United European Gastroenterology Journal

WILEY | ueg journal

ORIGINAL ARTICLE OPEN ACCESS

The Existence and Significance of Early Chronic Pancreatitis Within the AP–RAP–CP Sequence

Viktória Venglovecz[1,2,3] | Zsolt Abonyi-Tóth[4,5] | Petra Széplaki[4] | Vivien Vass[3] | Dalma Dobszai[3,4] | Daniel Marino[6] | Tamás Gonda[6] | Zsófia Román[4,7] | Bálint Erőss[3,4,7] | Péter Jenő Hegyi[4,7] | Áron Vincze[8] | Ferenc Izbéki[9] | Mária Papp[10] | Alexandra Mikó[3,11] | Katalin Márta[7] | Andrea Szentesi[3,4] | Péter Hegyi[2,3,4,7] | on behalf of the Hungarian Pancreatic Study Group

[1]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary | [2]Translational Pancreatology Research Group, Interdisciplinary Center of Excellence for Research Development and Innovation, University of Szeged, Szeged, Hungary | [3]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary | [4]Centre for Translational Medicine, Semmelweis University, Budapest, Hungary | [5]Department of Biostatistics, University of Veterinary Medicine, Budapest, Hungary | [6]Division of Gastroenterology, New York University Langone Health, New York, New York, USA | [7]Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary | [8]Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary | [9]Szent György Teaching Hospital of County Fejér, Székesfehérvár, Hungary | [10]Department of Gastroenterology, Institute of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary | [11]Department of Medical Genetics, Medical School, University of Pécs, Pécs, Hungary

Correspondence: Andrea Szentesi (szentesiai@gmail.com) | Péter Hegyi (hegyi2009@gmail.com)

Received: 29 June 2026 | **Revised:** 10 September 2026 | **Accepted:** 1 October 2026

Keywords: early chronic pancreatitis | endoscopic intervention | metabolic dysfunction | pancreatitis continuum | recurrent acute pancreatitis

ABSTRACT

Background: We previously proposed that three or more episodes of acute pancreatitis (AP) without radiological evidence of CP constitute early chronic pancreatitis (ECP), but it remains unclear whether ECP represents advanced recurrent acute pancreatitis (RAP) or a distinct clinical stage.

Methods: We performed a post hoc analysis of prospectively collected data from the AP Registry of the Hungarian Pancreatic Study Group, including 1717 patients enrolled between 2017 and 2025. Patients were categorized as AP (single episode; $n = 1143$), RAP (two episodes without CP morphology; $n = 215$), ECP (≥ 3 episodes without CP morphology; $n = 152$), or acute-on-chronic pancreatitis (ACP; radiological CP with at least one AP episode; $n = 207$). Demographic characteristics, risk factors, outcomes, and endoscopic interventions were compared across the groups.

Results: Male predominance increased progressively from RAP (58%) to ECP (72%) and ACP (79%). Similarly, alcohol-related etiology rose from 23% in RAP to 36% in ECP and 45% in ACP. Smoking prevalence increased markedly from 36% in RAP to 49% in ECP and 68% in ACP. A change in therapeutic indications became apparent in ECP. While endoscopic interventions in AP and RAP were predominantly prophylactic (71% and 67%, respectively), pancreatic duct–directed procedures emerged as a leading indication in ECP (42%) and became dominant in ACP (77%), consistent with increasing pancreatic duct involvement across disease stages.

Conclusions: ECP represents a distinct transitional phenotype between RAP and established CP and already exhibits characteristic epidemiological, etiological, and therapeutic features. Recognition of ECP may therefore identify a critical window for targeted intervention before irreversible morphological damage to the pancreas occurs.

The last two authors Co-corresponding authors contributed equally to this work.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2026 The Author(s). *United European Gastroenterology Journal* published by Wiley Periodicals LLC on behalf of United European Gastroenterology.

Key Summary

- Summarise the established knowledge on this subject.
  - Acute pancreatitis (AP) and chronic pancreatitis (CP) are increasingly recognized as part of a disease continuum rather than distinct diseases.
  - Recurrent acute pancreatitis (RAP) is associated with an increased risk of progression toward CP, particularly in patients with ongoing alcohol consumption and smoking.
  - Previous studies proposed that repeated inflammatory episodes may induce progressive pancreatic injury before classical radiological features of CP become detectable.
  - Early chronic pancreatitis (ECP), defined as three or more AP episodes without radiological evidence of CP, has been suggested as a possible intermediate disease stage, but its clinical relevance remains uncertain.
- What are the significant and/or new findings of this study?
  - ECP demonstrated epidemiological and etiological characteristics distinct from RAP, including increased male predominance, alcohol-related disease, and smoking prevalence.
  - ECP already shared several features with acute-on-chronic pancreatitis (ACP), whereas significant differences persisted between RAP and ECP for key etiological factors.
  - Endoscopic management patterns shifted at the ECP stage from predominantly prophylactic interventions toward pancreatic duct–related procedures, resembling ACP despite the absence of overt radiological CP.
  - ECP represents a clinically meaningful transitional phenotype requiring earlier targeted intervention.

1 | Introduction

Acute pancreatitis (AP) is one of the leading causes of gastrointestinal hospital admissions worldwide, with an increasing incidence over recent decades [1]. Although most patients experience a self-limiting disease course, a substantial proportion develop local or systemic complications, and recurrent episodes may ultimately progress to chronic pancreatitis (CP), a debilitating condition characterized by fibrosis, exocrine and endocrine insufficiency, and impaired quality of life [2–4]. Growing evidence suggests that AP and CP represent a disease continuum rather than distinct entities [5, 6]. The "sentinel acute pancreatitis event" (SAPE) concept proposes that an initial AP episode predisposes patients to recurrent attacks and chronic pancreatic injury [7]. Cohort studies have shown that patients with multiple episodes of AP are at increased risk of developing CP, particularly when modifiable risk factors such as smoking and alcohol consumption are present [8, 9]. Complementary evidence from experimental models also supports this framework; a murine model demonstrated that an initial AP episode can increase the severity of subsequent attacks, reinforcing the SAPE concept [10].

Hegyi J. et al. proposed a four-stage model of the pancreatitis continuum: (i) AP, defined as a single episode without chronic changes; (ii) recurrent AP (RAP), defined as two episodes without morphological alterations; (iii) early CP (ECP), representing three or more AP episodes without radiological evidence of CP; and (iv) established acute on chronic pancreatitis (ACP), defined by the presence of at least one AP episode and morphological changes consistent with CP [11]. International consensus statements similarly recognize ECP as a distinct disease stage preceding established CP [12]. This classification was based on the observation that the prevalence of CP increased sharply after the third episode of AP (0%, 1%, 16%, 50%, and 47% after 1, 2, 3, 4, and $\geq$ 5 episodes, respectively), identifying $\geq$ 3 episodes as a clinically meaningful threshold for disease progression. More recently, longitudinal follow-up studies have demonstrated accelerated metabolic and morphological progression following recurrent acute pancreatic injury, supporting the biological relevance of this transitional stage [13]. These findings highlight the importance of identifying early disease stages when interventions may still prevent or delay progression to irreversible pancreatic damage. Several studies have attempted to characterize risk factors and outcomes along this continuum. Cigarette smoking and regular alcohol consumption have consistently been identified as independent risk factors for progression [9, 14–16]. However, the precise clinical, laboratory, and imaging features that distinguish AP, RAP, ECP, and ACP remain incompletely understood. These findings highlight the need to validate the four-stage pancreatitis continuum model in large, well-characterized cohorts. Therefore, this study aimed to compare demographic, clinical, laboratory, and imaging characteristics, as well as disease outcomes, across AP, RAP, ECP, and ACP populations. We hypothesized that each stage exhibits distinct clinical features, supporting earlier recognition of ECP and enabling targeted interventions to prevent or delay the development of CP.

2 | Methods

2.1 | Data Collection and Ethical Permissions

Clinical data from 1717 patients diagnosed with AP were collected prospectively in the Acute Pancreatitis Registry, coordinated by the Hungarian Pancreatic Study Group (HPSG), between 2017 and 2025. All participating centers were tertiary referral institutions with a well-characterized AP population, providing high-quality prospectively collected clinical data for classification across the pancreatitis continuum (Supporting Information S1: Table S1). The study was conducted in accordance with the Declaration of Helsinki and approved by the relevant national and local ethics committees (reference numbers: 36305/2016/EKU and 17787-8/2020/EÜIG). Written informed consent was obtained from all participants. Clinical data were collected from structured patient interviews and medical records. Data quality was ensured through a four-level monitoring system; details of quality control procedures are provided in Supporting Information S1: Table S2. Importantly, this cohort is independent of that used to originally propose ECP as a distinct stage within the pancreatitis continuum [11],

20506414, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ueg2.70306 by CochraneItalia, Wiley Online Library on [07/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

thereby providing external validation of the concept and its clinical relevance.

2.2 | Study Population and Definitions

Patients were eligible for inclusion if they were ≥ 18 years of age and admitted with a diagnosis of AP. The diagnosis of AP followed the International Association of Pancreatology/American Pancreatic Association (IAP/APA) guideline recommendations [17–20] requiring at least two of the following three criteria: acute onset of abdominal pain consistent with AP; serum amylase and/or lipase levels ≥ 3 times the upper limit of normal; and characteristic imaging findings of AP on cross-sectional imaging. Severity and local/systemic complications, including organ failure, were defined and classified according to the Revised Atlanta Classification (2012) [17]. Patients were classified as AP (single episode without CP morphology), RAP (two episodes without CP morphology), ECP (≥ 3 episodes without CP morphology), or ACP (≥ 1 AP episode with radiological features of CP, including calcifications, ductal abnormalities, or parenchymal atrophy). Imaging assessment was based on radiological findings obtained during the acute phase as part of routine clinical care, including contrast-enhanced CT, MRI, and/or MRCP, according to clinical indications and local practice. No central radiological review was performed. Patient classification was based on the overall clinical and radiological assessments available during the disease course. Pancreatic duct findings identified during therapeutic ERCP were not considered in isolation but were interpreted together with cross-sectional imaging findings and the overall clinical context when assigning patients to the study groups. Patients aged < 18 years or with insufficient data or other eligibility/data-quality issues were excluded (Supporting Information S1: Figure S1).

2.3 | Outcomes

Demographic characteristics, risk factors, comorbidities, clinical and laboratory parameters, imaging findings, disease severity, interventions, length of hospital stay, and mortality were analyzed. Pre-existing diabetes mellitus (DM) was defined as previously documented type 2 DM or an HbA1c level ≥ 6.5% at admission. The primary objective was to identify clinically relevant differences among patients with AP, RAP, ECP, and ACP, while secondary analyses explored factors associated with disease stage across the pancreatitis continuum.

2.4 | Statistical Analysis

Statistical analyses were performed using R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean ± SD or median (IQR), and categorical variables as frequencies and percentages. Associations between pancreatic morphology groups and clinical outcomes were evaluated using ANOVA with Tukey's honestly significant difference post hoc test for continuous variables and Fisher's exact test for categorical variables. Associations between groups were assessed using multivariable regression models. Statistical significance was set at $p < 0.05$. Detailed statistical methods are provided in the Supporting Information S1: Methods.

3 | Results

3.1 | General Characteristics of the Analyzed Cohort

A total of 1717 patients were included in the analysis, comprising 1143 with AP (66.6%), 215 with RAP (12.5%), 152 with ECP (8.8%), and 207 with ACP (12.1%) (Table 1).

Overall, 56% of the cohort were male, and the mean age was 55.3 ± SD years (AP: 56.4 ± 17.1 years, RAP: 54.5 ± 18 years, ECP: 50.6 ± 16.4 years, ACP: 54.2 ± 14.6 years), with no significant age differences between disease stages. Biliary etiology was the most common cause of pancreatitis in the overall cohort and most patients presented with mild AP. The overall in-hospital mortality rate was 3.4%. Organ failure occurred in a substantial proportion of patients, reflecting the systemic impact of AP within the analyzed population.

3.2 | Epidemiology and Etiology

The proportion of male patients progressively increased along the pancreatitis continuum, from 50% in AP ($n = 565$) to 58% in

TABLE 1 | The table summarizes the baseline demographic, etiological, and clinical characteristics of the overall study population ($n = 1717$), including sex distribution, age, pancreatitis etiology, disease severity according to the revised Atlanta classification, in-hospital mortality, and the occurrence of organ failure.

Characteristic	Value
Groups	*n* (%)
• AP	1143 (67)
• RAP	215 (13)
• ECP	152 (9)
• ACP	207 (12)
Male sex, *n* (%)	958 (56)
Age, mean ± SD (years)	55.3 ± 16.09
Etiology, *n* (%)	
• Biliary	778 (45.3)
• Alcohol-related	374 (21.8)
• Alcohol + hypertriglyceridemia	53 (3.1)
• Hypertriglyceridemia	61 (3.6)
• Idiopathic	318 (18.5)
• Other	133 (7.7)
Severity (revised Atlanta), *n* (%)	
• Mild	1079 (62.8)
• Moderately severe	500 (29.1)
• Severe	138 (8)
In-hospital mortality, *n* (%)	59 (3.4)
Any organ failure, *n* (%)	249 (14.5)

Abbreviations: ACP, acute-on-chronic pancreatitis; AP, acute pancreatitis; ECP, early chronic pancreatitis; *n*, number of patients; RAP, recurrent acute pancreatitis; SD, standard deviation.
[a]Other etiologies included viral infections, trauma, drug-induced pancreatitis, congenital anatomical malformations, cystic fibrosis, gluten-sensitive enteropathy, and genetic causes.

20506414, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ueg2.70306 by CochraneItalia, Wiley Online Library on [07/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

RAP (n = 123), with a more pronounced increase in ECP (72%, n = 109) and ACP (79%, n = 161). Conversely, the proportion of female patients showed a steady decline from 50% in AP (n = 578) to 21% in ACP (n = 46) (Figure 1A). Biliary etiology was the leading cause of AP (55%, n = 632) and RAP (40%, n = 86), but became less prevalent in ECP (19%, n = 29) and ACP (15%, n = 31) (Figure 1B). In contrast, alcohol-related pancreatitis showed the opposite pattern, increasing from 16% in AP (n = 178) and 23% in RAP (n = 49) to 36% in ECP (n = 54) and 45% in ACP (n = 93). Hypertriglyceridemia, idiopathic, and other etiologies accounted for a smaller proportion of cases and remained relatively stable across groups.

3.3 | Disease Severity, Organ Failure, and Outcomes

Disease severity showed only modest differences across the pancreatitis continuum (Figure 2A). Mild disease predominated in all groups, whereas severe pancreatitis was most frequent in AP (10%) and less common in RAP (3%), ECP (7%), and ACP (2%). Multivariable analysis confirmed that RAP and ACP were independently associated with lower odds of severe disease compared with AP, while ECP did not differ significantly from AP and RAP (Supporting Information S1: Table S3). In-hospital mortality followed a similar pattern, with the highest rate observed in AP (4.5%) and progressively lower rates in RAP (1.4%), ECP (1.3%), and ACP (0.9%) (Figure 2B). Organ failure occurred most frequently in AP (16.6%) but remained clinically relevant in ECP (10.5%) and ACP (12.5%) (Figure 2C). Length of hospitalization was comparable across disease stages, with a median hospital stay of 6–7 days in all groups (Figure 2D). Detailed regression analyses of disease severity and mortality are provided in Supporting Information S1: Table S3.

3.4 | Laboratory Parameters

Serum pancreatic enzyme activities decreased progressively during hospitalization in all groups, with amylase and lipase levels peaking on day 1 (Supporting Information S1: Figure S2A and S2B, respectively). CRP followed a similar temporal pattern across groups, peaking around day 3, but remained significantly higher in AP during the later hospitalization period (Supporting Information S1: Figure S2C). Admission glucose and HbA1c levels were comparable across disease stages (Supporting Information S1: Figure S3A and S3B, respectively). Total bilirubin levels were highest in AP and significantly lower in RAP, ECP, and ACP, consistent with the decreasing contribution of biliary etiology along the disease continuum (Supporting Information S1: Figure S3C). Triglyceride levels were highest in RAP and ECP, while ACP exhibited significantly lower levels than RAP (Supporting Information S1: Figure S3D). Total cholesterol levels did not differ between the groups (Supporting Information S1: Figure S3E). In contrast, body mass index (BMI) declined progressively from AP to ACP. RAP and ECP already showed significantly lower BMI values than AP, while ACP had the lowest overall BMI, suggesting progressive metabolic and nutritional deterioration during disease progression (Supporting Information S1: Figure S3F). A detailed presentation of longitudinal laboratory and metabolic parameters, including pairwise statistical comparisons, is provided in the Supplementary material (Supporting Information S1: Results S1 and Table S4).

3.5 | Lifestyle-Related Risk Factors and Metabolic Profile

Alcohol consumption increased progressively along the disease continuum (Figure 3A). The proportion of patients reporting regular alcohol intake increased from 48% in AP (n = 537) to 53% in RAP (n = 113), 54% in ECP (n = 81), and 58% in ACP (n = 118), (overall p = 0.0316), reflecting the growing contribution of alcohol-related injury in later disease stages. Smoking prevalence showed an even more pronounced pattern (Figure 3B). While only 35% of AP (n = 391) and 36% of RAP (n = 76) patients were active smokers, the proportion increased to 49% in ECP (n = 74) and 68% in ACP (n = 140). Pairwise analysis demonstrated significant differences between AP and ECP, AP and ACP, and RAP and ACP, whereas no significant difference was observed between AP and RAP. These findings indicate that smoking becomes increasingly prevalent from the ECP stage onward and may contribute to the progression toward chronic pancreatic disease. The prevalence of pre-existing DM and lipid metabolism disorders was broadly similar across disease stages (Supporting Information S1: Figure S4A and S4B, respectively). Pre-existing DM affected 17%–27% of patients, with type 2 diabetes accounting for the vast majority of cases in all groups. Lipid metabolism disorders were less common, occurring in 9%–25% of patients, with a slight increase observed in ACP. Overall, the prevalence of these metabolic comorbidities showed only modest variation along the pancreatitis continuum.

3.6 | Endoscopic Interventions

The need for endoscopic interventions varied across the pancreatitis continuum (Figure 4A). Overall, 33% of patients

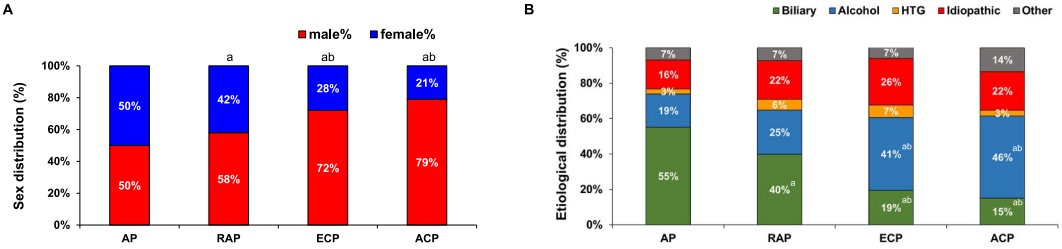


FIGURE 1 | Epidemiological and etiological characteristics of patients across the pancreatitis continuum. (A) Sex distribution across single acute (AP), recurrent acute (RAP), early chronic (ECP), and acute-on-chronic (ACP) pancreatitis. (B) Distribution of major etiological factors, including biliary, alcohol-related, hypertriglyceridemia (HTG), idiopathic, and other etiologies across disease stages. Significant differences are indicated as follows: $a = p \leq 0.05$ versus AP, $b = p \leq 0.05$ versus RAP (Fisher's pairwise test).

20506414, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ueg2.70306 by CochraneItalia, Wiley Online Library on [07/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

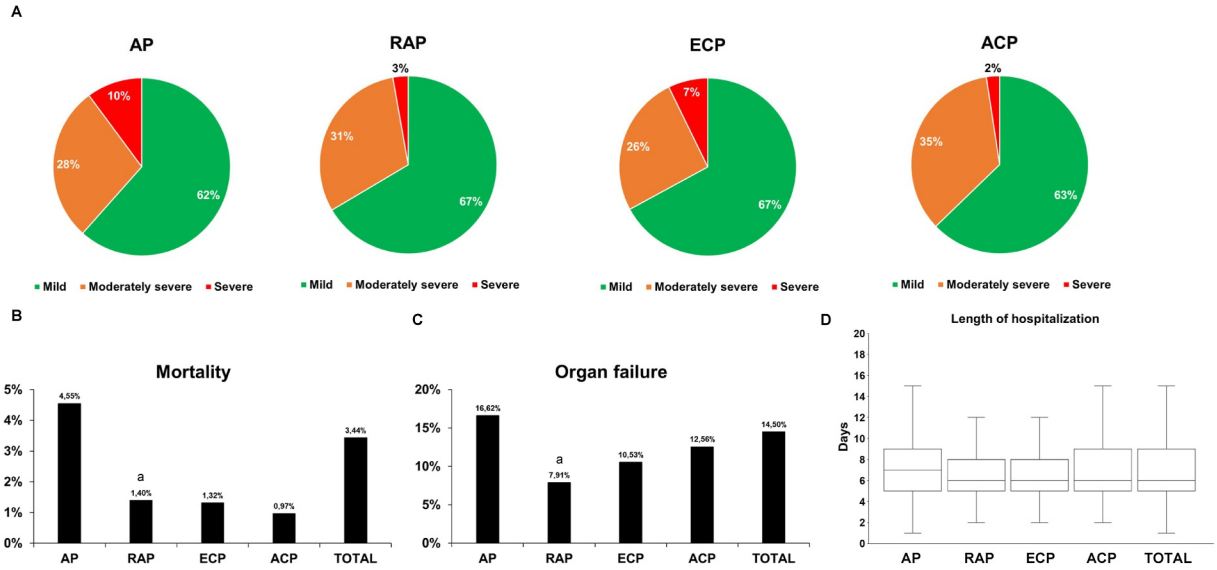


FIGURE 2 | Disease severity, organ failure, mortality, and hospital stay. The figure displays (A) severity categories based on the revised Atlanta classification, (B) in-hospital mortality rates across the four disease stages, (C) the incidence of organ failure in each group, and (D) the average length of hospitalization. Each patient was included only once in the analysis; therefore, hospitalization length refers to the index admission used for patient classification and does not represent cumulative hospital stay or readmissions. ACP, acute-on-chronic pancreatitis; AP, acute pancreatitis; ECP, early chronic pancreatitis; RAP, recurrent acute pancreatitis. Significant differences are indicated as follows: $a = p \leq 0.05$ versus AP (fisher's pairwise test).

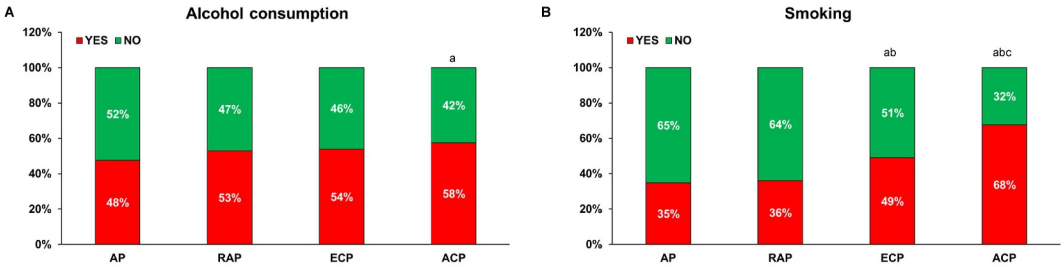


FIGURE 3 | Lifestyle-related risk factors and body composition. (A) Proportion of patients reporting alcohol consumption in acute (AP), recurrent acute (RAP), early chronic (ECP), and acute-on-chronic (ACP) pancreatitis. (B) Proportion of patients who smoke in each disease group. Significant differences are indicated as follows: a, $p < 0.05$ versus AP; b, $p < 0.05$ versus RAP; c, $p < 0.05$ versus ECP. Pairwise comparisons for categorical variables were performed using fisher's exact test.

($n = 572$) required at least one endoscopic procedure, with comparable proportions in AP (36%; $n = 417$), RAP (28%; $n = 61$), ECP (26%; $n = 40$), and ACP (26%; $n = 54$). The average number of procedures per treated patient showed minimal variation between the groups (Figure 4B), ranging from 1.38 in AP to 1.49 in RAP. A separate analysis examined how many patients underwent more than one endoscopic intervention (Figure 4C). Although no statistically significant differences were observed between the groups, ECP showed the highest proportion of patients requiring multiple endoscopic procedures (44%, $n = 17$), compared with AP (28%), RAP (26%), and ACP (30%). Indications for endoscopic intervention differed significantly across disease stages (overall Fisher's exact test, $p < 0.001$; Figure 4D). After separating biliary interventions from prophylactic pancreatic stent placement, prophylactic stenting was the most frequent indication in AP ($n = 48/68$) and RAP ($n = 8/12$), whereas pancreatic duct–directed interventions emerged in ECP ($n = 5/12$) and became predominant in ACP ($n = 10/13$). In ECP and ACP, these interventions were primarily performed to restore and maintain pancreatic juice drainage, most commonly through endoscopic dilation and/or stenting of pancreatic duct strictures. Pairwise comparisons with Holm correction showed significant differences between AP and ECP ($p < 0.001$), AP and ACP ($p < 0.001$), and RAP and ACP ($p < 0.001$), whereas AP versus RAP ($p = 0.195$), RAP versus ECP ($p = 0.164$), and ECP versus ACP ($p = 0.204$) were not significant.

4 | Discussion

The present study extends previous work on the pancreatitis continuum by demonstrating that ECP represents a clinically distinct transitional phenotype rather than simply a more advanced form of RAP. While earlier studies established ECP as a conceptual stage preceding CP [9] and documented accelerated progression following recurrent pancreatic injury [13], our findings provide clinical validation through distinct epidemiological, metabolic, and endoscopic characteristics. Although the proposed four-stage model conceptualizes pancreatitis as an AP–RAP–ECP–ACP continuum, individual patients may not necessarily pass sequentially through every stage before developing radiological features of chronic pancreatitis. Importantly,

20506414, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ueg2.70306 by CochaneItalia, Wiley Online Library on [07/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

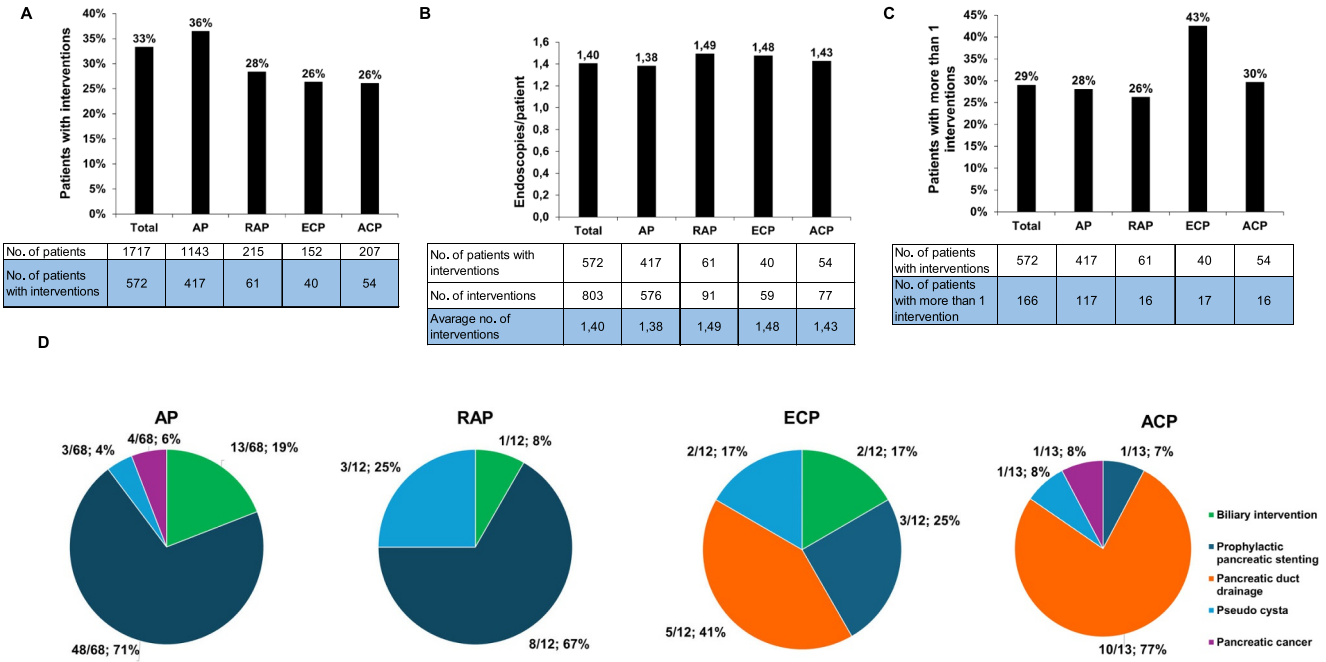


FIGURE 4 | Endoscopic interventions across disease stages. (A) Proportion of patients requiring endoscopic therapy. (B) Average number of procedures per treated patient. (C) Proportion of patients undergoing more than one endoscopic intervention. (D) Indications for endoscopic therapy. Prophylactic pancreatic stenting was the most frequent indication in acute (AP) and recurrent acute (RAP) pancreatitis, whereas pancreatic duct–directed interventions emerged in early chronic pancreatitis (ECP) and became predominant in acute-on-chronic pancreatitis (ACP).

ECP could not be distinguished from RAP based on disease severity alone, further supporting the concept that its clinical relevance lies in its unique phenotype and management profile. A conceptual summary of the major findings is presented in Figure 5.

Etiologic progression in this cohort strongly emphasizes modifiable risk exposure. Biliary pancreatitis dominated AP and RAP, but declined markedly in ECP and ACP. Importantly, the decreasing proportion of biliary etiology across disease stages may partly reflect effective recurrence-prevention strategies, such as cholecystectomy and endoscopic treatment of bile duct stones, rather than solely representing differences in the natural course of pancreatitis. In contrast, alcohol-related disease increased steadily. Consistent with these etiological shifts, total bilirubin levels were significantly higher in AP than in RAP, ECP, and ACP, further supporting the decreasing contribution of biliary obstruction in later disease stages. Importantly, pairwise analyses demonstrated that ECP already differed significantly from RAP with respect to both biliary and alcohol-related etiologies, whereas no significant differences were observed between ECP and ACP. Smoking prevalence increased from RAP to ECP and further to ACP. Male predominance increased progressively from AP to ACP and closely paralleled the rise in alcohol-related etiologies, suggesting that differential exposure to alcohol and tobacco may partly contribute to the observed sex distribution. These findings further support the view that ECP already shares several epidemiological characteristics with ACP rather than merely representing a more advanced form of RAP.

Disease severity and mortality were highest during the initial AP episode, whereas RAP, ECP, and ACP generally exhibited milder disease courses. This pattern is consistent with previous observations suggesting that progressive fibrosis may attenuate necrotizing inflammatory responses and reduce the severity of subsequent attacks [21]. Importantly, RAP and ECP did not differ significantly in disease severity, indicating that ECP is distinguished primarily by its epidemiological, metabolic, and ductal characteristics rather than by acute clinical severity.

A progressive decline in BMI was already evident in RAP and ECP and became most pronounced in ACP, suggesting that clinically relevant metabolic alterations emerge before the development of established CP. Although HbA1c levels did not differ significantly between groups, the observed reductions in BMI and changes in triglyceride levels support increased metabolic vulnerability during disease progression. These findings are consistent with previous studies demonstrating that pancreatic dysfunction and remodeling may begin early after recurrent pancreatic injury, preceding the development of established CP [11, 13].

During AP and RAP, endoscopic interventions were predominantly prophylactic, whereas pancreatic duct–directed interventions emerged in ECP and became predominant in ACP, consistent with increasing clinical relevance of pancreatic duct abnormalities across disease stages. The overall distribution of intervention indications differed significantly among the four groups. Pairwise analyses demonstrated significant differences between AP and ECP, AP and ACP, and RAP and ACP, whereas differences between AP and RAP, RAP and ECP, and ECP and ACP did not reach statistical significance. Importantly, patients with ECP exhibited the highest proportion of cases requiring more than one endoscopic intervention, compared with AP, RAP, and ACP, indicating an increased procedural burden once ductal disease becomes clinically manifest. Although this

20506414, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ueg2.70306 by CochraneItalia, Wiley Online Library on [07/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

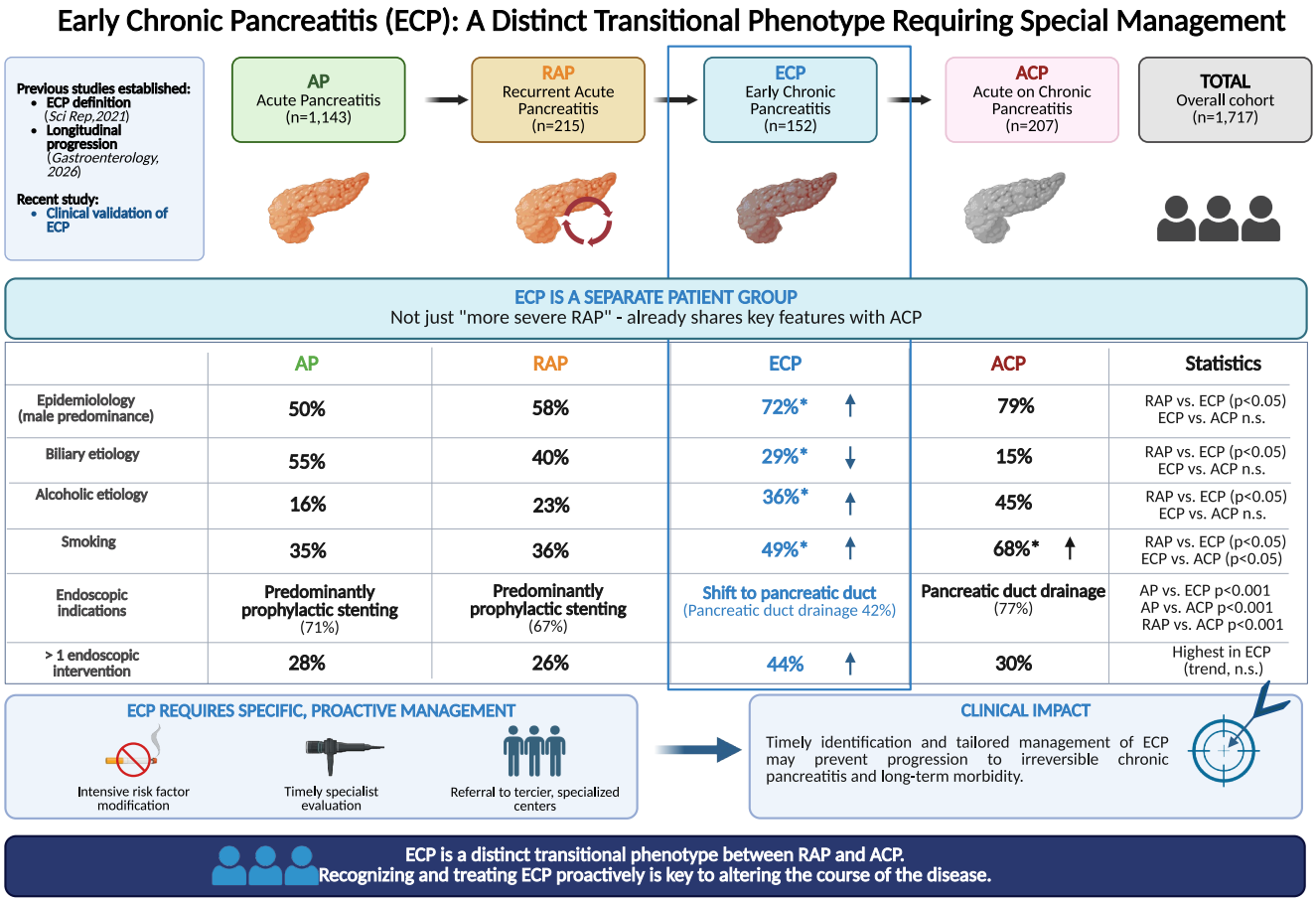


FIGURE 5 | Conceptual summary of ECP as a distinct transitional phenotype within the pancreatitis continuum. ECP demonstrates epidemiological, metabolic, and endoscopic characteristics that differ from those of RAP, while also sharing several similarities with ACP. These findings support the need for early recognition, targeted risk-factor modification, specialized endoscopic evaluation, and referral to tertiary pancreatic centers. * indicates a statistically significant difference. Details of the pairwise comparisons are provided in the Statistics column. n.s., non-significant. This figure was created using BioRender.com.

difference did not reach statistical significance, likely due to the relatively small number of interventions, it further supports the concept that ECP is associated with increased ductal complexity and recurrent therapeutic needs. Treatment of ductal stricturing is recommended to allow resolution of chronic pancreatic duct obstruction [22], which, over time, can result in parenchymal injury from elevated intraductal pressure and recurrent inflammation [23]. Endoscopic therapy for pancreatic strictures offers improvement in symptoms and reduction in exacerbation frequency, although it carries a procedural adverse event risk approaching 20% and a post-ERCP pancreatitis rate near 5% [24]. The need for expert technical performance for these challenging procedures, alongside the possibility of detecting pancreatic malignancy, which is present in approximately 1% of AP cases [25], reinforces the necessity of referral to high-expertise centers.

Taken together, these data position ECP as a clinically important and potentially modifiable juncture in the evolution of pancreatic disease. Patients at this stage require intensive optimization of modifiable risk factors, systematic assessment of metabolic impairment, and timely endoscopic evaluation to limit progression toward irreversible fibrosis and long-term morbidity. This approach is consistent with emerging concepts of precision prevention in pancreatology, emphasizing cause-oriented diagnostics and targeted interventions to prevent progression from RAP to chronic pancreatic disease [26]. Failure to recognize and manage patients with RAP and evolving ductal or metabolic abnormalities may allow progression to established CP, a condition associated with substantial disability and limited therapeutic options. Accordingly, RAP should prompt early consideration of specialist referral, as a significant proportion of such patients may already exhibit features consistent with ECP at the time of evaluation.

4.1 | Strengths and Limitations

The major strength of this study is the large, prospectively collected, multicentre cohort derived from a high-quality multicentre pancreatitis registry, which includes one of the largest reported ECP populations to date. The standardized definitions and comprehensive clinical, etiological, metabolic, and endoscopic assessments enabled characterization of disease stages across the AP–RAP–ECP–ACP continuum. Several limitations should be acknowledged. First, the present study was an observational post hoc analysis of prospectively collected registry data; therefore, causal relationships cannot be established. Second, ECP was defined using a clinically based framework

20506414, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ueg2.70306 by CochraneItalia, Wiley Online Library on [07/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

that required recurrent AP episodes in the absence of radiological CP, which may not fully capture all biological aspects of early disease. Third, specialized assessments of exocrine pancreatic function, as well as systematic endoscopic ultrasound data, were unavailable for all patients. Fourth, detailed longitudinal data on cholecystectomy and treatment of bile duct stones were not consistently available, limiting our ability to assess their contribution to the observed etiological differences. Another limitation is that longitudinal data on new-onset or post-pancreatitis diabetes were not available; therefore, the development of diabetes following AP could not be assessed. Finally, because imaging was performed as part of routine clinical care rather than according to a study-specific protocol, imaging modality was not uniform across patients, and no central radiological review was performed.

4.2 | Implications for Clinical Practice

Patients with three or more AP episodes should not be regarded as having merely advanced RAP. The emergence of characteristic etiological patterns, increased exposure to modifiable risk factors, and the transition toward pancreatic duct–directed interventions indicate that ECP represents a clinically relevant stage that requires proactive management. Early referral to specialized pancreatic centers may facilitate risk-factor modification, comprehensive evaluation, and timely intervention before irreversible pancreatic damage is established.

4.3 | Implications for Research

Future prospective longitudinal studies should validate ECP using morphological, functional, and biomarker-based endpoints and determine which patients are at the highest risk of progression to establish CP. Interventional studies are also needed to assess whether intensive risk-factor modification, structured surveillance, and early treatment of pancreatic duct abnormalities can alter the natural history of the disease and prevent progression to CP.

Funding

This study was supported by the National Research, Development and Innovation Office (SNN152834, K131996, K147265), the TKP2021-EGA-23 grant, and by the Albert Szent-Györgyi Research Grant of the Albert Szent-Györgyi Medical School, University of Szeged. Dr. János Szolcsányi Research Fund, Faculty of Medicine, University of Pécs (KA-2025-47).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. J. P. Iannuzzi, J. A. King, J. H. Leong, et al., "Global Incidence of Acute Pancreatitis Is Increasing Over Time: A Systematic Review and Meta-Analysis," *Gastroenterology* 162, no. 1 (2022): 122–134, https://doi.org/10.1053/j.gastro.2021.09.043.

2. G. Beyer, A. Habtezion, J. Werner, M. M. Lerch, and J. Mayerle, "Chronic Pancreatitis," *Lancet* 396, no. 10249 (2020): 499–512, https://doi.org/10.1016/s0140-6736(20)31318-0.

3. D. L. Conwell, L. S. Lee, D. Yadav, et al., "American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: Evidence-Based Report on Diagnostic Guidelines," *Pancreas* 43, no. 8 (2014): 1143–1162, https://doi.org/10.1097/mpa.0000000000000237.

4. J. Kleeff, D. C. Whitcomb, T. Shimosegawa, et al., "Chronic Pancreatitis," *Nature Reviews Disease Primers* 3, no. 1 (2017): 17060, https://doi.org/10.1038/nrdp.2017.60.

5. T. Edmiston, K. Vishnupriya, and A. Chanmugam, "Recurrent Acute Pancreatitis: A Harbinger for Irreversible Chronic Pancreatitis," *Hospital Practice* 52, no. 1–2 (2024): 5–12, https://doi.org/10.1080/21548331.2024.2348990.

6. I. C. Roberts-Thomson, "Progression From Acute to Chronic Pancreatitis," *JGH Open* 5, no. 12 (2021): 1321–1322, https://doi.org/10.1002/jgh3.12698.

7. D. C. Whitcomb, "Central Role of the Sentinel Acute Pancreatitis Event (SAPE) Model in Understanding Recurrent Acute Pancreatitis (RAP): Implications for Precision Medicine," *Frontiers in Pediatrics* 10 (2022): 941852, https://doi.org/10.3389/fped.2022.941852.

8. J. D. Machicado and D. Yadav, "Epidemiology of Recurrent Acute and Chronic Pancreatitis: Similarities and Differences," *Digestive Diseases and Sciences* 62, no. 7 (2017): 1683–1691, https://doi.org/10.1007/s10620-017-4510-5.

9. S. J. Sankaran, A. Y. Xiao, L. M. Wu, J. A. Windsor, C. E. Forsmark, and M. S. Petrov, "Frequency of Progression From Acute to Chronic Pancreatitis and Risk Factors: A Meta-Analysis," *Gastroenterology* 149, no. 6 (2015): 1490–1500.e1, https://doi.org/10.1053/j.gastro.2015.07.066.

10. A. Geisz and M. Sahin-Toth, "Sentinel Acute Pancreatitis Event Increases Severity of Subsequent Episodes in Mice," *Gastroenterology* 161, no. 5 (2021): 1692–1694, https://doi.org/10.1053/j.gastro.2021.06.013.

11. P. J. Hegyi, A. Soos, E. Toth, et al., "Evidence for Diagnosis of Early Chronic Pancreatitis After Three Episodes of Acute Pancreatitis: A Cross-Sectional Multicentre International Study With Experimental Animal Model," *Scientific Reports* 11, no. 1 (2021): 1367, https://doi.org/10.1038/s41598-020-80532-6.

12. D. C. Whitcomb, T. Shimosegawa, S. T. Chari, et al., "International Consensus Statements on Early Chronic Pancreatitis. Recommendations From the Working Group for the International Consensus Guidelines for Chronic Pancreatitis in Collaboration With the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, Pancreasfest Working Group and European Pancreatic Club," *Pancreatology* 18, no. 5 (2018): 516–527, https://doi.org/10.1016/j.pan.2018.05.008.

13. A. Miko, N. Farkas, A. Vincze, et al., "Progression of Pancreatic Morphologic Changes and Endocrine Dysfunction After Acute Pancreatitis: Preliminary Results of the Longitudinal Goulash-Plus Cohort Study," *Gastroenterology* 170, no. 3 (2026): 631–634, https://doi.org/10.1053/j.gastro.2025.09.034.

14. O. Eperjesi, M. Bucur, A. Rancz, et al., "Risk Factors for Pancreatic Exocrine Insufficiency After Acute Pancreatitis: A Systematic Review and Meta-Analysis," *Pancreatology* 26, no. 3 (2026): 404–411, https://doi.org/10.1016/j.pan.2026.03.001.

15. A. Szentesi, N. Farkas, Z. Sipos, et al., "Alcohol Consumption and Smoking Dose-Dependently and Synergistically Worsen Local Pancreas Damage," *Gut* 71, no. 12 (2022): 2601–2602, https://doi.org/10.1136/gutjnl-2021-326853.

20506414, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ueg2.70306 by CochaneItalia, Wiley Online Library on [07/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

16. D. Yadav, R. H. Hawes, R. E. Brand, et al., "Alcohol Consumption, Cigarette Smoking, and the Risk of Recurrent Acute and Chronic Pancreatitis," *Archives of Internal Medicine* 169, no. 11 (2009): 1035–1045, https://doi.org/10.1001/archinternmed.2009.125.

17. P. A. Banks, T. L. Bollen, C. Dervenis, et al., "Classification of Acute Pancreatitis—2012: Revision of the Atlanta Classification and Definitions by International Consensus," *Gut* 62, no. 1 (2013): 102–111, https://doi.org/10.1136/gutjnl-2012-302779.

18. info@internationalpancreatology.org IAEIJWGEa, Group IAEIJW, "International Association of Pancreatology Revised Guidelines on Acute Pancreatitis 2025: Supported and Endorsed by the American Pancreatic Association, European Pancreatic Club, Indian Pancreas Club, and Japan Pancreas Society," *Pancreatology* 25, no. 6 (2025): 770–814, https://doi.org/10.1016/j.pan.2025.04.020.

19. S. Tenner, S. S. Vege, S. G. Sheth, et al., "American College of Gastroenterology Guidelines: Management of Acute Pancreatitis," *American Journal of Gastroenterology* 119, no. 3 (2024): 419–437, https://doi.org/10.14309/ajg.0000000000002645.

20. Working Group IAPAPAAPG, "IAP/APA Evidence-Based Guidelines for the Management of Acute Pancreatitis," supplement, *Pancreatology* 13, no. 4S2 (2013): e1–e15, https://doi.org/10.1016/j.pan.2013.07.063.

21. C. Acharya, R. A. Cline, D. Jaligama, et al., "Fibrosis Reduces Severity of Acute-on-Chronic Pancreatitis in Humans," *Gastroenterology* 145, no. 2 (2013): 466–475, https://doi.org/10.1053/j.gastro.2013.05.012.

22. D. S. Strand, R. J. Law, D. Yang, and B. J. Elmunzer, "AGA Clinical Practice Update on the Endoscopic Approach to Recurrent Acute and Chronic Pancreatitis: Expert Review," *Gastroenterology* 163, no. 4 (2022): 1107–1114, https://doi.org/10.1053/j.gastro.2022.07.079.

23. V. K. Singh, D. Yadav, and P. K. Garg, "Diagnosis and Management of Chronic Pancreatitis: A Review," *JAMA* 322, no. 24 (2019): 2422–2434, https://doi.org/10.1001/jama.2019.19411.

24. S. Han, A. R. Attwell, P. Tatman, et al., "Adverse Events Associated With Therapeutic Endoscopic Retrograde Pancreatography," *Pancreas* 50, no. 3 (2021): 378–385, https://doi.org/10.1097/mpa.0000000000001769.

25. J. Kirkegard, F. V. Mortensen, U. Heide-Jorgensen, and D. Cronin-Fenton, "Predictors of Underlying Pancreatic Cancer in Patients With Acute Pancreatitis: A Danish Nationwide Cohort Study," *HPB* 22, no. 4 (2020): 553–562, https://doi.org/10.1016/j.hpb.2019.08.013.

26. P. Hegyi, "Precision Prevention of Recurrent Acute Pancreatitis: From Cause-Oriented Diagnostics to Targeted Intervention," *United European Gastroenterology Journal* 14, no. 2 (2026): e70191, https://doi.org/10.1002/ueg2.70191.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: ueg270306-sup-0001-suppl-data.docx.

20506414, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ueg2.70306 by CochraneItalia, Wiley Online Library on [07/11/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License