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The Disease Continuum from Acute to Recurrent and Chronic Pancreatitis: Progression Patterns in Children and Adults

Ph.D. Thesis Booklet

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1. Introduction

1.1. Overview of the topic

1.1.1. What is the topic?

Acute pancreatitis (AP) stands as one of the most common gastrointestinal diseases, with an incidence of 13 - 45 per 100,000 persons per year, while chronic pancreatitis (CP) affects 5 - 12 per 100,000 annually. AP carries significant morbidity, mortality, and prolonged hospitalization, whereas CP progresses incurably, impairing quality of life and shortening life expectancy. Emerging evidence positions AP, recurrent acute pancreatitis (RAP), and CP along a disease continuum, where repeated inflammation leads to irreversible pancreatic damage; the sentinel acute pancreatitis event (SAPE) model identifies RAP as the key intermediate stage. Pediatric AP, once rare, now matches adult rates at 3 per 100,000 yearly, with CP at 2 per 100,000; children often progress from AP to RAP or CP, driven by genetic, structural, or metabolic factors unlike adult alcohol and smoking risks.

1.1.2. What is the problem to solve?

Despite recognizing the AP - RAP - CP continuum, key gaps persist: progression estimates vary widely due to inconsistent follow-up, study designs, and diagnostics. Etiology- and severity-specific risks remain poorly quantified in adults with conflicting results, while pediatric factors differ fundamentally from adults, invalidating extrapolations. No comprehensive synthesis integrates adult and pediatric data using standardized methods, limiting identification of high-risk patients, disease forecasting, and timely interventions.

1.1.3. What is the importance of the topic?

AP, RAP, and CP impose major clinical and economic burdens: AP demands hospitalization with high morbidity; RAP causes repeated admissions and cumulative injury; CP brings chronic pain, exocrine/endocrine failure, distress, and reduced lifespan. In children, RAP and CP yield ongoing pain and quality-of-life declines. Clarifying progression, who, why, how fast, is vital since CP defies cure, making early risk detection essential to halt irreversible damage.

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

These findings deliver standardized, etiology- and age-specific (adult-child) progression estimates from AP to RAP/CP, sharpening high-risk patient identification. By pinpointing predictors across ages, results enable tailored surveillance and early interventions to avert permanent harm, potentially shaping clinical guidelines and boosting long-term outcomes.

2. Objectives

2.1. Study I. - The Incidence of Recurrent and Chronic Pancreatitis after Acute Pancreatitis: A Systematic Review and Meta-Analysis

This study characterizes progression from AP to RAP and CP by evaluating incidence rates, cumulative incidence, recurrence patterns, and progression rates, accounting for time-dependent evolution and stratifying by etiology and severity of the initial episode.

2.2. Study II. - Progression from Acute to Chronic Pancreatitis in Children: A Systematic Review and Meta-Analysis

This study synthesizes evidence on AP progression to RAP and CP in children, identifying key risk factors contributing to recurrence and chronicity.

3. Methods

3.1. Search Strategy

Both studies conducted systematic searches in MEDLINE (PubMed), Cochrane Library CENTRAL, and EMBASE from January 1, 1992, onward, using terms "acute AND chronic OR recurrent AND pancreatitis." Study I searched on December 19, 2023; Study II on December 21, 2024.

3.2. Study I.

Eligibility criteria followed the CoCoPop framework, including studies on first-episode acute pancreatitis (AP) diagnosed per Atlanta Classification (at least two of: characteristic pain, amylase/lipase >3x upper limit of normal, or typical imaging) that reported proportions or rates of RAP or CP. Primary outcomes were incidence

rates (IRs) of RAP after AP and CP after AP or RAP; no minimum follow-up was required, with samples of at least 10 patients eligible, excluding conference abstracts, case reports, reviews, and animal/in vitro studies. Study selection and data extraction adhered to Cochrane Handbook guidelines, using EndNote for deduplication and two-step screening (title/abstract then full-text) by independent reviewers, with Cohen's kappa assessing agreement and a third reviewer resolving discrepancies; data on author/year, design, location, sample size, follow-up, and outcomes (stratified by etiology/severity) were extracted via Excel, retaining the largest sample for overlaps and contacting authors for missing data. Quality assessment employed the Joanna Briggs Institute (JBI) Prevalence Tool across nine criteria, with higher scores indicating lower bias and disagreements resolved by consensus; overall risk was moderate due to incomplete follow-up and small samples. Data synthesis used R (v4.1.1) with meta and dmetar packages, applying random-effects models for IRs (calculated from events, patient numbers, and mean follow-up as person-time proxy) and proportions (forest plots for ≥3 studies),

quantifying heterogeneity via I^2, reporting prediction intervals, Egger's test for publication bias (≥10 studies), leave-one-out sensitivity (≥8 studies), and meta-regression for confounders like age/sex/severity (≥10 studies); 5-year cumulative incidence was estimated as $1 - e^{(-IR \times T)}$.

3.2.1. Study II

Eligibility criteria used CoCoPop and PECO frameworks for pediatric patients under 18 years with AP, RAP, or CP, including observational studies and case series reporting progression rates (AP to RAP/CP, RAP to CP) or comparative risk factor data (e.g., age, sex, etiology, severity), following study-specific diagnostics like INSPPIRE (used in 76% of studies), while excluding adult-only studies, case reports, reviews, editorials, and abstracts. Selection and extraction mirrored Study I: Cochrane Handbook methods, EndNote screening by independent reviewers with Cohen's kappa, third-reviewer resolution, Excel extraction of study characteristics and outcomes, largest-sample retention for overlaps, and author contacts. Quality assessment applied

JBI Prevalence Tool for progression studies and Quality In Prognostic Studies (QUIPS) tool for comparisons, with consensus resolution and moderate overall risk from small samples and confounding. Analyses in R (v4.2.1) with meta/dmetar used random-effects for pooled proportions, odds ratios (dichotomous outcomes), and mean differences (continuous), generating forest plots (≥3 studies), I^2 for heterogeneity, Peters test (≥10 studies), leave-one-out sensitivity, subgroups (e.g., diagnostic criteria, follow-up duration), and meta-regression, considering $P<0.05$ significant.

4. Results

4.1. Study I.

The search identified 18,483 records, yielding 119 studies for proportion analyses and 29 for incidence rates (IRs), primarily adult cohorts (24 studies: 9 prospective, 15 retrospective; Europe/Asia/North America; follow-up 19–120 months). Overall RAP IR after first AP was 5.26 per 100 person-years (CI: 3.99–6.94), comparable in children (4.64, CI: 2.73–7.87, p=0.671). CP IR after AP: 1.38 (CI: 0.97–1.96); after RAP: 4.31 (CI: 3.10–5.99). Etiology-

specific RAP IRs highest in hypertriglyceridemia (8.58, CI: 6.86–10.72) and alcohol (6.34, CI: 4.80–8.37); CP peaked with alcohol (2.66, CI: 1.58–4.48). Moderate AP showed highest RAP (7.56, CI: 4.63–12.34). Proportions: 20% overall RAP (28% hypertriglyceridemia, 24% alcohol, 21% idiopathic, 8% biliary); CP 8% after AP, 24% after RAP. Risks elevated by alcohol (6.87 vs 4.22), smoking (6.76 vs 4.23), no cholecystectomy in biliary (3.92 vs 1.67). The risk of bias was moderate due to follow-up and sample limitations; no publication bias was detected.

4.2. Study II

From 19,125 records, 68 studies included (4,104 children; 44 progression, 24 comparisons; mostly retrospective/single-center; Asia 55%, 1979–2022 enrollment). RAP after AP: 18% (16–22%), 21% (INSPPIRE only); direct AP to CP: 10% (6–16%); RAP to CP: 35% (24–49%). Etiology-specific RAP: hypertriglyceridemia 33% (6–79%), idiopathic 28% (18–39%), biliary 19% (11–32%), trauma 16%, drug 14%, virus 3% (p=0.001). Severe AP RAP: 39% (15–71%) vs

mild 21%. Key risks: anatomical anomalies OR 3.15 (1.51–6.56) for RAP, pancreas divisum OR 2.64 (1.51–4.63) for CP; PRSS1 OR 4.56 (3.06–6.80) for CP. No publication bias was detected.

5. Conclusions

5.1. Study I.

Progression from AP to RAP occurs frequently at 20% overall, with incidence rates of 5.26 per 100 person-years, while CP develops more rapidly after RAP (4.31 per 100 person-years) than after first AP (1.38). Persistent etiologies like hypertriglyceridemia (RAP IR 8.58) and alcohol (RAP IR 6.34, CP IR 2.66) drive highest risks, underscoring the role of ongoing metabolic or exposure-related insults in fostering recurrence and fibrosis. Modifiable factors substantially influence disease progression: alcohol consumption is associated with a higher incidence of recurrent acute pancreatitis (6.87 vs 4.22), smoking shows a similarly increased incidence (6.76 vs 4.23), whereas cholecystectomy is linked to a lower rate of biliary recurrence (1.67 vs 3.92). Moderate severity predicts highest RAP (7.56). By standardizing

time-dependent incidence rates across heterogeneous follow-ups, these findings enable precise risk stratification, personalized monitoring, and early preventive strategies to avert irreversible pancreatic damage in adults.

5.2. Study II.

In children, AP progresses to RAP in 18-21% and CP in 10% directly or 35% after RAP, mirroring adult frequencies but driven by distinct mechanisms: genetic (PRSS1 OR 4.56) and anatomical factors (anomalies OR 3.15, pancreas divisum OR 2.64) rather than exposures. Hypertriglyceridemia (33%) and idiopathic AP (28%) lead etiology-specific recurrence, with severe episodes trending higher (39%), emphasizing early structural evaluation over routine labs or demographics, which showed no predictive value. As the first pediatric-specific meta-analysis, these results advocate genetic screening, anatomical imaging, and tailored interventions distinct from adult models, supporting early risk identification to preserve pancreatic function and quality of life in young patients.

6. Bibliography

6.1. Publications related to the thesis:

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

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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.

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Journal subject: Scopus - Pediatrics Rank: D1

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

IF: 3.6 (2024)