CHALLENGES IN THE TREATMENT AND FOLLOW UP OF ACUTE PANCREATITIS

Kihívások az akut pancreatitis kezelésében és utánkövetésében

Ph.D. Thesis

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Szeged

2021

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Szeged

2021

Publications related to the subject of the thesis

I. **Halász A**, Pécsi D, Farkas N, Izbéki F, Gajdán L, Fejes R, Hamvas J, Takács T, Szepes Z, Czakó L, Vincze Á, Gódi S, Szentesi A, Párniczky A, Illés D, Kui B, Varjú P, Márta K, Varga M, Novák J, Szepes A, Bod B, Ihász M, Hegyi P, Hritz I, Erőss B. Outcomes and timing of endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis. **Digestive and Liver Disease** Vol 51, Issue 9, Sept. 2019, 1281-1286
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Scientific metrics

Number of publications **related to the subject** of the thesis: 2 (1 first author)

Cumulative impact factor of publications related to the thesis: 7.568 (3.57 first author)

Q1: 1 Q2: 1, Q3: -, Q4: -

Number of **total accepted/published** articles: 13 (1 first author)

Cumulative impact factor of the published articles: 38.862 (3.57 first author)

Q1: 7, Q2: 6, Q3: -, Q4: -

Number of total citation by **Google Scholar**: 322. Hirsch index: 10

Number of total citation by **MTMT**: 154 independent, 230 all. Hirsch index: 10

Table of contents

List of abbreviations

ABP	acute biliary pancreatitis
ALAT	alanine aminotransferase
ALP	alkaline phosphatase
AP	acute pancreatitis
APA	American Pancreatic Association
APACHE II	acute physiology and chronic health evaluation II
ASAT	aspartate aminotransferase
ASGE	American Society for Gastrointestinal Endoscopy
ATP	adenosine triphosphate
BISAP	bedside index of severity in acute pancreatitis
BMI	body mass index
BUN	blood urea nitrogen
CBD	common bile duct
CP	chronic pancreatitis
CRP	C-reactive protein
CT	Computer Tomography
CTSI	computer tomography severity index
mCTSI	modified computer tomography severity index
GGT	gamma-glutamyltransferase
ECP	early chronic pancreatitis
EPC	European Pancreatic Club
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
EST	Endoscopic sphincterotomy
EUS	Endoscopic ultrasonography
HPSG	Hungarian Pancreatic Study Group
IAP	International Association of Pancreatology
IQR	interquartile range
JPS	Japan Pancreatic Society
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging

PCT	procalcitonin
RAP	recurrent acute pancreatitis
RBC	red blood cell
RCT	randomized controlled trial
SAPE	sentinel acute pancreatitis event
SEM	standard error of mean
SOD	Sphincter of Oddi dysfunction
SD	standard deviation
USS	transabdominal ultrasound scan
WBC	white blood cells

I. Preface and general introduction

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract requiring acute hospitalization; it is associated with significant morbidity and mortality worldwide, with an increasing incidence of 5–100/100,000 cases per year [1]. Research on pancreatitis is continuously decreasing despite its importance, suggesting that more attention should be paid to this disease [2].

Gallstones are the leading cause of acute pancreatitis in developed countries and account for a range between 16 and 70% of all cases. Also, there is evidence that up to 20% of AP cases with idiopathic aetiology are caused by microlithiasis [3]. It is generally accepted that endoscopic retrograde cholangiopancreatography (ERCP) combined with endoscopic sphincterotomy (EST) is the effective treatment method in some selected cases in acute biliary pancreatitis (ABP). Additionally, same-admission cholecystectomy reduces the risk of recurrent gallstone-related complications in mild ABP with a very low risk of cholecystectomy-related complications [4]. With adequate treatment of the stone disease, recurrent pancreatic attacks are rarely associated with biliary aetiology. However, in some instances, recurrent biliary pancreatitis can be diagnosed for various reasons. This can be due to a common bile duct (CBD) stone not detected at the first episode, stones migrating from the gallbladder into the CBD, or stones developing in the bile duct after cholecystectomy.

Moreover some patients are not feasible for endoscopic or surgical therapy because of ageing or comorbidities. This repetitive inflammation of the pancreas can lead to irreversible damage of pancreatic parenchyma, namely chronic pancreatitis (CP) [5], [6]. CP is an end-stage disease with no specific curative therapy; therefore, an early diagnosis is crucial. According to the sentinel acute pancreatitis event (SAPE) model, the first episode of acute pancreatitis triggers a cellular activation cascade, leading to chronic pancreatic inflammation and fibrosis.

The Hungarian Pancreatic Study Group (HPSG) was created in 2011 to improve patient care in pancreatic diseases. The Registry for Pancreatic Patients was established in 2012 by the HPSG to record patients with pancreatic diseases to advance research and patient care. Based on the available international guidelines and evidence, HPSG prepared an evidence-based guideline for the medical and surgical management of acute pancreatitis in 2015 [7] and produced several pancreatic registries and trials within a short period [8]–[12]. One of its registries, concerning acute pancreatitis, records AP cases from all participating centres throughout Hungary and more

than a dozen countries [13]. The data of this unique program allows us a better insight into the disease course. We can monitor the diagnostic and therapeutic practices besides examing the two significant clinical problems mentioned above.

II. Motivation and aims of the PhD thesis

As a specialist in internal medicine and a trainee gastroenterologist, day-to-day patient management, especially quality care, is a prime necessity for me. I wanted to contribute to the better understanding and the widespread use of evidence-based medicine, which plays an integral part in the quality improvement and assurance in healthcare. I joined the workgroup of Professor Péter Hegyi in 2014 to analyze the management of Hungarian patients with acute pancreatitis, especially biliary pancreatitis. Nevertheless, I wished to acquire experience and expertise in modern clinical research methodologies.

I aimed to determine the role of endoscopic retrograde cholangiopancreatography (ERCP), sphincterotomy and stone clearance in ABP and provide an overview of the general use of ERCP in Hungary. Furthermore, we investigated the rate of recurrent acute pancreatitis events and the changing biomarkers to diagnose early chronic pancreatitis in an extensive international cohort analysis.

As we examined these two suggested clinical problems in separate projects, two different chapters are discussed below, first the connection between ABP and ERCP, then the definition of early chronic pancreatitis (ECP).

III. Chapter I. - Acute biliary pancreatitis (ABP)

III.1 Introduction

III.1.1 Pathophysiology of acute biliary pancreatitis

One of the main etiological factors in the pathogenesis of AP is the obstruction of the ampulla of Vater by gallstones or sludge or by hypertrophy of papilla and bile reflux into the pancreatic duct, contributing to 35–60% of all AP cases. This subtype of AP is termed acute biliary or gallstone pancreatitis (ABP) [14]. It is well known from the literature that bile is one of the critical etiological factors for acute pancreatitis [15]. Bile refluxing into the pancreatic ductal system induces toxic calcium signal [16], mitochondrial injury [17], adenosine triphosphate (ATP) depletion [18], both in acinar and ductal cells [19]. These mechanisms decrease the intraluminal pH [20] and enhance trypsinogen activation [21], leading to severe pancreas inflammation.

There are three essential hypotheses about how gallstones induce acute pancreatitis: (a) common channel, (b) duodenal reflux, and (c) ductal hypertension.

III.1.1.1 Common Channel Hypothesis

In 1901 Opie suggested that reflux of bile into the pancreatic duct is the trigger for pancreatitis. He presumed that partial obstruction of the ampulla or an impacted gallstone at the papilla creates a communication behind the stone connecting the common bile duct to the pancreatic duct. Bile acids could enter the pancreas through this common pancreaticobiliary channel, thus initiating pancreatitis [22], [23]. Many observations, however, suggest that the common channel hypothesis is inaccurate; basically, a transient obstruction of the pancreatic duct is a sufficient cause to provoke AP.

III.1.1.2 Duodenal Reflux Hypothesis

A number of mechanisms prevent the reflux of duodenal contents into the pancreatic duct. The passage of gallstones through the ampulla may cause sphincter dysfunction that allows reflux of duodenal contents, affecting the pancreas [24].

III.1.1.3 Ductal Hypertension Hypothesis

The mechanism by which increased ductal pressure leads to pancreatitis has been debated over the years. The main finding is the obstruction of the pancreatic duct with consequent intracellular changes. In case of increased intraductal pressure, the expression of the proinflammatory cytokines (Interleukin 1, interleukin 6, tumour necrosis factor) is up-regulated and associated with altered tight junction integrity. These hydrostatic pressures also affect pancreatic acinar cells and generate sustained aberrant Ca2+ signals. There is evidence that this pressure induces a significant decrease in mitochondrial membrane potential, which likely results in reduced ATP production [25]. These are the critical events in the blockage of digestive enzyme secretion and initiation of premature digestive intra-acinar enzyme activation [24], [26].

III.1.1.4 The two-phase hypothesis of acute gallstone pancreatitis

The three proposed pathogenetic mechanisms are not mutually exclusive and may compound each other. A two-phase hypothesis has been proposed to explain the development of acute pancreatitis [27]. Initially, small migrating common bile duct stones induce the attack while free drainage of activated pancreatic enzymes is maintained. If common bile duct (CBD) stones persist or oedema of the head of the pancreas or the ampulla occurs, further obstruction in the outflow of matured enzyme-rich pancreatic juice results in a predisposition to a severe attack of pancreatitis and acute cholangitis. That is a reason why removal of CBD stones following sphincterotomy results in improvement of pancreatitis.

III.1.1.5 Other causes of acute biliary pancreatitis

Some other less common etiologies cause biliary pancreatitis via obstruction of the pancreatic duct more proximal or at the level of the ampulla of Vater. Biliary sludge, cholesterol polyps may cause transient pancreaticobiliary obstruction. Biliary sludge should not be ignored in patients with idiopathic recurrent episodes of acute pancreatitis. It has been implicated as the aetiology in up to two-thirds of patients [28], [29]. Sphincter of Oddi dysfunction (SOD type I, II, and III) also may contribute to the risk of recurrent acute pancreatitis by increasing intraductal pressure and lead to abnormal biliary and pancreatic juice outflow [30].

Biliary surgery involving transduodenal bile duct exploration has been linked with acute pancreatitis [31]. Parasites also may cause acute pancreatitis by obstruction of the ampulla of Vater, either by inducing the formation of gallstones or by a direct infestation of the main pancreatic duct, commonly in Africa and Asia [32].

Tumours at or around the level of the ampulla of Vater and more proximal may present as acute pancreatitis due to ampullary obstruction in around 6% of cases [33], [34].

III.1.2 Clinical features, diagnosis, and management of acute biliary pancreatitis

The accurate diagnosis of the cause of acute pancreatitis is very relevant because it affects the therapeutic strategy. In biliary pancreatitis, around 80% of patients have a mild attack, but in 15–20%, AP is complicated by substantial morbidity and mortality. 5-10% mortality via local or systemic complications can increase to 15-20% [35]. Without definitive treatment, the risk of a recurrent attack within the next several months is about 30-50% [36].

Gallstone pancreatitis is usually more common in women. This fact is evidenced by the higher prevalence of gallstone disease in women in most countries, representing a significant health burden [37]. The epidemic of obesity and metabolic syndrome predicts a rising prevalence of cholesterol gallstones [38]. As the incidence of gallstone disease escalates, there is a concomitant increase in complications like gallstone-related pancreatitis. The frequency of gallstones increases with age, escalating markedly after age 40 to become 4 to 10 times more likely in older individuals [39].

III.1.3 Diagnosis of acute pancreatitis (AP) and ABP

Diagnosis of AP is based on the recommendation in the IAP (International Association of Pancreatology) /APA (American Pancreatic Association) guidelines [40]. It requires at least 2 of 3 criteria: (1) abdominal pain; generally, a sudden, epigastric, abdominal pain radiating to the back; (2) serum amylase and/or lipase increased three times greater than the upper limit of normal; and/or (3) radiographic evidence of pancreatitis.
Gallstone pancreatitis can be suspected when patients have a prior history of biliary colic, so a detailed history and careful physical examination are the first steps towards making the diagnosis.

Laboratory parameters are critical for diagnosis when a patient presents with gallstone pancreatitis. Serum amylase and lipase levels are more than three times the upper limit of

normal, caused by acute pancreatitis. The ratio of lipase to amylase may help distinguish alcoholic from nonalcoholic pancreatitis, with a decreased ratio suggesting acute gallstone-related pancreatitis [41], [42]. The amylase and lipase levels do not correlate with disease severity and do not help determine prognosis.

An increase in serum liver enzyme concentrations (alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and bilirubin) might help in the prediction of gallstones. An elevated ALAT level is the best laboratory indicator of biliary pancreatitis; a level of more than three times the upper limit of normal has a positive predictive value of 95% for biliary pancreatitis. However, a normal ALAT does not exclude gallstones as a cause [43], [44]. Almost 15–20% of patients with ABP manifest with normal liver function tests [45].

Radiological investigations are crucial for diagnosis and prediction of prognosis when a patient is supposed to have ABP. The dilation of CBD greater than 8 mm in a patient with an intact gallbladder aged ≤ 75 years and >10mm in patients aged >75 years indicates biliary obstruction. The finding of cholecystolithiasis or biliary sludge lends further support to the diagnosis of gallstone pancreatitis.

Although transabdominal ultrasound is the primary investigation of choice for gallbladder stones, with an overall accuracy of over 95%, it is much less accurate in the emergency setting, detecting stones in only 70–80% of cases [46], [47]. A Chinese study, published by Liu et al., reported a false negative rate of 25% for a transabdominal ultrasound scan (USS) in detecting cholecystolithiasis [48]. The sensitivity of USS in detecting gallstones was only 89%, whereas endoscopic ultrasonography (EUS) was 100%. USS was also significantly inferior to EUS regarding their detection rates of choledocholithiasis (21% vs 98%). Therefore, patients with a negative abdominal USS for cholecysto- or choledocholithiasis but with clinico-biochemical parameters suggestive of a biliary cause should not be excluded from the diagnosis of biliary pancreatitis and should undergo repeated imagine techniques or endoscopic intervention to uncover gallstones.

Besides USS, computer tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and EUS are essential modalities for the detection of gallstones and complications of pancreatitis. International guidelines advocate performing CT examination at least 72 to 96 hours after the onset of symptoms [7], [40] because pancreatic necrosis rarely appears within 48 hours from disease onset. The leading role of CT

or MRI during the initial presentation of AP is to validate the unclear diagnosis or detect possible pancreatic complications when there is no clinical improvement within the first 48 to 72 hours after hospital admission.

MRCP is one of the non-invasive tests that can visualize the biliary and pancreatic trees. It is very accurate in detecting choledocholithiasis, with a sensitivity of 85–100% [49]. But as we know, its ability to diagnose small stones in nondilated ducts is limited. In contrast, the accuracy of EUS does not seem to be as dependent on larger stone size; it is highly sensitive and comparable with USS, CT, MRI, MRCP, and ERCP in detecting occult CBD stones [50]–[52]. So this tool is necessary for the selection of patients with choledocholithiasis for therapeutic ERCP. It is postulated that EUS can prevent unnecessary diagnostic ERCP and its complications in patients with suspected CBD stones [53].

III.1.4 The severity of AP

The severity of AP is classified into three categories based on clinical and morphologic findings according to the revised Atlanta classification [54]:

1. Mild –No organ failure and no local or systemic complications.
2. Moderate –Presence of transient organ failure less than 48h and/or presence of local complications.
3. Severe –Persistent organ failure > 48 hours.

Organ failure is defined as a score of 2 in 1 or more of the three organ systems described in the modified Marshall score (Table 1) [54].

Table 1 Definitions of acute pancreatitis and biliary pancreatitis used in the study

Diagnostic criteria of acute pancreatitis (based on IAP/APA guidelines 2013 [40])
2 out of 3 from the following criteria: (1) clinical symptoms (upper abdominal pain) (2) laboratory tests (serum amylase or lipase levels >3 times upper limit of normal) (3) abdominal imaging (e.g., ultrasonography, computed tomography, magnetic resonance imaging)

Criteria of biliary pancreatitis (laid down Dutch Pancreatitis Study Group [55])

(a) gallstones and/or sludge diagnosed on transabdominal ultrasound or computed tomography (CT) performed on admission or (b) dilated common bile duct on ultrasound or CT (diameter: >8mm for age ≤75 years and diameter: >10 mm for age>75 years)or (c) 2 of the following three laboratory abnormalities: (1) serum bilirubin level >1.3 mg/dL [>40 μmol/L]; (2) alanine aminotransferase (ALAT) level >100 U/L with an ALAT level greater than the aspartate aminotransferase level; (3) alkaline phosphatase level>195 U/L with a gamma-glutamyltransferase level >45 U/L. Other causes of acute pancreatitis (e.g., alcohol abuse) and signs of chronic pancreatitis (history and CT) had to be absent.

Definition of acute cholangitis (based on the Tokyo guideline 2018 [56])

A. *Systemic inflammation*

A-1. Fever and/or shaking chills

A-2. Laboratory data: evidence of inflammatory response

B. *Cholestasis*

B-1. Jaundice

B-2. Laboratory data: abnormal liver function tests

C. *Imaging*

C-1. Biliary dilatation

C-2. Evidence of the aetiology on imaging (stricture, stone, stent, etc.)

Suspected diagnosis: one item in A + one item in either B or C

Definite diagnosis: one item in A, one item in B, and one item in C

Modified Marshall scoring system for organ dysfunction (based on revised Atlanta classification 2012)

Score

Organ system	**0**	**1**	**2**	**3**	**4**
Respiratory (PaO2/FiO2)	>400	301–400	201–300	101–200	≤101
Renal* (serum creatinin umol/l)	≤134	134–169	170–310	311–439	>439

Cardiovascular (systolic blood pressure, mmHg) †	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2
For non-ventilated patients, the FiO2 can be estimated from below: Supplemental oxygen (l/min)	FiO2 (%)				
Room air	21				
2	25				
4	30				
6–8	40				
9–10	50				
A score of 2 or more in any system defines the presence of organ failure. *A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/l or ≥1.4 mg/dl. †Off inotropic support.					

The Bedside Index for Severity in Acute Pancreatitis (BISAP) is an accurate prognostic tool for early stratification of patients at risk for in-hospital mortality [57]. It is to be used in the first 24 hours of presentation and consists of 5 parts: blood urea nitrogen (BUN) level >25mg/dl (8.93mmol/l), impaired mental status, development of systemic inflammatory response syndrome (SIRS), age > 60 years, and presence of pleural effusion, ranging from 0-5 score. SIRS is defined by the presence of 2 or more of the following criteria: pulse >90 / min, respiratory rate >20 /min, or $PaCO_2$ < 32 mm Hg, temperature >38°C or <36°C and white blood cell count >12,000 or < 4,000 cells/mm^3.

Balthazar et al. developed a numerical scoring system, the CT severity index (CTSI) [58], to estimate the severity of AP. It combines the quantification of pancreatic and peripancreatic

inflammation with the extent of pancreatic parenchymal necrosis. In 2004 Mortele et al. defined the modified CTSI (mCTSI), including a simplified evaluation of complications [59]. The first meta-analysis, which quantifies the accuracy of CTSI and mCTSI scores for predicting severity and mortality of AP and compares them with other commonly used scoring systems, was recently published by the HSPG [60]. In the prediction of mortality in AP, CTSI was shown as equally valuable as BISAP, mCTSI, CRP, or Ranson score; only APACHE II score overcame its predicting ability. There was no difference in the prediction value of the score considering severity. If CT scans are performed, CTSI and mCTSI can be easily calculated and used in addition to the other scoring systems.

III.1.5 Management of ABP

Management of ABP requires two treatment strategies in most cases. The general, conservative medical treatment consists of appropriate fluid resuscitation (preferably lactated Ringer's solution) [61], correction of electrolyte and metabolic disturbances, analgesic therapy, treatment of associated biliary tract infection, management of respiratory, cardiac, renal, and vascular failure and enteral nutrition in some cases [62].

Since its introduction in 1968, ERCP has become the gold standard interventional strategy in ABP to achieve biliary decompression.

Although as we know, most cases of ABP are self-limiting, and there is no need for invasive treatment because most gallstones spontaneously pass to the duodenum. In addition, the incidence of post-ERCP complications, including pancreatitis, cholangitis, bleeding, perforation, cholecystitis, and adverse events related to sedation, radiation, biliary stent occlusion, is relevant [63], [64].

The data provided by meta-analyses of randomized controlled trials (RCTs), where the most recent ones analyzed 10 and 11 RCTs, demonstrated a significant decrease in complications, hospital stay, and cost in patients with ABP managed with early ERCP (within 72 hours) compared to conservative management [65], [66].

In 2010 the American Society for Gastrointestinal Endoscopy (ASGE) practice guideline suggested a stratified approach to investigate suspected choledocholithiasis based on the three likelihood categories: high, intermediate, and low. If suspicion of gallstone pancreatitis is high, ERCP is the advocated therapy. While with intermediate probability of CBD stone, sequential EUS and ERCP must be considered preferred modality [67].

In cases of concomitant acute cholangitis, the need for urgent (within 24 hours) ERCP is recommended. As previous studies have shown, it is not necessarily the severity of ABP that should determine the urgency of ERCP but the duration of the biliary obstruction. A recent RCT published by the Dutch Pancreatitis Study Group investigated early ERCP's role with biliary sphincterotomy in predicted severe ABP without cholangitis. It proved that early ERCP did not reduce the composite endpoint of major complications (organ failure, cholangitis, bacteremia, pneumonia, pancreas necrosis, insufficiency of pancreas in 6 months) or mortality [68], [69]. Notably, CBD stones were found only in 43% of patients.

There is also a clear indication of ERCP in cases of obstruction where biliary drainage must be adequately resolved in a short time [1], [40], [56], [70]. Most international guidelines recommend that ERCP be performed within 72 hours in patients with bile duct obstruction without cholangitis. However, there is still no definite consensus about the optimal timing for endoscopy.

On the other hand, without apparent signs of cholangitis or obstruction (manifest systemic inflammation, biliary stones or dilatation on imaging, and jaundice or abnormal liver function test), the indication of ERCP in the setting of ABP is still debated because of the lack of available evidence [1], [40].

An ongoing multicenter RCT organized by the HPSG called PREPAST trial is set to determine the role of preventive pancreatic stents in managing gallstone pancreatitis [71]. It hypothesizes that maintaining the outflow of the pancreatic duct with stents at the early ERCP improves the outcome of ABP.

Despite the studies noted above, optimal comprehensive endoscopic management of ABP still lacks clear evidence.

National and international guidelines recommend cholecystectomy in mild ABP during the index hospital admission [11], [72] to prevent further recurrent biliary events.

III.2 Materials and methods

III.2.1 Inclusion criteria

All patients with AP were enrolled, and their data were prospectively collected in the HPSG AP Registry, approved by the Scientific and Research Ethics Committee of the Medical Research Council (TUKEB-22254-1/2012/EKU). All patients were informed about the data

collection and signed the informed consent forms. According to the IAP/APA guidelines, an AP diagnosis was made, with at least two of the following three criteria met: abdominal pain, pancreatic enzyme exceeding more than three times the upper normal level, and features of pancreatitis on imaging.

In this cohort study, we selected patients who fit the criteria previously laid down by the Dutch Pancreatic Study Group, which were used to determine biliary origin: (a) gallstones and/or sludge diagnosed on transabdominal USS or CT or (b) dilated CBD on USS or CT (diameter: >8mm for age ≤75 years and diameter: >10mm for age>75 years) or (c) two of the following three laboratory abnormalities: (1) serum bilirubin level >1.3 mg/dL [>40 µmol/L]; (2) ALAT level >100 U/L with an ALAT level greater than the ASAT level; and (3) ALP level>195 U/L with a GGT level >45 U/L. Other causes of AP, such as alcohol, hypertriglyceridemia, diet, drug, trauma, viral infection, post-ERCP, and idiopathic AP, had to be absent [55].

691 patients with AP were enrolled in the AP registry between January 2013 and August 2015 from 14 centres.

III.2.2 Exclusion criteria

Patients under the age of 18 years and those with non-biliary pancreatitis were excluded from the analysis.

III.2.3 Data extraction

Data on demographics (sex and age), aetiology, severity, and mortality of AP were extracted for all subjects with AP, and a descriptive statistical analysis was performed. The severity of AP was classified according to the revised Atlanta classification as mild, moderately severe, and severe [54]. Main outcomes were the severity of pancreatitis, local (peripancreatic fluid, pseudocyst, necrosis of pancreas on imaging, diabetes mellitus, and abdominal compartment syndrome) and systemic (transient or persistent organ failure based on the modified Marshall scoring system for organ dysfunction) complications, mortality, and length of hospital stay.

Detailed demographics, including body mass index, co-morbidities, and data on outcomes for ERCP, were collected on patients with ABP, such as the indication of ERCP, successful cannulation rate, management of CBD stones by sphincterotomy and duct clearance, biliary and pancreatic stenting, anatomy of the papilla (naïve/not naïve), and complication rates (bleeding and perforation). The timing of ERCP was calculated from admission. The outcomes for ABP

(severity of pancreatitis, local and systemic complications, mortality, and length of hospital stay) were analyzed in relation to ERCP timing. No follow-up was carried out after hospital discharge.

III.3 Statistical analysis

Continuous measures are summarized and presented as means and standard deviations (SD) or medians and interquartile ranges (IQR). Categorical data are presented as observed and as percentages. To determine differences between continuous parameters, depending on the data distribution, we used the independent Student's t-test or the Mann–Whitney U test for two groups and one-way ANOVA with the Bonferroni post-hoc test or Kruskal–Wallis test in comparing more than two groups. We used the Chi-square test or Fisher's exact test to analyze the relations between the factors under examination. All analyses were performed with SPSS 24 statistical software (IBM Corporation).

III.4 Results

III.4.1 General characteristics of the AP cohort

Biliary etiology was found in 356 (51.5%) patients, and 335 (48.5%) patients had other aetiological factors (alcohol, hypertriglyceridemia, diet, drug-induced, trauma, viral infection, post-ERCP, and idiopathic AP). Among the subjects with ABP, there were more women, and they were older than patients with a different aetiology [204/356 (57.3%) vs 106/335 (31.6%) ($P < 0.001$)] and mean age [61.5 ± 17.32 vs 51.47 ± 15.73 years ($P < 0.001$)]. The course of pancreatitis with biliary etiology was milder in contrast to non-ABP disease [mild ABP: 248/356 (69.7%) vs non-ABP: 183/335 (54.6%); moderately severe ABP: 86/356 (24.2%) vs non-ABP: 121/335 (36.1%); severe ABP: 22/356 (6.2%) vs non-ABP: 31/335 (9.2%) ($P < 0.001$)]. There was no difference in mortality between the two groups [ABP: 8/336 (2.4%) vs non-ABP: 13/322 (4.0%) ($P = 0.242$)] [73].

III.4.2 Characteristics of the ABP cohort

Acute pancreatitis diagnosis was based on upper abdominal pain and elevated pancreatic enzymes in 327/356 (91.8%).

ABP occurs more commonly in women [204/356 (57.3%) female vs 152/356 (42.7%) male]. In almost 10% of the cases, ABP developed after a cholecystectomy [35/356 (9.4%)] and more frequently in women [28/204 (13.9%) vs 7/152 (4.6%) (P = 0.004)].

Diabetes mellitus as a co-morbidity was found in 16.6% (59/356) of the patients, significantly more often in men [26/204 (12.7%) vs 33/152 (21.7%) (P = 0.023)].

Age, a previously documented episode of pancreatitis, body mass index (BMI), and co-morbidity were not different between the two sexes. A considerable number of ABP patients had more than two co-morbidities [43.5% (155/356)] (Table 2).

Table 2 General characteristics of the acute biliary pancreatitis cohort

	All [n (%)]	**Women [n (%)]**	**Men [n (%)]**	**P-value**
Gender	356	204 (57.3%)	152 (42.7%)	-
Age	61.65 ± 17.32	61.3 ± 18.1	62.1 ± 16.1	NS
Prior cholecystectomy	35 (9.4%)	28 (13.9%)	7 (4.6%)	**0.004**
Previously documented pancreatitis	42 (11.8%)	26 (12.7%)	16 (10.5%)	NS
Diabetes mellitus	59 (16.6%)	26 (12.7%)	33 (21.7%)	**0.023**
Body mass index (available for 160 women and 123 men)	28.31 ± 6.1	28.24 ± 6.03	28.40 ± 6.22	NS
At least 2 co-morbidities	155 (43.5%)	85/204 (41.7%)	70/152 (46.1%)	NS

According to the revised Atlanta classification, the majority of the cases (69.6%) were mild, 24.2% were moderate, and 6.2% were severe course of disease [54]. The incidence of severe cases was higher in older patients, though the rate was statistically not significant. Mortality was 2.4% in total, and the median days of hospital stay were 9 days. Both mortality and length of hospital stay showed significant differences between the mild, moderate and severe groups as shown in Table 3.

The most common local complication was the formation of peripancreatic fluid collection in 17.7% of ABP cases. Necrosis developed in 11.8%, mostly in severe AP.

Table 3. Characteristics of ABP patients according to the severity

	Mild	**Moderately severe**	**Severe**	**Total**	**P- value**
Total /%:	**248/ 69.6%**	**86/ 24.2%**	**22/ 6.2%**	**356/ 100%**	
Age (years):	61.93±17.44	59.19±18.08	68±10.17	61.65±17.32	NS
Local complications:	-	80/86 (93%)*	18/22 (81.8%)	98/356 **(27.5%)**	***<0.001**
Peripancreatic fluid collections:	-	53/86 (61.6%)	10/22 (45.4%)	63/356 **(17.7%)**	
Necrosis:	-	28/86 (32.6%)	14/22 (63.6%)	42/356 **(11.8%)**	
Systemic complications:	-	8/86 (9.3%)	18/22 (81.8%)*	26/356 **(7.3%)**	***<0.001**
Respiratory failure:	-	3/86 (3.5%)	17/22 (77.3%)	20/356 **(5.6%)**	
Hospital stay (median days):	8 (6-11)*	14.5 (10-24)	19.5 (8-54)	**9** (6-13)	**<0.001**
Mortality:	0	1/86 (1.2%)	7/22 (31.8%)*	8/336 **(2.4%)**	**<0.001**

III.4.3 Indications for endoscopic retrograde cholangiopancreatography (ERCP)

Out of the 356 patients, 267 underwent ERCP (75.0%) for suspected cholangitis or cholestasis without cholangitis based on raised inflammatory markers, dilated biliary ducts and increased liver function tests. 89 patients did not undergo ERCP, although it would have been indicated in 50 cases of suspected cholangitis (56.2%). ERCP was not performed in these cases due to an improving clinical picture, lack of patient consent, or rapid multi-organ failure deterioration.

Based on the available data, endoscopic ultrasonography (EUS) was performed in only five patients with bile duct stones identified in two cases, and one patient had MRCP reporting clear bile ducts.

III.4.4 Quality indicators and findings of ERCP

The key performance indicators for ERCP met the criteria set out in the American Society of Gastrointestinal Endoscopy (ASGE) guidelines [74]. Successful biliary cannulation was achieved in 233 subjects with naïve papilla (90.7%), but the successful cannulation rate was 84.0% (216 procedures) at the first attempt. In 80 subjects, extractions of stones smaller than 1 cm were successful in 93.7% of the cases.

Stones were removed by Dormia basket in 59.6% and with ballon in 12.8% of cases. There were 12.4% of patients where Dormia and ballon techniques were used together to achieve extraction. In the rest of the subjects, either precut or sphincterotomy resulted in the migration of stones.

Stent implantation below the bifurcation was successfully carried out in all cases after successful deep biliary cannulation (33/33). Perforation occurred in 1/267 (0.4%) of the cases. Clinically significant bleeding requiring blood transfusion developed in 3/267 (1.2%) of the patients.

Common bile duct (CBD) stones, sludge, and/or dilation of the bile ducts were reported in 97 (36.3%), 91 (34.1%), and 124 (46.4%) cases, respectively. Spontaneous passage of a bile duct stone was suspected in 19.5% (52/267) of the patients during ERCP. In 30 cases (11.2%), no biliary pathology was found by ERCP. Endoscopic ultrasound was only carried out in five cases because of limited access at the time of data collection.

315 ERCPs were performed in 267 patients until completion or abandoning the intervention or treatment, 43 patients had two ERCPs, and five had three procedures.

III.4.5 Outcomes for ABP in relation to success rates of ERCP

Data on cannulation success rate and clearance of the bile ducts were available in all cases. The success rate for bile duct cannulation in all patients was 83.5% (223/267) during the first ERCP, and any further endoscopic attempts resulted in a higher rate of success [90.6% (242/267)]. Successful cannulation was achieved in 84.0% (216/257) of patients with naïve papilla, and

clearance of the bile duct was successful in 71.5% (191/267) at the first ERCP attempt. Endoscopic biliary sphincterotomy was done in 86.5% (231/267) of the ERCPs, whereas pancreatic sphincterotomy was only performed in 1.1% (3/267) of the cases. Biliary stents were placed in 12.4% (33/267) and pancreatic stents in 16.8% (45/267) cases. Successful cannulation was associated with significantly lower rates of local and systemic complications. Successful clearance was linked to lower rates of local complications. Successful cannulation and clearance correlated with a less severe course of ABP and shorter hospitalization (Tables 4 and 5).

Table 4 Successful cannulation versus failure to cannulate the common bile duct (CBD) with the first endoscopic retrograde cholangiopancreatography in the acute biliary pancreatitis cohort

	Successful bile duct cannulation with 1st ERCP [n (%)]	**Failure to cannulate the bile duct with 1st ERCP [n (%)]**	**P-value**
Total (n=267)	**223 (83.5%)**	**44 (16.5%)**	
Rates of severe disease	8 (3.6%)	7 (15.9%)	**0.001**
Local complications	51 (22.9%)	18 (40.9%)	**0.012**
Systemic complications	11 (4.9%)	6 (13.6%)	**0.042**
Mortality	4 (1.8%)	1 (2.3%)	NS
Hospital stay, median (IQR)	9 (6–13)	14 (8–21.5)	**0.00021**

Table 5 Successful clearance versus failure to achieve clearance of the common bile duct for all endoscopic retrograde cholangiopancreatographies in the acute biliary pancreatitis cohort

	Successful bile duct clearance [n (%)]	**Failure of clearance the bile duct [n (%)]**	**P-value**
Total (n=267)	**218 (81.6%)**	**49 (18.3%)**	
Rates of severe disease	9 (4.1%)	6 (12.2%)	**0.033**
Local complications	49 (22.5%)	20 (40.8%)	**0.008**
Systemic complications	13 (6.0%)	4 (8.2%)	NS

Mortality	4 (1.8%)	1 (2.0%)	NS
Hospital stay, median (IQR)	9 (6–13)	11 (7–21)	**0.021**

Complete failure of clearance and decompression of the bile ducts were related to a higher frequency of local complications, a more severe course of ABP, and longer hospital stay (Table 6).

Table 6 Successful clearance versus failure of clearance and decompression of common bile duct for all endoscopic retrograde cholangiopancreatographies in the acute biliary pancreatitis cohort

	Successful clearance of bile duct [n (%)]	**Unsuccessful clearance and decompression of bile duct [n (%)]**	**P-value**
Total	**218/267 (81.6%)**	**32/250 (12.8%)**	
Rates of severe disease	9 (4.1%)	6 (18.7%)	**0.001**
Local complications	49 (22.5%)	16 (50.0%)	**0.001**
Systemic complications	13 (6.0%)	4 (12.5%)	NS
Mortality	4 (1.8%)	1 (3.1%)	NS
Hospital stay median (IQR)	9 (6–13)	16 (8.5–24.5)	**0.001**

III.4.6 Outcomes for ABP in relation to the timing of ERCP

ERCP was performed in 75% (267/356) of the cases, most of them during the first 24 hours after admission. Data on the timing of ERCP were available in 256 (95.9%) cases. ERCP was performed on 64.8% (166/256) of the patients within 24 hours after admission, in 18.4% (47/256) of them between 24 and 48 hours after admission, and 16.8% (43/256) cases later than 48 hours after admission. A tendency of an increased rate of local complications was observed if ERCP was performed later [ERCP in 24 hours: 21.1% (35/166); between 24 and 48 hours: 23.4% (11/47); after 48 hours: 37.2% (16/43) (P = 0.088)].

We note that only 1.1% (7/267) of the endoscopic interventions described signs of purulent cholangitis.

The length of hospitalization was significantly longer in all patients if ERCP was delayed (Table 7).

Table 7 Outcomes for acute biliary pancreatitis in relation to the timing of endoscopic retrograde cholangiopancreatography in all patients with acute biliary pancreatitis

	<24 hours [n (%)]	**24–48 hours [n (%)]**	**>48 hours [n (%)]**	**P-value**
Total (n=256)	**166 (64.8%)**	**47 (18.4%)**	**43 (16.8%)**	
Rates of severe disease	5 (3%)	3 (6.4%)	3 (7.0%)	NS
Local complications	35 (21.1%)	11(23.4%)	16 (37.2%)	**0.088**
Systemic complications	7 (4.2%)	4 (8.5%)	4 (9.3%)	N/A*
Mortality	2 (1.2%)	1 (2.1%)	0 (0%)	N/A*
Hospital stay, median (IQR)	8 (6–12)	10 (5.5–15)	13 (9.5–21)	**<0.001**

**Statistical analysis was not carried out in cases of systemic complications, mortality, and rates of severe disease due to low numbers of subjects.*

III.4.7 Other relevant findings

There was no statistically significant difference in ABP outcomes between the patients treated with or without ERCP. (Table 8).

Table 8. Outcomes of patients treated with endoscopic management or conservative therapy

	Endoscopic retrograde cholangiopancretography [n (%)]	**Conservative therapy [n (%)]**	**P-value**
Total (n=356)	**267 (75%)**	**89 (25%)**	
Rates of severe disease	15 (5.6%)	7 (7.9%)	NS

Local complications	69 (25.8%)	29 (32.6%)	NS
Systemic complications	17 (6.4%)	9 (10.1%)	NS
Mortality	5 (1.9%)	3 (3.4%)	NS

The use of antibiotics was a common practice. 87.6% (312/356) of all the patients received antibiotics, for which the indication was suspected cholangitis in 85.3% (266/312). They were administered to treat infections outside the biliary tree, such as pneumonia and urinary tract infections, in 11.9% (37/312) of the cases. The first choice among antibiotics for cholangitis was a combination of cephalosporin and metronidazole.

Enteral nutrition was administered in 27.5% of patients; nearly all of them (99%) received nasojejunal feeding. Parenteral nutrition was employed in only 4% of the cases.

III.5 Discussion

III.5.1 Epidemiology of ABP

This multicenter study analysed the prospectively collected, real-world data and presented considerable coverage of Hungarian acute biliary pancreatitis cases. The data shown above depict current management strategies used in Hungary.

Although a clear-cut diagnosis of definite cholangitis would have been desirable in our analysis, currently, there is no validated definition of cholangitis in the setting of ABP. Simple AP can result in a transient and self-resolving biliary obstruction with deranged liver function tests and dilated biliary tree, which can mimic cholangitis with the raised inflammatory markers and fever driven by pancreatitis. Thus, the definition of definite cholangitis as termed by the Tokyo criteria had to be avoided [55].

As described in other studies, we found that patients with ABP are older, and there are more women among them than AP of other etiologies [14]. Though we saw only an association between old age and severity of pancreatitis, it is already proven that ageing modifies the outcome and predicts the severity of AP [75], [76].

ABP tended to have a less severe natural course in the Hungarian cohort, but the mortality was the same as in other etiologies, as reported in a large study [2].

A previous cholecystectomy was relatively common and more so in women. This could be explained by the fact that biliary stone disease is more common in females and that stone disease of the gallbladder increases the risk of ABP, most likely even after a previous cholecystectomy.

Guidelines recommend cholecystectomy after ABP during the same admission or within 7 days of discharge in mild pancreatitis [7], [40]. The PONCHO trial revealed that early cholecystectomy after mild ABP is safe and reduces the risk of pancreatitis recurrence and other stone–related diseases [4]. An elective endoscopic biliary sphincterotomy is offered to patients who are unfit for surgery because of old age or comorbidities [7], [77]. A recent and ongoing prospective randomized-controlled, multicentric trial, called EMILY, investigates whether endoscopic sphincterotomy with delayed cholecystectomy compared to sphincterotomy with early cholecystectomy could reduce recurrent biliary events after an ABP attack [78].

A previous episode of AP occurred in more than 10% of the patients. Although data on the aetiology of the previous attack was not available, we believe that most of the cases were likely

driven by gallstone disease, similar to data reported by Bakker et al. [8]. Diabetes is a known risk factor for AP, and significantly more men had diabetes in the Hungarian cohort, which was reported in AP with all etiologies [11].

III.5.2 ERCP and other modalities for diagnosis and treatment of gallstone pancreatitis

ERCP was performed in 75% of the patients presenting with ABP. To our best knowledge, there are no previous cohort studies where the rate of ERCP in ABP was published and analyzed. We found that our ERCP practice in ABP is in line with the current guidelines; however, we must highlight that very limited access to urgent endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) resulted in several avoidable ERCPs. At the same time, a small proportion of the patients with suspected cholangitis were not amenable to ERCP.

As it is well known that most ABP patients have spontaneous passage of stones into the duodenum [79], ERCP could be avoidable in a greater part of the cases. The presence of cholestatic liver enzymes and dilated common bile duct are proven not to be reliable factors for detecting the presence of common bile duct stones [67]. Hence, in patients with a clinical probability of CBD stones, ESGE recommends performing EUS or MRCP [80].

This statement is also supported by a systematic review of RCTs and clinical trials comparing EUS and ERCP published by De Lisi. EUS before ERCP resulted in avoidable ERCP in 71.2% of AP cases [81].

The sensitivity of MRCP in detecting choledocholithiasis is 85–100% [49], but it decreases to about 65% when investigating stones smaller than 5 mm. MRCP is a less invasive method, less dependent on the examiner, although patients with claustrophobia or implantable electronic devices and some metal prostheses are contraindications for MRI.

The sensitivity of EUS is about 90%, independently of stone size [50]. The presence of pancreatitis did not significantly impact the overall diagnostic ability of EUS in a study published by Garrow et al. [50]. Stones <4mm in dilated CBD may not be revealed during ERCP, as it is known. By performing EUS first, about two-thirds of ERCPs can be avoided, although this invasive intervention requires proper patient selection. Moreover, the advantage is that EUS and ERCP can be performed in a single session if needed.

The diagnostic value of EUS in suspected biliary obstruction has been approved over MRCP. However, its spread in Hungary has been slow because of technical, staffing and financing issues. This clinical practice needs to be improved.

III.5.3 Quality indicators of ERCP

The monitoring of quality indicators of ERCP is crucial in current practice as this endoscopic intervention has the highest rate of complications. For this reason, a national data-collecting system, the so-called Hungarian Endoscopic Retrograde Cholangiopancreatography Registry, was initiated by the Institute for Translational Medicine in 2017 in Pécs [82]. Therefore the indications, the methods, the success rate and the complications of the intervention can be evaluated. The quality indicators were established according to the ASGE.

The first Registry data published in 2018 presented the success rate of cannulation in 93.8% in all cases. The successful cannulation with native papilla was achieved in 81.0% during the first procedure. Post-ERCP pancreatitis was developed in 2.2%, clinically significant post-papillotomy bleeding in 0.3%, and the perforation rate was 1.3%. The success rate of extractions of biliary stones and biliary stenting has achieved the criterion recommended by ASGE. The main indication of ERCP was acute cholangitis in 41.0%, whereas acute biliary pancreatitis in only 5.4%.

Some of the key performance indicators describing the ERCP practices in our large cohort across many centres described suboptimal ERCP practices. Most importantly, a success rate of 84 % at the first attempt (216 patients) is below the quality benchmark of >90% recommended by ASGE. This may well be driven by the fact that some of the ERCPs were performed in low volume centres. It also reminds us that, if indicated, high-quality ERCP with maximal pancreas protection and high competence of alternative biliary access techniques should be mandatory.

One of our main findings is that failed cannulation, and bile duct clearance are associated with a higher incidence of local complications and severity of ABP. This result can be interpreted in two ways. Firstly, successful clearance and decompression of the bile ducts can result in a quicker resolution of pancreatitis and less progression leading to complications. Secondly, it may be explained by the difficult access to the bile ducts in already complicated AP, driven by difficult intubation of the duodenum, poor visualization of the papilla, limited manoeuvrability of the duodenoscope, and challenging cannulation of the edematous papilla. ERCPs are

therefore done for the indication of acute biliary pancreatitis classified as grade 3 difficulty on the modified Schutz grade, on a scale of 1–4, where 4 is the most difficult [83].

In this situation, high success rates can only be expected from competent, highly skilled endoscopists with substantial case numbers. This is how we explain the slightly suboptimal quality indicators (ASGE guideline) of ERCP in this cohort [74]. Cannulation of naïve papilla was successful at first attempt in 84.1% of all ERCPs (desired: 90%), perforation occurred in 0.4% (desired: ≤ 0.2%), and bleeding requiring transfusion resulted in 1.2% (desired: ≤ 1%). We note that this analysis contained data from 267 patients, hence the two latter measures. Quality indicators of stone extraction and stenting of obstructions below the level of bifurcation met the criteria for the guidelines.

In most cases, the indication was suspected cholangitis, and these are the patients who could have benefited most from additional diagnostic imaging [12], [84].

A prospective national cohort from the hungarian ERCP Registry was published by Pécsi et al. initiated to compare patients with ABP and patients with acute cholangitis without ABP [85]. These data support that ERCP is more difficult in ABP supported the ASGE grading. It is worthy of note that they found a normal cholangiogram in 20.0% of ABP cases. This also supports our statement that acute cholangitis is complicated to diagnose in ABP. The lack of access to additional diagnostic tools (EUS or MRCP) resulted in many unnecessary and avoidable ERCPs. Exclusion of pancreaticobiliary abnormalities on EUS is a key method for diagnosing idiopathic acute pancreatitis as well.

In summary, we believe that ERCP for ABP will be reduced with an accurate prediction of CBD stones as access to EUS and MRCP improves.

We did not find a significant decrease in the rate of local complications and hospital stay in the cohort when ERCP was performed within two days. Evidence suggests that early ERCP in ABP with cholangitis is indicated [1], [40], [56], [70], but our findings could not reinforce these previous data. In predicted severe ABP without cholangitis, urgent ERCP with biliary sphincterotomy is proven not to be superior to early endotherapy [55], [69], [86]. On the other hand, regardless of disease severity, in patients with a clear-cut diagnosis of acute cholangitis, endoscopic sphincterotomy should be considered as soon as possible to provide a better outcome [87].

According to the latest report by Párniczky et al. [88], antibiotics are overused worldwide in acute pancreatitis. There is agreement that besides acute cholangitis, in the infection of necrotic pancreatic tissue and any other extrapancreatic infections, antibiotic treatment is indicated. It is verified that CRP and WBC are not feasible biomarkers for antibiotic therapy in the early phase of AP. Procalcitonin level can be the indicator in the absence of proven pancreatic or extrapancreatic infection [88]. Just like the need for ERCP, the high rate of antibiotic use reported in our study (87.6%) could be reduced by better access to EUS and MRCP in the case of suspected cholangitis. However, cholangitis is one of the most feared sources of abdominal infection and can lead to sepsis, multiple organ failure, and death. Therefore, any strategy to delay or withhold antibiotics in the context of suspected cholangitis should be carefully assessed.

Educational activities should be organized and materials disseminated to ensure strict adherence to international guidelines [1], [40].

III.6 Strengths and weaknesses of the study

This cohort represents a general, diverse, multicenter (not only tertiary centres participated) acute biliary pancreatitis sample. For this reason, broader, more generalizable conclusions could be drawn. Limitations of this study are the relatively low case numbers in subgroups and the retrospective design with post-hoc question raising, which is susceptible to biases, thus limiting the conclusions considerably. Lastly, many participating ERCP units without a structured approach to the timing of ERCP procedures in ABP limits the statistical findings on associations with the outcomes of pancreatitis.

IV. Chapter II. - Evidence for diagnosis for early chronic pancreatitis after three episodes of acute pancreatitis

IV.1 Introduction

Chronic pancreatitis (CP) is a severe condition that greatly deteriorates the quality of life and decreases life expectancy. Importantly, there is no specific curative intervention available [9], [89], [90]. Patients with CP typically struggle with pain, stigmatization, unemployment and depression [91], [92]. The diagnostic criteria for CP only allow us to detect the disease at the end-stage. Around 90% of pancreatic parenchyma is already irreversibly damaged, resulting in endocrine and exocrine insufficiency [93]. Another issue is that 68% of cases are caused by alcohol, which negatively influences patients' compliance with any therapy [94].

Biliary tract disease rarely causes CP. Cholestasis is usually temporarily caused by oedema of the pancreas, obstruction or compression of the bile duct via stones, sludge or local complications of pancreatitis. It can resolve spontaneously or via endoscopic intervention. Therefore CP with biliary aetiology is not a common entity.

The Japanese Pancreatic Society has already provided a definition of early CP (ECP). They recommend that patients who fail to qualify for a definitive or probable diagnosis of CP, continuously drink more than 80 g/day alcohol and show at least two out of seven characteristic findings on endoscopic ultrasonography should be diagnosed with ECP. However, this diagnosis may be uncertain since it includes patient- and observer-reported components [95]. The four leading pancreatic societies (IAP, APA, JPS (Japan Pancreatic Society) and EPC (European Pancreatic Club) have attempted to agree on the definition of ECP; however, even after long and exhaustive discussions, the consensus has not been reached. The board of investigators stated that any single biomarker could not diagnose ECP since all early biomarkers are nonspecific [96].

Several pathomechanisms were proposed earlier to describe disease progression towards CP [97], [98]. Sankaran et al., based on their meta-analysis, investigated a frequency of progression from AP to CP. They have found that more than 10% of patients with a first episode of AP and 36% of patients with recurrent AP develop CP [99]. Another model approaching the transition of AP towards CP is the sentinel acute pancreatitis event (SAPE) [100].

DeSouza et al. reported a high-quality MR study that demonstrated “pancreas shrinkage” after ≥ 3 attacks of AP [101]. However, extensive cohort analyses are still lacking.

IV.2 Materials and methods

This study is a comparative cross-sectional study. We extracted and analysed data from the AP and CP registries of HPSG. The AP registry contained data from 1435 patients from 28 centres in twelve countries collected between June 2012 and September 2017, and 1315 were eligible for analysis. The CP registry had clinical data from 366 patients from 25 centres in two countries collected between June 2012 and September 2017, 324 of whom (88.5%) were eligible for inclusion. No additional biomarkers from the CP registry were investigated.

IV.2.1 Definition of pancreatitis

Diagnosis of AP was established based on the recommendations of the HPSG guideline (adapted and updated from IAP/APA guideline)[40], while that of CP was based on the HaPanEU criteria[11], [89], [102]

IV.2.2 Patient groups

We formed three groups based on the morphology of the pancreas and the number of recurrent acute episodes. The first episode of AP without any chronic morphological change of the pancreas was labelled AP (983 cases). Cases with two or more episodes of AP without clinical signs and symptoms of CP or pancreatic morphological alterations were labelled recurrent acute pancreatitis (RAP) (270 cases). RAP was further divided into four subgroups based on the number of acute episodes (RAP2: two episodes of AP; RAP3: three episodes; RAP4: four episodes; and RAP5 + : five or more episodes). RAP 5 + consisted of 30 cases: twelve cases with five acute episodes, four cases with six, six cases with seven, three cases with eight, two cases with ten, two cases with eleven, and one with twelve. Any acute episodes based on clinical signs and symptoms and pancreatic morphological changes attributed to chronic inflammation were labelled CP (62 cases). The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council (22,254–1/2012/EKU). All participants in this study provided written informed consent.

IV.3 Statistical analysis

The mean ± standard error of the mean (SEM) values were calculated for descriptive statistics. The numbers and percentages of cases were computed for categorical variables. To check the normality of the data, we used the Kolgomorov-Smirnov test and/or visual inspection of the Q–Q plots. In the case of non-normal distributed variables, e.g., bilirubin, GGT, ASAT, ALAT, amylase and lipase, we transformed our data into the logarithmic scale to achieve normal distribution. We applied parametric tests (graphs were prepared from the raw data without transformation). To identify significant differences between groups, we used the following statistical tests for the whole dataset and subgroups. To observe differences between two groups, the independent t-test was applied to compare more than two groups; we used one-way ANOVA with a Tukey post hoc test to adjust the results for alpha error. The association between categorical variables was examined with the Chi-square test and the Fisher's exact test, depending on the sample size. All statistical tests were performed using SPSS statistical software version 25 (IBM Corporation, Armonk, NY).

IV.4 Results

1. One out of five patients with an acute episode suffers from RAP, in contrast to one out of twenty who has CP.

Out of the 1315 patients in the AP registry, a cohort of 983 (74.8%) patients had AP without CP, as opposed to 270 (20.5%) suffering from RAP without CP; 62 (4.7%) of the acute episodes were accompanied by already existing CP. Two-thirds of RAP cases had fewer than three attacks, in contrast to one-third experiencing three or more attacks. As regards sex and age, there is a clear trend in the groups. The male/female ratio was 53.4/46.6% with AP, 64.8/35.2% with RAP, in contrast to 72.6/27.4% with CP. The average age in years at the first attack in patients with AP was 56.7 ± 0.55, RAP was 52.7 ± 0.93, and CP was 55.5 ± 1.84 (**Figure 1.**).

Figure 1. Sex and age distribution across groups

	Groups	n	%	Epidemiology					
				Male	Female	Male%	Female%	Age (average/y)	Age (SEM/y)
	AP	983	74.8%	525	458	53.4%	46.6%	56.7	0.55
RAP-2	second AP	173	13.2%	111	62	64.2%	35.8%	52.6	1.21
RAP-3	third AP	43	3.3%	25	18	58.1%	41.9%	51.9	2.25
RAP-4	fourth AP	24	1.8%	16	8	66.7%	33.3%	50.7	3.59
RAP-5+	fifth AP	30	2.3%	23	7	76.7%	23.3%	52.57	3.56
	RAP	270	20.5%	175	95	64.8%	35.2%	52.7	0.93
	CP	62	4.7%	45	17	72.6%*	27.4%	55.5	1.84
	Total	1315	100.0%	745	570				

2. Bidirectional changes in alcoholic and biliary aetiologies in AP, RAP and CP patients.

50.2% of AP cases had biliary origin; however, the rate of this etiological factor continuously decreased towards CP (20.7% with RAP and 11.3% with CP). The distribution of alcoholic aetiology moved in the opposite direction: 19.4% with AP, 39.1% with RAP and 51.6% in the CP group (**Figure 2.**). The increasing proportion of cases with an unknown aetiology deteriorating from AP (19.6%) to CP (29%) could be due to a higher rate of genetic predisposition or the attrition of alcohol-dependent patients.

Figure 2. Aetiology of AP, RAP, CP and recurrent acute pancreatitis events in the cohorts

Leading aetiology						
Groups	AP		RAP		CP	
	number	%	number	%	number	%
Biliary	493	50.2%	63	20.7%	7	11.3%*
Alcohol	191	19.4%	119	39.1%	32	51.6%*
Lipid	48	4.9%	29	9.5%	1	1.6%
Idiopathic	189	19.6%	72	23.8%	18	29.0%

Leading aetiology								
Groups	RAP-2 (n=173)		RAP-3 (n=43)		RAP-4 (n=24)		RAP-5+ (n=30)	
	number	%	number	%	number	%	number	%
Biliary	43	24.9%[a]	4	9.3%[b]	2	8.3%[c]	6	20%[d]
Alcohol	65	37.6%[a]	21	48.8%[b]	9	37.5%	12	40.0%
Lipid	17	9.8%	1	2.3%	3	12.5%	3	10.0%
Idiopathic	41	23.7%	12	27.9%	6	25.0%	5	16.7%

3. Local complications are more frequent in CP than in AP or RAP, whereas systemic complications and mortality are less.

The demographic, epidemiological, and primary outcome parameters suggest that patients move closer to CP after each acute episode of AP. Therefore, investigating all biomarkers collected from patients during episodes of AP, irrespective of its relationship with the pancreas, may help us recognise ECP. Thus, in the next part of the study, we systematically analysed all the 102 biomarkers.

4. Fifteen out of 102 biomarkers showed significant alterations between the AP, RAP and CP groups.

Epidemiology-based markers (age, sex, smoking, alcohol consumption and BMI), aetiology-based parameters (biliary and alcoholic aetiology, serum levels of bilirubin, GGT, ASAT and ALAT), laboratory value (RBC), and pancreas-dependent parameters (rate of pseudocyst formation, serum amylase and lipase) showed significant differences between the groups as we published currently. In the level of serum lipase and amylase, due to the distorting effect of the low *n* number in the CP group, no significant differences were detected between the AP and CP groups [103]. However, the statistical difference could be seen when we elevated the n numbers in the CP group by merging the CP and RAP5+ groups (as the latter is biologically very close to the CP group). All in all, the dynamic changes of these parameters indicate that RAP represents a continuous transition from AP to CP.

5. The significant differences between the biomarkers measured during acute episodes in AP and CP disappear after 2–3 attacks.

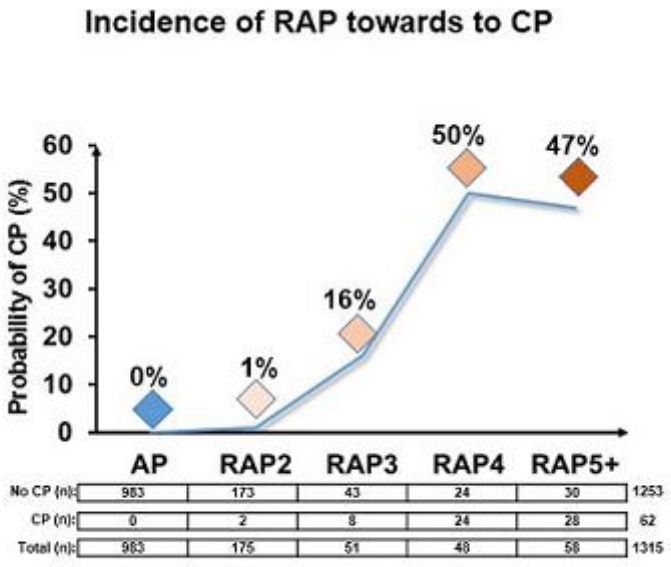
In these series of analyses, we aimed to determine the number of episodes of AP (without pancreatic morphological changes) required for significant differences in biomarkers to vanish compared to CP. The significant difference in eleven parameters disappears after the second episode of AP (RAP2; age, sex, aetiology, alcohol consumption, bilirubin, ASAT, GGT, RBC count, pseudocysts, amylase and lipase). The significant difference in BMI and ALAT disappears after the third episode of AP (RAP3). There is no difference in smoking after the fourth episode of AP (RAP4). Calculating the rate of morphological alterations after each episode revealed that 0.3% of AP, 1% of RAP2, 16% of RAP3, 33% of RAP4 and 32% of RAP5+ cases already have either CT-, MRI-, US- or EUS-based morphological alterations.

These data indicate a stage in CP development in which biomarkers show the disease progression earlier than pancreatic morphological changes.

6. In the RAP3 group, 16% of patients already have established CP, while the figure is nearly 50% in the RAP4+ group.

We also investigated whether the incidence of recurrent episodes increases the chance of CP development. Patients having had one or two episodes of acute inflammation had negligible odds of developing CP (less than 1%); however, patients who had experienced three episodes had a 16% chance of developing CP, and patients with four or more episodes had a 50% likelihood. These data demonstrate that three or more episodes of AP are considered a significant risk factor for the development of CP (**Figure 3.**).

Figure 3.



7. RAP patients have an average of three attacks, whereas CP patients have an average of four to five.

RAP patients had an average of 3.07±1.85 AP attacks at the time of diagnosis, whereas CP patients had 3.76±2.24 in the AP registry. We continued our analysis of data from the CP registry, which includes 366 patients. Out of this population, 324 cases had data on the number of attacks at the time of enrolment in the CP registry. In CP, 318 out of 324 patients had at least

one acute episode: 69 CP patients had one acute episode (21.6%), 66 had two (20.8%), 66 had three (20.8%), 29 had four (9.1%), and 88 had five or more (27.7%). The average number of attacks was 4–5 (4.07±3.82).

IV.5 Discussion

A large amount of data is available on AP and CP; however, much less is known about RAP and ECP. Therefore, it is not surprising that clinicians of the four major pancreatic associations disagreed on diagnostic criteria for ECP. The only association that has attempted to describe ECP is the Japan Pancreas Society. However, their guidelines are complicated, with only a limited possibility for use in general practice [95], [104]. Experimental models show that repetitive acute episodes of AP lead to CP [105], [106]; however, only a few data are available in clinical investigations. Two nationwide studies have already highlighted that repetitive inflammation of the pancreas can lead to CP [5], [6]. In a cross-sectional epidemiological study, Masamune et al. showed that 26.5% of ECP cases had previous acute episodes [5], [6] Importantly, the incidence rate of RAP was much higher in a two-year prospective follow-up study, in which 75% of patients had AP before ECP was diagnosed. These data support the SAPE model describing the transition of AP towards CP. According to this model, the first (so-called sentinel) episode of acute pancreatitis triggers a cellular activation cascade, which leads to chronic pancreatitis. The model proposes a tipping point when, in line with the multihit theory model, the effects of risk factors, such as alcohol consumption and smoking, turn into etiological factors, triggering the cascade that results in CP[96]. Findings from a cohort study by Sheel et al. were in line with this model [100].

Our international cohort investigated uniformly and prospectively collected 130,744 pieces of high-quality data from 1315 patients. Our epidemiological analysis revealed that one out of five AP patients suffers from RAP. In contrast, one out of twenty suffers from CP, which data were reported by the Japanese cohort studies. Of note, almost all the CP cases (98%) had a previous episode of AP, which is surprisingly high compared to earlier data by Olesen et al. (47%) [107]. We found 15 variables that were significantly different in the first AP and CP, and, importantly, the differences start disappearing after recurrent episodes of AP. Epidemiological data showed that the male gender, younger age and lower BMI are associated with RAP and CP, which data are in accordance with the findings of the Cleveland cohort, where the average age in years of the first AP was 55.5±16.6, that of the second was 53.8±18.5, and that of the third 45.2±12.4.

Importantly, no further changes were observed after the third attack of AP (45.7±16.5y), suggesting that three or more AP attacks may be a separate group of RAP [108].

One of the key findings of this study is that the incidence of recurrent episodes increases the risk of CP development. The first two attacks have small effects (0–1%) on the odds for developing CP, whereas the third and fourth (16–50%) episodes have large ones. At least three factors could explain the striking difference between RAP2 and RAP3: (1) The biliary aetiology decreased from 24.9% to 9.3%, whereas the alcoholic aetiology elevated from 37.6% to 48.8%. While the biliary aetiology is usually a one-time hit on the pancreas, alcohol has a continuous deleterious effect. (2) RAP3 occurs in a more damaged pancreas, which is confirmed by our experimental settings. (3) RAP3 seems to be more severe than RAP2 (mortality: 4.7% vs 2.3%; systemic complications: 4.7% vs 2.3%).

In a longitudinal study by Lankisch et al. [109] from Germany, CP was diagnosed after the second RAP in nine patients, after the third RAP in seven and after the fourth in three. Heavy smoking (>30 cigarettes per day) predisposed patients to CP after the first AP attack. The role of smoking was also confirmed by the findings of Yadav et al. [110]. Importantly, they found that the strongest predictor for a subsequent diagnosis of CP was RAP (HR=4.57, 95% CI: 3.40–6.14).

Our significant biomarkers clearly showed bidirectional changes in alcoholic and biliary etiologies in AP, RAP and CP patients. Similar changes were found in the Cleveland [108], Chinese [111] and Central European [89] cohorts as well.

A meta-analysis created by Zhong in 2019 proved that for patients with mild acute gallstone pancreatitis, early laparoscopic cholecystectomy is safe and effective and can shorten hospital stays, decrease the incidence of gallstone-related events, and reduce the overall usage of ERCP during the disease without increasing postoperative complications, conversion to open cholecystectomy, re-admission, and operation time [112]. In patients who are unfit for cholecystectomy because of old age or comorbidities, an elective endoscopic biliary sphincterotomy is offered to reduce recurrent biliary events after an ABP attack [7], [77].

Before the routine cholecystectomy era, biliary AP was even more frequent in RAP than in general AP [113]. Using endoscopic and/or surgical therapy, the biliary aetiology in CP (11.3%) is five times less than in the first episode of AP (50.1%); furthermore, it also suggests that repetitive episodes are one of the key determinants of CP.

Notably, Bertilssom et al. from Denmark reported that one or more AP episodes are among the strongest predictors for the development of CP [114].

The linear changes in the values of pancreas-dependent parameters (rate of pseudocysts, serum amylase and lipase) suggest that repetitive attacks lead to local damage of the pancreas, which is one of the hallmarks of CP. The elevation of local complication rates was reported in earlier published cohorts as well [13], [108], [111], [114]–[116].

We report that the on-admission elevation of serum lipase and amylase levels decrease from AP to CP via RAP. One of the most likely explanations is that these changes are due to the loss of pancreatic acinar cells. Therefore, since histological samples were unavailable in our cohort, we investigated this hypothesis in an experimental CP model [103]. As with human observations, the serum amylase level continuously decreased after the second and third attacks, which were associated with the loss of pancreatic parenchyma and enhanced fibrosis. The episode-dependent decrease in the elevation of amylase activity highlights the loss of acinar cells in the pancreas and the functional reduction in pancreatic enzyme secretion/leakage from acinar cells. Importantly, these data also indicate that the three-fold elevation of serum pancreatic enzymes may not be suitable for setting up a diagnosis in patients suffering from RAP. Taken together, both the clinical and experimental studies suggest that three or more episodes of RAP can be considered as ECP.

IV.6 Strengths and weaknesses of the study

One of the study's major limitations is the cross-sectional design: the patients were not followed longitudinally from AP through RAP to CP. Therefore, we have no information on the time of diagnosis of CP and the time relationships of RAP and CP. We decreased the limitations by analysing our CP cohort, in which patients were collected separately from our AP cohort. It is also important to note that some of the patients suffering from CP had no reported AP before their CP diagnosis. Therefore, our definition of ECP does not cover all ECP patients. Most cases of CP were confirmed with abdominal US and CT, which modalities have less diagnostic specificity and sensitivity for CP than EUS or MRCP. When abdominal US and CT showed main pancreatic duct dilatation or calcification and the aetiology was known (usually with a background of alcoholism), investigators did not use EUS or MRCP. Therefore, a more detailed analysis of the results of EUS or MRCP was not possible in this study. Our patient registries record only routine laboratory parameters, while analysing cytokine levels may have added extra information on the pathogenesis of transition. Statistical limitations include the fact that, since our publication has a hypothesis-generating purpose, we did not adjust tests for

multiplicity (except in the ANOVA model). In addition, data quantity and quality did not allow us to perform multivariate statistics. Mild differences in management strategies across centres may affect disease outcomes. We started a new international, observational, longitudinal investigation of acute pancreatitis, entitled the GOULASH PLUS study, to decrease the limitations described here. We will monitor all AP patients for six years to characterise ECP more precisely [117].

In addition to the limitations noted above, our research has several significant advantages: (1) it can be used easily in all hospitals, (2) no additional laboratory measurements or imaging techniques are necessary after ruling out CP with imaging to establish a diagnosis of ECP, and (3) it allows us to start clinical trials and encourage patients to implement lifestyle changes to prevent the development of CP from ECP.

In conclusion, we have provided the first widely usable definition of ECP. Our study shows that three or more episodes of RAP with no pancreatic morphological alterations should be considered ECP. Results from validation studies, such as the GOULASH PLUS study, are still forthcoming.

V. Conclusions

1. Indication and benefit of ERCP in patients with ABP but without a clear-cut diagnosis, cholangitis remains a contentious issue.
2. There is no validated definition of cholangitis in ABP, so the Tokyo Guideline can not be interpreted in ABP.
3. ERCP and cannulation of papilla is difficult in ABP (Shutz grade 3). Failed cannulation and bile duct clearance are associated with a higher incidence of local complications and severity of ABP.
4. Suboptimal ERCP practices are likely to be associated with poorer outcomes of ABP.
5. Invasive procedures should be performed by experts in high-volume centres.
6. Quality indicators of ERCP must be closely monitored.
7. Non-invasive diagnostic approach (EUS, MRCP) should be maximized to select the most suitable subgroup of ABP patients for ERCP.
8. RAP represents a continuous transition from AP to CP.
9. There is a stage in CP development in which biomarkers show the disease progression earlier than pancreatic morphological changes.
10. Three or more episodes of AP should be considered a significant risk factor for the development of CP.
11. Using endoscopic and/or surgical therapy, the biliary aetiology in CP is five times less than in the first episode of AP; furthermore, it also suggests that repetitive episodes are one of the key determinants of CP.

VI. My own work and future plans

As a specialist in internal medicine and a trainee gastroenterologist, I aimed to prove my professional skills and have a clear view of managing patients with acute pancreatitis. I actively recruited AP patients and monitored their data in the Registry for Pancreatic Patients by HPSG for three years.

I was involved in the thesis design, data extraction and interpretation, consulted with the biostatistician, reviewed the literature and worked on publication progress. I prepared the first version of the main article I. related to this thesis and took part in writing the final version. I worked in data collection and revised the final version of the main article II..
In the future, I wish to continue the work in the registries and clinical studies; nevertheless, I want to become a gastroenterologist and widen my skills and experience in the endoscopic management of patients, especially in acute pancreatitis. Through my contribution to this work, I believe that the quality of care for AP patients will improve in Hungary.

VII. Acknowledgement

I want to express my gratitude to my supervisor **Bálint Erőss M.D.**, the leader of the Medical Group at the Centre for Translational Medicine in Pécs, for his helpful advice and support. Without his outstanding supervision, this thesis would not have been possible.

I also would like to thank the program director, **Professor Péter Hegyi**, the Centre for Translational Medicine in Pécs. He allowed me to expand my theoretical knowledge and supported me to write this work. As a clinician, he drove me to the pancreas patient care and gave lots of helpful instructions.

I want to say special thanks to **Professor Ferenc Izbéki**, the head of I. Department of Internal Medicine in Szent György Teaching Hospital in Székesfehérvár, for his trust in me. He encouraged and empowered me to work on this project, and he always stood up for me. This work would not have been imaginable without the support and active participation of the Hungarian Pancreatic Study Group members. Special thanks shall go to our lead biostatistician **Nelli Farkas**.

Last but not least, I would like to show appreciation to my **family**, precisely to my **husband**, my **parents** and my **sister,** for the love and support that I got from them from the beginning.

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