Dis. 2013;45(10):827-32.

40. Cavestro GM, Leandro G, Di Leo M, Zuppardo RA, Morrow OB, Notaristefano C, et al. A single-centre prospective, cohort study of the natural history of acute pancreatitis. Digestive and Liver Disease. 2015;47(3):205-10.

41. Halonen KI, Pettilä V, Leppäniemi AK, Kemppainen EA, Puolakkainen PA, Haapiainen RK. Long-term health-related quality of life in survivors of severe acute pancreatitis. Intensive Care Med. 2003;29(5):782-6.

42. Hu X, Yang B, Li J, Bai X, Li S, Liu H, et al. Individualized Prediction of Acute Pancreatitis Recurrence Using a Nomogram. Pancreas. 2021;50(6):873-8.

43. Hui CK, Lai KC, Yuen MF, Wong WM, Chan AOO, Ng M, et al. The role of cholecystectomy in reducing recurrent gallstone pancreatitis. Endoscopy. 2004;36(3):206-11.

44. Kaw M, Al-Antably Y, Kaw P. Management of gallstone pancreatitis: cholecystectomy or ERCP and endoscopic sphincterotomy. Gastrointest Endosc. 2002;56(1):61-5.

45. Kim SB, Kim TN, Chung HH, Kim KH. Small Gallstone Size and Delayed Cholecystectomy Increase the Risk of Recurrent Pancreatobiliary Complications After Resolved Acute Biliary Pancreatitis. Dig Dis Sci. 2017;62(3):777-83.

46. Kim YS, Chang JH, Kim TH, Kim CW, Kim JK, Han SW, et al. Prolonged hyperamylasemia in patients with acute pancreatitis is associated with recurrence of acute pancreatitis. Medicine (United States). 2020;99(3).

47. Lee JM, Chung WC, Sung HJ, Kim YJ, Youn GJ, Jung YD, et al. Factor analysis of recurrent biliary events in long-term follow up of gallstone pancreatitis. J Dig Dis. 2017;18(1):40-6.

48. Nikkola J, Laukkarinen J, Lahtela J, Seppänen H, Järvinen S, Nordback I, et al. The Long-term Prospective Follow-up of Pancreatic Function After the First Episode of Acute Alcoholic Pancreatitis: Recurrence Predisposes One to Pancreatic Dysfunction and Pancreatogenic Diabetes. J Clin Gastroenterol. 2017;51(2):183-90.
49. Sargen K, Kingsnorth AN. Management of gallstone pancreatitis: effects of deviation from clinical guidelines. Jop. 2001;2(5):317-22.
50. Stigliano S, Belisario F, Piciucchi M, Signoretti M, Delle Fave G, Capurso G. Recurrent biliary acute pancreatitis is frequent in a real-world setting. Dig Liver Dis. 2018;50(3):277-82.
51. Valverde-López F, Ortega-Suazo EJ, Wilcox CM, Fernandez-Cano MC, Martínez-Cara JG, Redondo-Cerezo E. Endoscopic ultrasound as a diagnostic and predictive tool in idiopathic acute pancreatitis. Ann Gastroenterol. 2020;33(3):305-12.
52. Vipperla K, Somerville C, Furlan A, Koutroumpakis E, Saul M, Chennat J, et al. Clinical Profile and Natural Course in a Large Cohort of Patients With Hypertriglyceridemia and Pancreatitis. J Clin Gastroenterol. 2017;51(1):77-85.
53. Ruiz-Rebollo ML, Muñoz-Moreno MF, Busta-Nistal R, Rizzo-Rodríguez MA, Izquierdo-Santerv Ás S. Recurrent acute pancreatitis is not uncommon in our clinical setting. Rev Gastroenterol Peru. 2023;43(1):31-7.
54. Wang Y, Attar BM, Hinami K, Jaiswal P, Yap JE, Jaiswal R, et al. Concurrent Diabetic Ketoacidosis in Hypertriglyceridemia-Induced Pancreatitis: How Does It Affect the Clinical Course and Severity Scores? Pancreas. 2017;46(10):1336-40.
55. Yoon LY, Moon JH, Choi HJ, Kim DC, Seo JY, Lee TH, et al. Clinical usefulness of intraductal ultrasonography for the management of acute biliary pancreatitis. J Gastroenterol Hepatol. 2015;30(5):952-6.
56. Yu B, Li J, Li N, Zhu Y, Chen Y, He W, et al. Progression to recurrent acute pancreatitis after a first attack of acute pancreatitis in adults. Pancreatology. 2020;20(7):1340-6.
57. Al Hindi S, Khalaf Z, Nazzal K, Nazzal O, Ahmed A, Alshaibani L. Acute Pancreatitis in Children: The Clinical Profile at a Tertiary Hospital. Cureus. 2021;13(5):e14871.

58. Poddar U, Yachha SK, Borkar V, Srivastava A, Kumar S. A report of 320 cases of childhood pancreatitis: increasing incidence, etiologic categorization, dynamics, severity assessment, and outcome. Pancreas. 2017;46(1):110-5.
59. Zhong R, Tan S, Peng Y, Xu H, Jiang X, Yan Y, et al. Clinical characteristics of acute pancreatitis in children: a single-center experience in Western China. BMC gastroenterology. 2021;21:1-7.
60. Ridtitid W, Kulpatcharapong S, Piyachaturawat P, Angsuwatcharakon P, Kongkam P, Rerknimitr R. The impact of empiric endoscopic biliary sphincterotomy on future gallstone-related complications in patients with non-severe acute biliary pancreatitis whose cholecystectomy was deferred or not performed. Surg Endosc. 2019;33(10):3325-33.
61. Zeng J, Zhang J, Hu Y, Wang X, Deng Z. Risk factors for the progression from acute recurrent to chronic pancreatitis among children in China. Frontiers in Pediatrics. 2022;Volume 10 - 2022.
62. Alabdulkareem A, Almahmoud T, Al-Tahan H, Javad S, Al Hatlani M. Etiology and clinical characteristics of pediatric acute pancreatitis in Saudi Arabia: a 20-year experience from a single tertiary center. Int J Pediatr Adolesc Med. 2018;5(1):13-7.
63. Anafy A, Mirkin Y, Galai T, Ben-Tov A, Moran-Lev H, Yerushalmy-Feler A, et al. Acute pancreatitis in children with inflammatory bowel disease: Risk factors, clinical course, and prognosis. J Pediatr Gastroenterol Nutr. 2024;79(2):325-34.
64. Anushree N, Lal SB, Rana SS, Saxena A, Venkatesh V, Sharma AK, et al. Morphological and functional recovery following acute and acute recurrent pancreatitis in children: A prospective sequential 2-point evaluation. Pancreatology. 2022;22(6):698-705.
65. Appak YC, Karakoyun M, Cetin G, Akmaz N, Baran M. Diagnosis and management of pancreatitis in childhood: a single-centre experience. Iranian Journal of Pediatrics. 2018;28(2).
66. Badru F, Saxena S, Breeden R, Bourdillon M, Fitzpatrick C, Chatoorgoon K, et al. Optimal timing of cholecystectomy in children with gallstone pancreatitis. Journal of Surgical Research. 2017;215:225-30.

67. Berney T, Belli D, Bugmann P, Beghetti M, Morel P, LeCoultre C. Influence of severe underlying pathology and hypovolemic shock on the development of acute pancreatitis in children. Journal of pediatric surgery. 1996;31(9):1256-61.
68. Bhanot A, Majbar A, Candler T, Hunt L, Cusick E, Johnson P. Acute pancreatitis in children–morbidity and outcomes at 1 year. BMJ Paediatr Open. 2022; 6: e001487.
69. Bolia R, Srivastava A, Yachha SK, Poddar U, Kumar S. Prevalence, natural history, and outcome of acute fluid collection and pseudocyst in children with acute pancreatitis. Journal of Pediatric Gastroenterology and Nutrition. 2015;61(4):451-5.
70. Alvarez Calatayud G, Bermejo F, Morales JL, Claver E, Huber LB, Abunaji J, et al. Acute pancreatitis in childhood. Rev Esp Enferm Dig. 2003;95(1):40-4, 5-8.
71. Grzybowska-Chlebowczyk U, Jasielska M, Flak-Wancerz A, Więcek S, Gruszczyńska K, Chlebowczyk W, et al. Acute pancreatitis in children. Gastroenterology Review/Przegląd Gastroenterologiczny. 2018;13(1):69-75.
72. Devecí U, Ünsal S, Dogan Y. A Retrospective Review of Children followed up with the Diagnosis of Acute Pancreatitis. Nigerian Journal of Clinical Practice. 2023;26(12):1876-85.
73. Galai T, Cohen S, Yerushalmy-Feler A, Weintraub Y, Moran-Lev H, Amir AZ. Young Age Predicts Acute Pancreatitis Severity in Children. J Pediatr Gastroenterol Nutr. 2019;68(5):720-6.
74. Geetha M, Saumya M, Balakrishnan V. Spectrum of pancreatitis in children and adolescents. Indian Journal of Gastroenterology. 2012;31:175-8.
75. Getsuwan S, Tanpowpong P, Lertudomphonwanit C, Junhasavasdikul T, Tim-Aroon T, Treepongkaruna S. Etiology and outcome of acute recurrent pancreatitis and chronic pancreatitis. Pediatrics International. 2022;64(1):e15145.
76. Guo Q, Li M, Chen Y, Hu H, Hu W. Predictors for mortality following acute pancreatitis in children. Pediatric surgery international. 2014;30:1111-5.
77. Hao F, Guo H, Luo Q, Guo C. Disease progression of acute pancreatitis in pediatric patients. Journal of Surgical Research. 2016;202(2):422-7.
78. Kandula L, Lowe ME. Etiology and outcome of acute pancreatitis in infants and toddlers. The Journal of pediatrics. 2008;152(1):106-10. e1.
79. Kim HJ. Potential Predictors of Severe and Recurrent Pancreatitis in Children: A Single-Center Experience. Pediatric Emergency Care. 2024;40(4):302-6.

80. Laugel V, Escande B, Entz-Werle N, Mazingue F, Ferster A, Bertrand Y, et al. Severe acute pancreatitis in children receiving asparaginase: multicenter retrospective study. Archives de Pediatrie: Organe Officiel de la Societe Francaise de Pediatrie. 2005;12(1):34-41.

81. López MM, Herrero MM, Puente MH, Hernani MT, Sánchez CS, Calatayud GÁ. Pancreatitis aguda: nuestra experiencia/Acute pancreatitis: our experience. Acta pediátrica española. 2013;71(1):3.

82. Majbar AA, Cusick E, Johnson P, Lynn RM, Hunt LP, Shield JP. Incidence and clinical associations of childhood acute pancreatitis. Pediatrics. 2016;138(3).

83. Mengdi L QZ, Liang G. Predictive efficacy of BISAP, Pane 3 and HAP scores in children with acute pancreatitis. ZHONGHUA XIAOER WAIKE ZAZHI / CHINESE JOURNAL OF PEDIATRIC SURGERY. 2022;43(11).

84. Minen F, De Cunto A, Martelossi S, Ventura A. Acute and recurrent pancreatitis in children: exploring etiological factors. Scandinavian journal of gastroenterology. 2012;47(12):1501-4.

85. Mirza N, Mehta S, Kumar K, Malhotra S, Sibal A. Clinical profile of acute pancreatitis in children and adolescents from a single center in Northern India. Journal of Indian Association of Pediatric Surgeons. 2023;28(1):35-40.

86. Nasr A, Hornung L, Thompson T, Lin TK, Vitale DS, Nathan JD, et al. Prevalence of gastrointestinal symptoms and impact on quality of life at 1-year follow-up of initial attack of acute pancreatitis. Journal of pediatric gastroenterology and nutrition. 2023;76(2):199-205.

87. Nauka PC, Weinstein TA, Dolinger MT, Miller JM, Kohn N, Bitton S, et al. Validation of lipase and systemic inflammatory response syndrome as prognostic indicators in pediatric acute pancreatitis: a retrospective analysis. Journal of pediatric gastroenterology and nutrition. 2019;68(3):389-93.

88. Ohta K, Okanishi T, Sasaki M, Kawaguchi T, Murakami J, Maegaki Y. Tendency and risk factors of acute pancreatitis in children with severe motor and intellectual disabilities: A single-center study. Brain and Development. 2023;45(2):126-33.

89. Park A, Latif SU, Shah AU, Tian J, Werlin S, Hsiao A, et al. Changing referral trends of acute pancreatitis in children: a 12-year single-center analysis. Journal of pediatric gastroenterology and nutrition. 2009;49(3):316-22.

90. Pezzilli R, Morselli-Labate A, Castellano E, Barbera C, Corrao S, Di Prima L, et al. Acute pancreatitis in children. An Italian multicentre study. Digestive and Liver Disease. 2002;34(5):343-8.
91. Poddar U, Yachha SK, Borkar V, Srivastava A. Is acute recurrent pancreatitis in children a precursor of chronic pancreatitis? A long-term follow-up study of 93 cases. Digestive and Liver Disease. 2017;49(7):796-801.
92. Singh SK, Srivastava A, Rai P, Yachha SK, Poddar U. Yield of endoscopic ultrasound in children and adolescent with acute recurrent pancreatitis. Journal of Pediatric Gastroenterology and Nutrition. 2018;66(3):461-5.
93. Stringer MD, Davison SM, McClean P, Rajwal S, Puntis JW, Sheridan M, et al. Multidisciplinary management of surgical disorders of the pancreas in childhood. Journal of pediatric gastroenterology and nutrition. 2005;40(3):363-7.
94. Tiao M-M, Chuang J-H, Ko S-F, Kuo H-W, Liang C-D, Chen C-L. Pancreatitis in children: clinical analysis of 61 cases in southern Taiwan. Chang Gung Medical Journal. 2002;25(3):162-8.
95. Wang C, Fu B, Su D, Huang P, Fu X. Acute Pancreatitis and Recurrent Acute Pancreatitis in Children: A 10-Year Retrospective Study. Gastroenterology Research and Practice. 2022;2022(1):5505484.
96. Yeung C-y, Lee H-c, Huang F-y, Ho M-y, Kao H-a, Liang D-c, et al. Pancreatitis in children—experience with 43 cases. European journal of pediatrics. 1996;155:458-63.
97. Zheng Q, Yan X, Ge L, Zhang S, Sun Y, Jia J, et al. Risk factors of recurrent acute pancreatitis after conservative treatment in pediatric population: a single-center study. World Journal of Pediatric Surgery. 2021;4(1):e000209.
98. Zhu Y-M, Liu F, Zhou X-Y, You J-Y, Xu Z-Y, YK D. Clinical characteristics of children with acute pancreatitis. Zhonghua er ke za zhi= Chinese Journal of Pediatrics. 2011;49(1):10-6.
99. Whitcomb DC. Central role of the sentinel acute pancreatitis event (SAPE) model in understanding recurrent acute pancreatitis (RAP): Implications for precision medicine. Front Pediatr. 2022;10:941852.
100. Sun Y, Jin J, Zhu A, Hu H, Lu Y, Zeng Y, et al. Risk Factors for Recurrent Pancreatitis After First Episode of Acute Pancreatitis. Int J Gen Med. 2022;15:1319-28.

101. Nikkola J, Laukkarinen J, Huhtala H, Sand J. The Intensity of Brief Interventions in Patients with Acute Alcoholic Pancreatitis Should be Increased, Especially in Young Patients with Heavy Alcohol Consumption. Alcohol Alcohol. 2017;52(4):453-9.
102. Smith I, Ramesh J, Kyanam Kabir Baig KR, Mönkemüller K, Wilcox CM. Emerging Role of Endoscopic Ultrasound in the Diagnostic Evaluation of Idiopathic Pancreatitis. Am J Med Sci. 2015;350(3):229-34.
103. Aronen A, Guilabert L, Hadi A, Kiudelis V, Panaitescu A, Wlodarczyk B, et al. Idiopathic acute pancreatitis (IAP)-a review of the literature and algorithm proposed for the diagnostic work-up of IAP. Transl Gastroenterol Hepatol. 2024;9:71.
104. Umans DS, Timmerhuis HC, Anten MGF, Bhalla A, Bijlsma RA, Boxhoorn L, et al. Prospective multicentre study of indications for surgery in patients with idiopathic acute pancreatitis following endoscopic ultrasonography (PICUS). Br J Surg. 2023;110(12):1877-82.
105. Abu-El-Haija M, Kumar S, Quiros JA, Balakrishnan K, Barth B, Bitton S, et al. Management of Acute Pancreatitis in the Pediatric Population: A Clinical Report From the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Pancreas Committee. J Pediatr Gastroenterol Nutr. 2018;66(1):159-76.
106. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology. 2013;144(6):1292-302.
107. Liu QY, Abu-El-Haija M, Husain SZ, Barth B, Bellin M, Fishman DS, et al. Risk Factors for Rapid Progression From Acute Recurrent to Chronic Pancreatitis in Children: Report From INSPPIRE. J Pediatr Gastroenterol Nutr. 2019;69(2):206-11.
108. Lin TK, Abu-El-Haija M, Nathan JD, Palermo JP, Barth B, Bellin M, et al. Pancreas Divisum in Pediatric Acute Recurrent and Chronic Pancreatitis: Report From INSPPIRE. Journal of Clinical Gastroenterology. 2019;53(6):e232-e8.
109. Struyvenberg MR, Martin CR, Freedman SD. Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC Med. 2017;15(1):29.
110. Husain SZ, Srinath AI. What's unique about acute pancreatitis in children: risk factors, diagnosis and management. Nat Rev Gastroenterol Hepatol. 2017;14(6):366-72.
111. Glaubitz J, Asgarbeik S, Lange R, Mazloum H, Elsheikh H, Weiss FU, et al. Immune response mechanisms in acute and chronic pancreatitis: strategies for therapeutic intervention. Front Immunol. 2023;14:1279539.

16. BIBLIOGRAPHY

16.1. Publications Related to the Thesis

1. Incidence of recurrent and chronic pancreatitis after acute pancreatitis: a systematic review and meta-analysis

Gagyi Endre Botond, Teutsch Brigitta, Veres Daniel Sandor, Palinkas Daniel, Vorhendi Nora, Ocskay Klementina, Marta Katalin, Hegyi Peter Jeno, Hegyi Péter, Eross Balint

THERAPEUTIC ADVANCES IN GASTROENTEROLOGY 17: 1 Paper: 17562848241255303, 16 p. (2024)

DOI: 10.1177/17562848241255303

Journal subject: Scopus - Gastroenterology Rank: Q1

IF: 3.4 (2024)

2. Progression from acute to chronic pancreatitis in children: a systematic review and meta-analysis.

Gagyi Endre Botond, Obeidat Mahmoud, Tari Edina, Váncsa Szilárd, Veres Daniel Sandor, Banovcin Peter, Hegyi Peter Jeno, Hegyi Peter, Eross Balint

CLINICAL AND EXPERIMENTAL PEDIATRICS (2025)

DOI: 10.3345/cep.2025.01879

Journal subject: Scopus - Pediatrics Rank: D1

Journal subject: Scopus - Pediatrics, Perinatology and Child Health Rank: Q1

IF: 3.6 (2024)

16.2. Publications not Related to the Thesis

1. Association of Pancreatic Cancer with Acute Pancreatitis: A Systematic Review and Meta-analysis

Lee Jimin, Creanga-Matariu Ioana, Németh Jázmin, **Gagyi Endre Botond**, Veres Dániel Sándor, Szalai Eszter Ágnes, Obeidat Mahmoud, Papp Renáta, Hegyi Péter

CLINICAL AND TRANSLATIONAL GASTROENTEROLOGY (2025)

DOI: 10.14309/ctg.0000000000000927

Journal subject: Scopus - Gastroenterology Rank: Q1

IF: 3.0 (2024)

2. New machine-learning models outperform conventional risk assessment tools in Gastrointestinal bleeding

Eszter Boros, József Pintér, Roland Molontay, Kristóf Gergely Prószéky, Nóra Vörhendi, Orsolya Anna Simon, Brigitta Teutsch, Dániel Pálinkás, Levente Frim, Edina Tari, **Endre Botond Gagyi,** Imre Szabó, Roland Hágendorn, Áron Vincze, Ferenc Izbéki, Zsolt Abonyi-Tóth, Andrea Szentesi, Vivien Vass, Péter Hegyi & Bálint Erőss

SCIENTIFIC REPORTS (2045-2322): 15 1 Paper 6371. 10 p. (2025)

DOI: 10.1038/s41598-025-90986-1

Journal subject: Scopus - Multidisciplinary Rank: Q1

IF: 3.9 (2024)

3. Hemoglobin decrease predicts untoward outcomes better than severity of anemia

Brigitta Teutsch, Zsolt Abonyi Tóth, Orsolya Ferencz, Nóra Vörhendi, Orsolya Anna Simon, Eszter Boros, Dániel Pálinkás, Levente Frim, Edina Tari, Patrícia Kalló, **Endre Botond Gagyi**, Tamás Hussein, Szilárd Váncsa, Vivien Vass, Andrea Szentesi, Áron Vincze, Ferenc Izbéki, Péter Hegyi, Roland Hágendorn, Imre Szabó, Bálint Erőss

SCIENTIFIC REPORTS (2045-2322): 14 1 Paper 31056. 10 p. (2024)

DOI: 10.1038/s41598-024-82237-6

Journal subject: Scopus - Multidisciplinary Rank: Q1

IF: 3.9 (2024)

4. Morphology of the papilla can predict procedural safety and efficacy of ERCP-a systematic review and meta-analysis.

Edina Tari, **Endre Botond Gagyi**, Anett Rancz, Dániel Sándor Veres, Szilárd Váncsa, Péter Jenő Hegyi, Krisztina Hagymási, Péter Hegyi, Bálint Erőss

SCIENTIFIC REPORTS (2045-2322): 14 1 Paper 7341. 12 p. (2024)

DOI: 10.1038/s41598-024-57758-9

Journal subject: Scopus - Multidisciplinary Rank: Q1

IF: 3.9 (2024)

5. No Association between Gastrointestinal Rebleeding and DOAC Therapy Resumption: A Systematic Review and Meta-Analysis

Pálinkás Dániel, Teutsch Brigitta, **Gagyi Endre Botond**, Engh Marie Anne, Kalló Patrícia, Veres Dániel S, Földvári-Nagy László, Hosszúfalusi Nóra, Hegyi Péter, Erőss Bálint

BIOMEDICINES 11: 2 Paper: 554, 14 p. (2023)

DOI: 10.3390/biomedicines11020554

Journal subject: Scopus - Biochemistry, Genetics and Molecular Biology (miscellaneous) Rank: Q1

Journal subject: Scopus - Medicine (miscellaneous) Rank: Q1

IF: 3.9 (2023)

6. One third of cases of new-onset diabetic ketosis in adults are associated with ketosis-prone type 2 diabetes-A systematic review and meta-analysis

Kovacs Adrienn, Bunduc Stefania, Veres Daniel S, Palinkas Daniel, **Gagyi Endre B**, Hegyi Peter J, Eross Balint, Mihaly Emese, Hegyi Peter, Hosszufalusi Nora

DIABETES-METABOLISM RESEARCH AND REVIEWS 40: 3 Paper: e3743, 10 p. (2024)

DOI: 10.1002/dmrr.3743

Journal subject: Scopus - Endocrinology Rank: Q1

Journal subject: Scopus - Endocrinology, Diabetes and Metabolism Rank: Q1

Journal subject: Scopus - Internal Medicine Rank: Q1

IF: 6.0 (2024)

17. ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my scientific methodology supervisors, Dr Brigitta Teutsch and Dr Mahmoud Obeidat, for their continuous guidance, critical insight, and dedicated support throughout my PhD years. Their expertise, constructive feedback, and commitment to scientific rigor were invaluable not only for this dissertation, but also for my overall academic development.

I am especially grateful to my supervisor, Dr Bálint Erőss, for his mentorship, encouragement, and trust during my PhD studies. His scientific vision, high standards, and long-term support profoundly shaped my approach to research and academic work. I would also like to thank Prof. Péter Hegyi, without whose support and vision this academic journey could not have begun.

I would also like to thank my family for their constant support, patience, and understanding throughout these PhD years. Their encouragement provided the stability and motivation needed to persevere.

Finally, I am thankful to my friends and colleagues for their collaboration, support, and shared experiences, which made my PhD journey both professionally rewarding and personally meaningful.