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3426.

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CHALLENGES IN ACUTE PANCREATITIS MANAGEMENT

Ph.D. Thesis

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Budapest

2026

“Research is formalized curiosity.”

Zora Neale Hurston

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1. LIST OF ABBREVIATIONS

ALB	Albumin
AP	Acute Pancreatitis
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
Ca	Calcium
CECT	Contrast-Enhanced Computed Tomography
CI	Confidence Interval
Crea	Creatinine
CRP	C-Reactive Protein
CT	Computed Tomography
D-dim	D-dimer
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS	Endoscopic Ultrasound
FNA	Fine-Needle Aspiration
GCS-F	Granulocyte Colony-Stimulating Factor
GRADE	Grading of Recommendation, Assessment, Development, and Evaluation
HCT	Hematocrit
HELLP	Hemolysis, Elevated Liver Enzymes, Low Platelet Count
IQR	Interquartile Range
IL-6	Interleukin-6
INP	Infected Necrotizing Pancreatitis
LDH	Lactate Dehydrogenase
NICU	Neonatal Intensive Care Unit
NPV	Negative Predictive Value

PCT	Procalcitonin
PC	Percutaneous
PEP	Post-ERCP Pancreatitis
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
ROC	Receiver Operating Characteristic
SAP	Severe Acute Pancreatitis
SE	Sensitivity
SICAM-1	Soluble Intercellular Adhesion Molecule-1
SNP	Sterile Necrotizing Pancreatitis
SP	Specificity
sTREM-1	Soluble Triggering Receptor Expressed on Myeloid Cells-1
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNF-α	Tumor Necrosis Factor-alpha
US	Ultrasound
WBC	White Blood Cell

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to enhance clinical outcomes and quality of care for patients with pancreatic and biliary diseases by implementing evidence-based, patient-centered approaches. My mission is to generate high-quality, clinically relevant evidence to improve the management of acute pancreatitis (AP), particularly in vulnerable populations such as pregnant patients, by clarifying risks, optimizing intervention timing, and supporting evidence-based, multidisciplinary decision-making. The primary goals of this research were to improve the management of AP by identifying clinically useful biomarkers for the early detection of infection in necrotizing pancreatitis, to evaluate the safety and effectiveness of interventional strategies, particularly cholecystectomy and ERCP, in pregnant patients with biliary acute pancreatitis, and to define the optimal timing and indications for these interventions to reduce recurrent biliary events, hospital readmissions, and preventable complications.

2.2. Scientometrics

Number of all publications:	10
Cumulative IF:	89.3
Av IF/publication:	8.93
Ranking (SCImago):	D1:3, Q1:7
Number of publications related to the subject of the thesis:	2
Cumulative IF:	11.6
Av IF/publication:	5.8
Ranking (Sci Mago):	D1:1, Q1:1
Number of citations on Google Scholar:	174
Number of citations on MTMT (independent):	133
H-index:	6

The detailed bibliography of the student can be found on pages 60.

2.3. Future plans

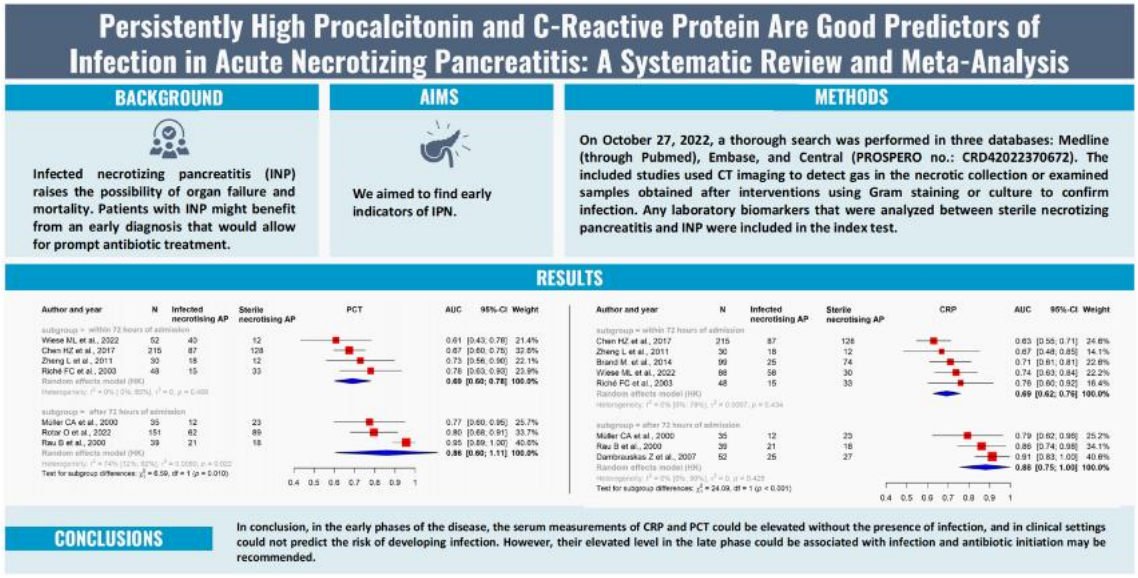
My future plans include completing my gastroenterology residency and continuing my clinical and academic career in a teaching hospital. I aim to remain actively involved in clinical research, initiating and participating in multicenter studies, and translating research findings into everyday clinical practice. Through this dual clinical–academic pathway, my goal is to contribute to evidence-based care, medical education, and the continuous improvement of patient outcomes in gastroenterology.

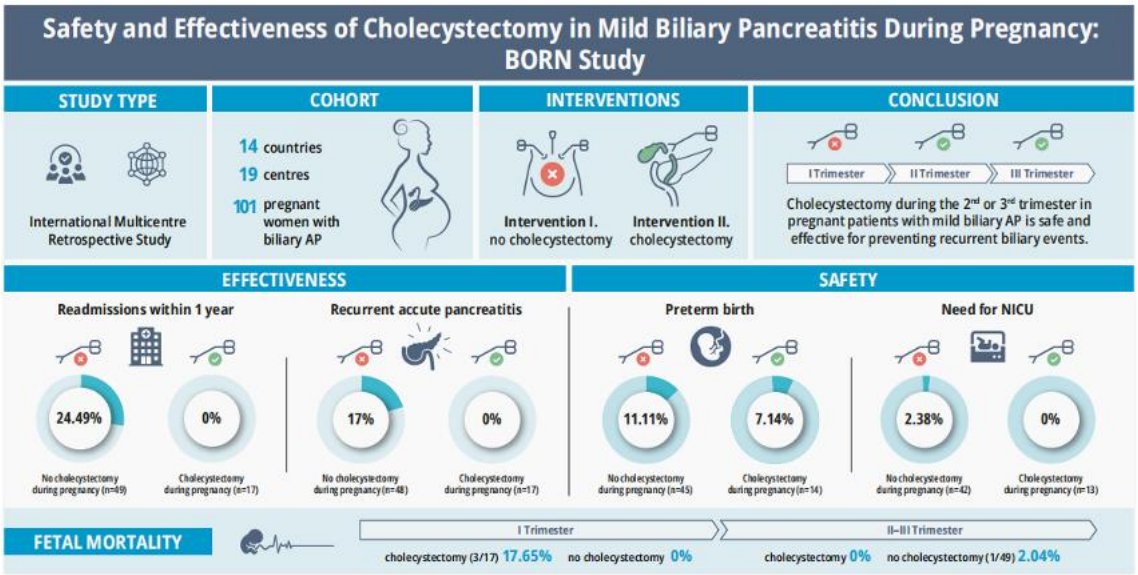
3. SUMMARY OF THE THESIS

This thesis summarizes two distinct and clinically relevant investigations in the field of acute pancreatitis (AP). The first project is a comprehensive systematic review and meta-analysis that examined laboratory biomarkers for infected necrotizing pancreatitis (INP). Infected necrotizing pancreatitis (INP) is associated with an increased risk of organ failure and mortality, making early recognition and timely initiation of antibiotic therapy critical. In the included studies, INP was confirmed using reference standards such as the presence of gas within necrotic collections on computed tomography or positive Gram staining or cultures from sampled necrosis. Laboratory biomarkers served as index tests, with diagnostic performance assessed using sensitivity, specificity, the receiver operating characteristic (ROC) curve, and area under the ROC curve. In the early phase of AP, the identification of a clinically applicable biomarker for differentiation between sterile necrotizing pancreatitis and INP remains elusive; however, C-reactive protein (CRP) and procalcitonin (PCT) demonstrate a sufficiently high predictive value for clinical use in the late phase of the disease. Therefore, in cases of persistently high PCT or CRP levels, antibiotics can be recommended.

Biliary AP during pregnancy poses a significant clinical challenge, as existing pancreatitis, obstetric, and surgical guidelines offer limited management guidance. In the second project, we evaluated the safety and effectiveness of cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy using data from an international retrospective multicenter cohort, including patient characteristics, management strategies, and maternal and fetal outcomes. A total of 101 cases were analyzed. Our study demonstrated that cholecystectomy performed during pregnancy after mild biliary pancreatitis was associated with a marked reduction in recurrent biliary events and hospital readmissions, without an increase in surgical complications compared with postpartum surgery. Rates of preterm birth were comparable between patients who underwent cholecystectomy and those managed conservatively. Fetal loss following surgery was observed only when cholecystectomy was performed in the first trimester. Comparisons between cholecystectomy and ERCP during pregnancy revealed no significant differences in maternal or fetal outcomes. ERCP, when performed for appropriate indications, was not associated with an increased fetal risk, but it did not reduce readmissions compared with surgical management.

4. GRAPHICAL ABSTRACT





(1)

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. Acute pancreatitis

Acute pancreatitis (AP) is the most common gastrointestinal condition requiring emergency hospital admission, affecting 34 people per 100,000 each year in high-income countries (2). The associated mortality rate is 1.60 deaths per 100,000 person-years (95% CI 0.85–1.58), and patients typically require a median hospital stay of 7 days (interquartile range [IQR] 5–10 days) (3, 4).

AP is primarily an inflammatory disease involving the pancreatic parenchyma, with extension to peripancreatic tissues and distant organ systems in severe cases. AP arises from injury to pancreatic acinar cells, leading to inappropriate intracellular activation of trypsinogen to trypsin and subsequent activation of other digestive enzymes, the kinin system, and the complement cascade, resulting in autodigestion of the pancreatic parenchyma. This process drives a systemic inflammatory response characterized by cytokine release, immune cell activation, fever, and, in severe cases, multiorgan failure. Additional pathogenic mechanisms include disordered intracellular calcium signaling, mitochondrial dysfunction, impaired autophagy, endoplasmic reticulum stress, and exosome-mediated signaling (5-7).

The diagnosis of AP is established based on the presence of at least two of the following three criteria: (i) characteristic abdominal pain, (ii) serum amylase or lipase levels exceeding three times the upper limit of normal, and/or (iii) typical radiological features on abdominal imaging (8). Gallstone disease, accounting for 40–70% of cases, and alcohol misuse, responsible for 25–35%, represent the predominant causes of AP. Other, less common etiologies include medications, metabolic disturbances such as hypercalcaemia and hypertriglyceridaemia, infections, genetic predispositions, autoimmune disorders, and iatrogenic injury associated with endoscopic retrograde cholangiopancreatography (ERCP) or trauma. In addition, obstruction of the main pancreatic or biliary ducts by a benign or malignant mass can cause AP (8, 9).

According to the revised Atlanta classification, mild AP is defined by the absence of organ failure and local complications. Moderately severe AP is characterised by transient organ failure lasting <48 hours or by local complications, which include, in the early phase, acute peripancreatic fluid collections and acute necrotic collections, and in the late phase, pseudocysts and walled-off necrosis. Severe acute pancreatitis (SAP) is defined by persistent organ failure (10).

Approximately 45% of patients with necrotizing pancreatitis develop organ failure, frequently necessitating prolonged intensive care unit admission and multiple invasive interventions. Mortality rises substantially when organ failure and infected pancreatic necrosis coexist during the disease course, with the risk of death being nearly twice as high compared with patients who have organ failure or infected necrosis alone (11, 12).

Early prediction of SAP is crucial for enabling the timely initiation of appropriate treatment and management. Patients identified as being at high risk should therefore be admitted to a high-dependence or monitored care unit (8). Current approaches to risk stratification can be broadly categorised into three groups. Several univariate biochemical markers have been investigated as early predictors of SAP; however, their overall predictive performance remains limited. On admission, levels of C-reactive protein (CRP) and white blood cell count (WBC), as well as elevated blood urea nitrogen (BUN), creatinine, and hematocrit (HCT), are associated with disease severity; however, none demonstrate sufficient accuracy for routine clinical application (13-16). As the next step, multiple scoring systems combining four to twenty-five variables have been developed to predict disease severity. Although widely used, these systems often require parameters not routinely measured and depend on data collected over more than 24 hours. The Bedside Index of Severity in Acute Pancreatitis (BISAP) score was developed to predict early disease severity and mortality, and can be applied within the first 24 hours of admission. It incorporates BUN levels and the presence of systemic inflammatory response syndrome (SIRS)(17). In contrast, the Acute Physiology and Chronic Health Examination II (APACHE II) score, although widely used, is not specific to AP, as it was initially designed to predict outcomes in critically ill patients in the intensive care setting (18, 19). Finally, artificial intelligence represents a promising future strategy for risk stratification in AP, enabling the modeling of complex, non-linear relationships between multiple biochemical variables and clinical outcomes. Our research group, among others,

is currently developing EASY-APP, an easy-to-use machine learning–based tool that utilises continuous admission-level variables. This web-based application is designed to function even with incomplete datasets, highlighting its potential for early and practical use at the time of hospital admission, pending further validation (17).

In the initial therapeutic management of AP, moderately aggressive fluid resuscitation is recommended with isotonic crystalloid solutions, tailored to the patient's intravascular volume status, with escalation in cases of hypovolaemia and careful monitoring in patients at risk of fluid overload, particularly those with cardiovascular comorbidities (8). Adequate pain control is also essential and can be provided with non-steroidal anti-inflammatory drugs and opioids, according to patient needs (3). Early enteral nutrition is recommended to reduce infectious complications, whereas routine nil per os management and parenteral nutrition should be avoided (8). Confirmed infected pancreatic necrosis requires treatment with broad-spectrum intravenous antibiotics that achieve adequate penetration into necrotic tissue. Interventional management, including drainage and/or debridement, is indicated for patients with infected necrotizing pancreatitis (INP). This approach is also recommended in case of persistent symptoms such as abdominal pain, nausea, vomiting, or nutritional failure. Additionally, intervention may be necessary for patients who develop complications such as gastrointestinal or biliary obstruction, recurrent AP, fistula formation, or persistent SIRS. A step-up approach is recommended, favouring minimally invasive strategies over open surgical necrosectomy because of their lower associated morbidity. Percutaneous drainage and transmural endoscopic drainage are both appropriate first-line, non-surgical interventions for managing walled-off pancreatic necrosis; however, endoscopic transmural drainage is preferred, as it reduces the risk of pancreatocutaneous fistula formation (3, 20).

Early cholecystectomy is indicated during the index admission for mild biliary pancreatitis, while delayed surgery is recommended for moderate and severe cases, particularly when necrosis or peripancreatic collections are present, to prevent recurrent AP and other gallstone-related complications. ERCP is indicated in patients with confirmed choledocholithiasis or acute cholangitis; however, urgent ERCP is not recommended in predicted SAP, as it does not improve clinical outcomes or mortality (8, 21, 22).

5.1.2. Infected necrotizing pancreatitis

Most cases of AP are mild, presenting as interstitial edematous pancreatitis, whereas 5-10% of patients develop pancreatic necrosis, which results from impaired pancreatic perfusion, highlighting the critical role of ischemia and microcirculatory disturbances in disease progression (10). Approximately 30% of patients with acute necrotizing pancreatitis (ANP) develop infected necrosis due to translocation of intestinal microbial flora. When sepsis occurs, the condition becomes significantly more complex, with mortality rates reaching up to 40% (23, 24).

Diagnosing and managing infected necrosis remains challenging, as AP is an inflammatory condition that presents with systemic manifestations such as fever, tachycardia, hypotension, leukocytosis, and elevated CRP and WBC (13, 25, 26). These features are common to both sterile inflammation and infection, making it difficult to distinguish between the two and resulting in frequent overuse of antibiotics across all severities (27).

Antibiotic therapy is best reserved for cases with culture-confirmed infected necrosis or when there is strong clinical suspicion of infection, such as the presence of gas within the collection, bacteremia, sepsis, or signs of clinical deterioration. Prophylactic antibiotics are not recommended for preventing infection in sterile necrosis. Early initiation of enteral nutrition in patients with pancreatic necrosis is recommended to lower the risk of infection by maintaining mucosal barrier integrity and reducing bacterial translocation in the gastrointestinal tract. Drainage and/or debridement is indicated in cases of infected pancreatic necrosis. Interventions should be avoided during the early acute phase (first 2 weeks), as it is associated with higher morbidity and mortality, and is preferably postponed until around 4 weeks (20, 28).

5.1.3. Acute biliary pancreatitis during pregnancy

Acute biliary pancreatitis during pregnancy is uncommon but presents substantial clinical challenges (29). Pregnancy itself predisposes individuals to gallstone formation because elevated estrogen and progesterone levels promote cholestasis and cholesterol supersaturation of bile. Symptomatic gallstone disease is one of the most frequent causes of non-obstetric hospitalizations and surgical procedures in pregnancy and has been

linked to an increased risk of preterm delivery (30, 31). The incidence of AP in pregnancy is estimated at 1 per 1,000 to 1 per 4,000 pregnancies, with gallstone disease accounting for more than 65% of cases (32, 33). Most episodes occur during the third trimester or in the postpartum period (33).

Recent progress in maternal and neonatal care, combined with earlier detection, has led to a reduction in maternal and fetal mortality (34). A recent meta-analysis reported a maternal mortality rate of 2.8%, similar to that of the general population, while the pooled fetal mortality rate was 12.3% (35). Additional studies have shown that the risk of preterm labor is increased by approximately 3.5-fold in pregnant women with AP (35, 36). Despite these advances, AP continues to exhibit one of the highest fetal loss rates among pregnancy-related surgical emergencies, including appendicitis and cholecystitis (35).

5.1.4. What is the problem to solve?

5.1.4.1. Study I.

Although several scoring systems exist to assess the severity of AP, no validated tools are currently available to predict the presence of infection specifically (37, 38).

5.1.4.2. Study II.

Early cholecystectomy is recommended after mild biliary pancreatitis in nonpregnant patients to prevent recurrence; the optimal management strategy in pregnant women remains unclear (39). Pregnancy itself is an independent risk factor for higher readmission and recurrence rates following AP (40, 41). Yet, pregnant patients are significantly less likely to undergo cholecystectomy or ERCP compared with nonpregnant individuals. Despite guideline recommendations supporting laparoscopic cholecystectomy for symptomatic biliary disease and ERCP for urgent indications, such as choledocholithiasis or cholangitis, uncertainty regarding safety - particularly regarding timing - continues to result in hesitancy among clinicians. This highlights a critical gap in evidence-based guidance for managing biliary pancreatitis during pregnancy.

5.1.5. What is the importance of the topic?

First, early identification of infection is essential for timely intervention and appropriate management, particularly in high-risk patients who may benefit from early antibiotic therapy.

Biliary pancreatitis in pregnancy poses unique maternal and fetal risks, with recurrence rates reported as high as 50% in the first trimester and readmission rates significantly higher than in nonpregnant women (40). Clear, evidence-based recommendations are essential, as delayed or avoided intervention may expose patients to preventable complications.

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

By conducting a meta-analysis on laboratory markers to evaluate their ability to predict infection in AP, our research may help identify clinically useful predictors, improve early diagnosis, and assist in guiding appropriate treatment decisions.

Our second research provides evidence to support safer and more confident clinical decision-making regarding cholecystectomy and ERCP in pregnant patients with biliary pancreatitis. By clarifying outcomes, complication rates, and recurrence risks, the findings may help refine guideline recommendations, reduce unwarranted practice variation, and encourage timely intervention when appropriate. Ultimately, the study has the potential to reduce maternal readmissions, decrease the recurrence of pancreatitis, and improve maternal - fetal outcomes by providing more precise guidance on the timing and safety of these procedures during pregnancy.

6. OBJECTIVES

6.1. Study I. – Identifying early predictors for infected necrosis in acute pancreatitis

The objective of this study was to perform a comprehensive meta-analysis evaluating laboratory markers as early predictors of infected necrotizing pancreatitis (INP).

6.2. Study II. – Investigating the safety and effectiveness of cholecystectomy and ERCP in biliary pancreatitis during pregnancy

This international retrospective cohort study aimed to analyze current practices and outcomes of managing biliary AP in pregnant patients, focusing on the role of cholecystectomy and ERCP.

7. METHODS

In our first study, a systematic review and meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and adhered to the recommendations of the Cochrane Handbook **(42, 43)**. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42022370672 in advance, and we fully adhered to it.

7.1. Study I.

7.1.1. Systematic search

A systematic literature search was performed in Medline (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception until 27 October 2022. The search key used was the following:

acute AND pancrea* AND necro* AND infect*.

7.1.2. Eligibility Criteria

The research question was developed using the PIRD framework (patient, index test, reference test, diagnosis of interest). We included randomized controlled trials and both prospective and retrospective observational cohort studies that met the following criteria:
(1) studies conducted in adult patients with necrotizing pancreatitis, where the diagnosis of AP adhered to the International Association of Pancreatology and American Pancreatic Association “two out of three” criteria, namely: (a) characteristic upper abdominal pain, (b) serum amylase or lipase levels at least three times the upper limit of normal, and (c) characteristic imaging findings of pancreatitis;
(2) infection confirmed using a reference standard, defined as either the presence of gas within a necrotic collection on computed tomography imaging or positive Gram stain or culture from samples obtained via intervention;
(3) the index test involved at least one laboratory biomarker compared between sterile necrotizing pancreatitis (SNP) and infected necrotizing pancreatitis (INP); and
(4) the study provided data on sensitivity, specificity, receiver operating characteristic (ROC) curve, or area under the ROC curve (AUC) for differentiating SNP from INP (10, 44). We excluded animal and in vitro studies, case reports, case series, and conference abstracts. No limits were applied regarding publication date or language.

7.1.3. Selection processes

EndNote (version 20.4.1.16297) was used to organize and process the publications. Following duplicate removal, two reviewers (DT and ML) independently screened titles and abstracts. Subsequently, the full texts of the eligible studies were retrieved and independently assessed. Inter-reviewer agreement between reviewers was assessed using Cohen's kappa at all screening levels. Any disagreements were resolved through consultation with a third author (AM). Reference lists of selected reviews and included articles were screened to identify any further eligible studies. Additionally, CitationChaser was utilized to perform both backward and forward citation searches for the included studies (45).

7.1.4. Data Collection Process and Data Items

Two independent reviewers examined the eligible studies and extracted data using a standardized data collection form, including: first author, country, design, study period, patient demographics, number of IPN cases, type of reference test, timing and type of laboratory biomarker assessments, and diagnostic performance metrics including sensitivity, specificity, AUC, true and false positives/negatives, and cut-off values.

7.1.5. Risk of Bias Assessment

The risk of bias for all included studies was independently assessed by two authors (D.T. and M.L.) using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool (46). Items were assessed as having low, unclear, or high risk of bias. Disagreements were settled by a third reviewer (A.M.).

7.1.6. Certainty of Evidence

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, and a summary table was generated with the GRADEpro tool (47).

7.1.7. Statistical methods

Statistical analyses were performed using R software (version 4.1.2) along with the R script of the online tool described by Freeman (48). A threshold of p-value of less than 0.05 was used to determine statistical significance in all analyses.

AUC values and associated confidence intervals (CIs) of the diagnostic scores were collected from the eligible studies. Standard deviations of the AUC values were calculated from CIs, and a classical inverse-variance random-effects meta-analysis with the restricted maximum likelihood estimator was applied to gain pooled AUC estimates with 95% CI. A test is considered to have excellent discrimination ability when the AUC ranges from 0.90 to 1.00; AUC values of 0.80–0.90, 0.70–0.80, 0.60–0.70, and 0.50–0.60 are interpreted as good, fair, poor, and failed discrimination, respectively (49). Due to the limited number of studies included in the meta-analyses, the Hartung–Knapp adjustment was applied. Heterogeneity was assessed using the I^2 statistic with its confidence interval, along with the Cochrane Q test. I^2 values of 25%, 50%, and 75% were interpreted as indicating low, moderate, and high heterogeneity, respectively. Subgroup analyses were performed according to different time horizons, without assuming that the random-effects standard deviations were identical across subgroups.

For the short-term diagnostic performance of PCT and CRP, sufficient data were available from multiple studies, including the total number of patients with and without infected necrosis, along with sensitivity, specificity, and, in most cases, the corresponding thresholds. Using these data, two-by-two contingency tables were calculated for each threshold, containing true positive, false positive, false negative, and true negative values. Due to the heterogeneity of thresholds across studies, we fitted the summary ROC (SROC) curve using the non-Bayesian version of the approach (50). For clarification, Harbord et al. demonstrated that this method is mathematically equivalent to the bivariate model (51-53). The SROC curves were plotted on ROC graphs, together with study-level estimates with their CIs. The SROC curve illustrates how sensitivity and specificity change in relation to varying diagnostic thresholds. Assessment of publication bias was not feasible, as fewer than 10 studies were included.

7.2. Study II.

7.2.1. International cohort

The project was completed under the Systems Education research-training model, guided by the Centre of Translational Medicine at Semmelweis University and the Hungarian Pancreatic Study Group (40, 41). This study aimed to examine multicenter data on the safety and efficacy of performing cholecystectomy during pregnancy, adhering to the

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (54). In March 2023, we invited members of the International Association of Pancreatology and the European Pancreatic Club to participate in the study, and 19 centers from 14 countries ultimately joined this retrospective cohort. Ethical approval was granted by the National Center for Public Health (17787-8/2020/EÜIG).

The study population included pregnant patients diagnosed with acute biliary pancreatitis who were treated at participating centers from January 2011 onward. To promote complete case inclusion and reduce selection bias, centers were asked to enroll all eligible patients consecutively during the study period. Inclusion criteria followed the Atlanta classification, with biliary etiology suspected in the presence of gallstones, biliary sludge, a dilated common bile duct on imaging, or biochemical evidence of cholestasis (44). Exclusion criteria comprised chronic pancreatitis, postpartum pancreatitis, and pancreatitis of non-biliary origin. Maternal complications recorded included mortality, hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, placental abruption, antepartum hemorrhage, and eclampsia. Fetal outcomes were based on fetal loss, preterm birth (defined as birth before 37 weeks of gestation), neonatal intensive care unit (NICU) admission, and complications such as reduced movements, cardiac irregularities, structural defects, and acid–base abnormalities. Intraoperative complications assessed were trocar-site bleeding, liver bed injury, bile leakage, bleeding, gallstone spillage, and common bile duct injury; postoperative complications included wound infection, bleeding, and bile leaks.

The data sheet collected information on patient demographics, clinical features, treatment strategies, the timing and approach of cholecystectomy, ERCP procedures, associated complications, and outcomes, including one-year readmission for recurrent AP or other gallstone-related complications, and maternal and fetal results. AP severity was categorized according to the revised Atlanta classification (10).

Following confirmation of participation, collaborators were provided with a follow-up email containing detailed study instructions and either a pre-defined Microsoft Excel template or a secure Research Electronic Data Capture (REDCap) link for individual patient data collection. The study protocol was developed over two months by a panel comprising three expert gastroenterologists and one surgeon. Data collection was

conducted over a period of one and a half years, using a standardized survey to ensure consistency across participating centres. To prevent duplicate entries, participating centres, departments, affiliations, and submitted data were closely monitored, and collaborators were restricted from accessing datasets submitted by others. All patient data were collected and stored in a fully anonymised manner, with no personal identifiers recorded. Any queries arising during data submission were addressed directly with the data uploader. The questionnaire predominantly consisted of closed-ended questions, with selected items allowing open-ended responses when the "Other" option was chosen.

7.2.2. Statistical Analysis

Descriptive statistics were reported as medians with interquartile ranges (IQR) for continuous variables and as frequencies with percentages for categorical variables. For group comparisons, we applied the Welch Two-Sample t-test to continuous variables. Categorical variables were analyzed using Pearson's Chi-squared test when expected frequencies were sufficiently high; otherwise, Fisher's exact test was used. A p-value below 0.05 was considered statistically significant. Data analyses were performed in R statistical environment (R version 4.4.2; R Core Team, 2024). Missing data were systematically captured and summarized in Table 1.

Table 1. Data quality for assessed variables (1)

Number	Title	Total	Exist	Percent
1	**DATE of admission due to AP**	101	101	100%
2	**Number of previous pregnancies**	101	97	96%
3	**Age (years) in the year of index admission**	101	99	98%
4	**Weeks of pregnancy at the time of index admission**	101	100	99%
5	**Other etiology factors**	101	100	99%
6	**Chronic pancreatitis**	101	101	100%
7	**Diabetes**	101	101	100%
8	**Number of AP in the past**	101	101	100%
9	**Previously known symptomatic cholelithiasis**	101	100	99%
10	**If yes, how long the symptomatic cholelithiasis is known (months)**	37	32	86%
11	**Imaging modality**	101	100	99%
12	**Number of gallstones**	101	99	98%
13	**Approx. size of gallstones (in mm)**	101	65	64%
14	**Sludge**	101	84	83%
15	**Choledocholithiasis**	101	97	96%
16	**Diameter of common bile duct (in mm)**	101	80	79%

17	Total bilirubin level on admission (mg/l)	101	95	94%
18	Direct bilirubin level on admission (mg/l)	101	56	55%
19	GOT level on admission (U/l)	101	95	94%
20	GPT level on admission (U/l)	101	98	97%
21	GGT level on admission (U/l)	101	85	84%
22	ALP level on admission (U/l)	101	88	87%
23	WBC level on admission (G/l)	101	100	99%
24	CRP level on admission (mg/l)	101	97	96%
25	PCT level on admission (ng/l)	101	8	8%
26	Concomitant diagnosis	101	101	100%
27	Antibiotic use during hospitalization	101	99	98%
28	Enteral feeding	101	99	98%
29	LMWH use during hospitalization	101	91	90%
30	ERCP	101	100	99%
31	Sphincterotomy during ERCP	22	22	100%
32	Stent placement	22	22	100%
33	Cannulation time in minutes	22	6	27%
34	Number of cannulation attempts	22	9	41%
35	Use of advannced biliary cannulation techniques	22	9	41%
36	Complication post-ERCP pancreatitis	22	22	100%
37	Complication post-ERCP bleeding	22	22	100%
38	Complication post-ERCP perforation	22	22	100%
39	Succesful stone extraction (for stones at most 10mm)	22	19	100%
40	Evidence of stone(s) on ERCP	22	21	95%
41	Evidence of sludge on ERCP	22	21	95%
42	Evidence of pus on ERCP	22	21	95%
43	Radiation time in minutes	22	9	41%
44	Cholecystectomy during pregnancy	101	101	100%
45	Time of cholecystectomy	29	29	100%
46	Cholecystectomy after pregnancy	101	64	63%
47	Time of cholecystectomy	49	44	90%
48	Methods of surgery	78	73	94%
49	Intraoperative cholangiogram	78	68	87%
50	Intraoperative complication	78	71	91%
51	Specify the intraoperative complication	5	5	100%
52	Postoperative complication	78	70	90%
53	Specify the postoperative complication	3	3	100%
54	Length of hospitalization (days)	101	100	99%
55	Severity of AP	101	101	100%
56	Maternal mortality	101	101	100%
57	Local complications	14	10	71%
58	HELLP syndrome	101	100	99%
59	Date of HELLP syndrome	-	-	-

60	**Other maternal complication**	101	59	58%
61	**Fetal mortality**	101	97	96%
62	**Date of fetal loss**	6	6	100%
63	**Premature rupture of membrane**	101	83	82%
64	**Amniotic infection**	101	83	82%
65	**Preterm birth**	111	83	75%
66	**Date of preterm birth**	10	10	100%
67	**Need for neonatal intensive care unit**	111	78	70%
68	**Other fetal complications**	111	49	44%
69	**Readmission after AP (within 1 year)**	101	95	94%
70	**Number of readmissions**	16	15	94%
71	**Date of the readmission**	16	15	94%
72	**Etiology of readmission**	16	15	94%
73	**Severity of AP (second episode)**	10	10	100%

AP - acute pancreatitis
GOT - glutamic-oxalacetic transaminase
GPT - glutamic-pyruvic transaminase
GGT - gamma-glutamyl transferase
ALP - alkaline phosphatase
WBC - white blood cell
CRP - C-reactive protein
PCT - procalcitonin
LMWH - low molecular weight heparin
ERCP - endoscopic retrograde cholangiopancreatography

8. RESULTS

8.1. Study I

8.1.1. Systematic search and selection

In total, 7,975 records were identified through the systematic search. After removing duplicates, 5,400 titles and abstracts were screened, and 122 articles were selected for full-text assessment. Sixty studies were excluded because they did not compare SNP with INP, but instead most frequently compared severe AP with INP. An additional 48 studies were excluded because they did not report any data on laboratory parameters, and one study was excluded due to overlapping patient populations. Citation chasing did not yield any additional studies relevant to our research question. Of the thirteen studies included, eight (55-62) were eligible for meta-analysis, while the remaining five (63-67) were incorporated into the systematic review. The study selection process is illustrated in Figure 1.

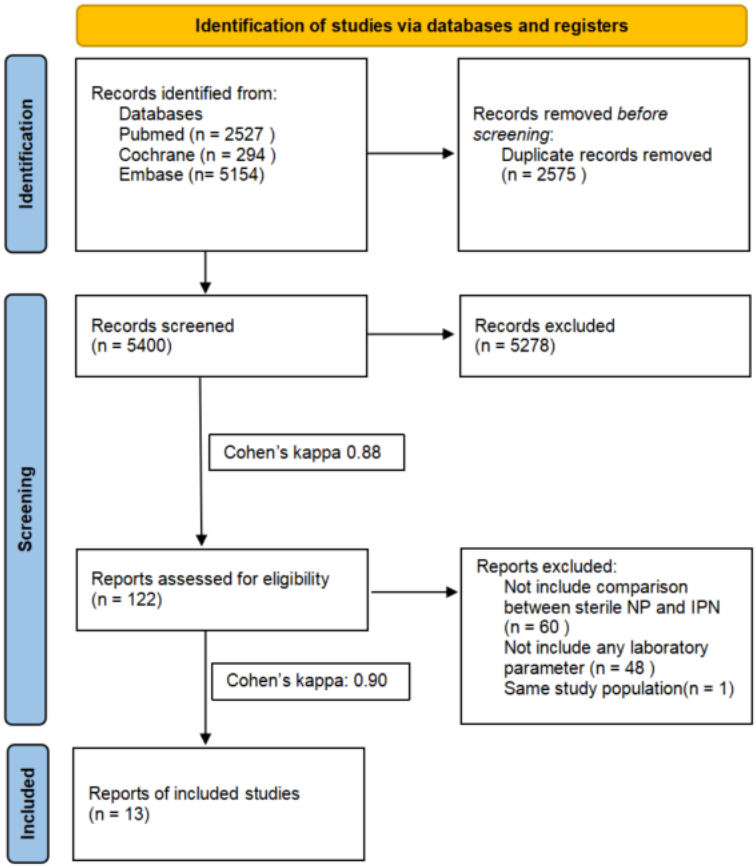


Figure 1. PRISMA 2020 flowchart of the study selection process (68)

8.1.2. Study Characteristics

All studies were observational, with four conducted retrospectively and nine prospectively (Table 2). The quantitative analysis included 758 patients with necrotizing AP, of whom 324 had INP. Nine studies were published before the 2012 revision of the Atlanta classification, which redefined necrotizing pancreatitis to include peripancreatic necrosis (10).

INP was diagnosed based on the presence of gas within the necrotic collection on computed tomography, or through microbiological confirmation from samples obtained during intervention or fine-needle aspiration using Gram staining, culture, or both. Interventions included percutaneous or endoscopic drainage, as well as percutaneous, endoscopic, or surgical necrosectomy.

CRP and PCT were the most commonly evaluated biomarkers. Several other laboratory parameters - including albumin, HCT, BUN, creatinine, lymphocyte count, lactate dehydrogenase (LDH), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alfa), soluble intercellular adhesion molecule-1 (sICAM-1), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), presepsin, and granulocyte colony-stimulating factor (G-CSF)—were assessed in only one study each. Due to the limited number of comparable studies, these markers could not be included in the quantitative synthesis.

Table 2. Basic characteristics of the included studies (68)

Publication Data	Study Design	Demography			Reference Test	Index Tests	Assessed Outcomes	Time Points for Laboratory Parameter Measurements	The Time Interval between the Onset of Abdominal Pain and the Measurements of Laboratory Parameters
		Country	Population	Age (Years)					
Block et al. † (1987) [37]	cross-sectional (cohort-type accuracy study); prospective	Germany	161	N/A	surgery	Alb; Ca; HCT; WBC	Se, Sp	within 48 h	N/A
Brand et al. (2014) [36]	cross-sectional (cohort-type accuracy study); retrospective	Germany	99	52 [a] (18–84) [b]	FNA	Alb, Ca, CRP, WBC	AUC; ROC; Se, Sp	within 36 h (most within 24 h)	N/A
Chen et al. (2017) [29]	cross-sectional (cohort-type accuracy study); retrospective	China	215	42.2 [c] (11.6)[d]	CECT, US- or CT-guided FNA, invasive therapeutic procedures	BUN; Cr; CRP; D-dim; HCT; PCT; PLT; WBC	AUC; ROC; Se; Sp	within 48 h	<48 h before hospital admission

Dambraus kas et al. (2007) [35]	cross-sectional (cohort-type accuracy study); prospective	Lithuania	52	51.15 [c]	CECT, FNA	CRP, WBC	AUC; NPV; PPV; ROC; Se; Sp	every fourth day until discharge	measurement of laboratory parameters occurred between days 21 and 40 after the onset of the disease in the subgroup analysis
Mándi et al. † (2000) [38]	cross-sectional (cohort-type accuracy study); prospective	Hungary	20	45.5 [c] (18.2) [d] (20–63) [b]	CECT, US-guided FNA	IL-6; sICAM-1; PCT	NPV;PPV; Se;Sp	within 48 h, blood samples daily	N/A
Müller et al. (1999)[32]	cross-sectional (cohort-type accuracy study); prospective	Switzerlan d	35	56.3 [c] (27–87) [b]	CECT, US- or CT-guided FNA	CRP; GCSF; PCT	AUC; ROC; Se; Sp	1–14 days daily and thereafter every third day	from day 0 until day 14 after the onset of the symptoms
Rau et al. (2000) [34]	cross-sectional (cohort-type accuracy study); prospective	Germany	61	(14–87) [b]	CECT, US-guided FNA	CRP, PCT	AUC; ROC; Se; Sp	in 24 h intervals over 14 days	abdominal pain less than 120 hours before hospital admission
Riché et al. (2003) [31]	cross-sectional (cohort-type accuracy study); prospective	France	48	(24–91) [b]	CECT, CT-guided FNA, surgical drainage	CRP; IL-6; PCT; TNF-alpha	AUC, ROC	within 72 h daily	N/A
Rotar et al. (2022) [33]	cross-sectional (cohort-type accuracy study); prospective	Ukraine	151	(18–80) [b]	CECT, therapeutic intervention ,	PCT	AUC; ROC; Se; Sp	72 h before intervention	after the 4th week in case of 41 patients, before the 4th week in case of 74 patients
Rotar et al. † (2019) [39]	cross-sectional (cohort-type accuracy study); prospective	Ukraine	70	(18–80) [b]	CECT, therapeutic intervention	Presepsi n	AUC; ROC; Se; Sp	72 h	N/A
Ueda et al. † (2007) [40]	cross-sectional (cohort-type accuracy study); retrospective	Japan	75	52 [c] (2) [d]	CECT, blood culture, US-guided FNA	LDH, Lympho cyte count	AUC; ROC	within 72 h	within 72 h
Wiese et al. (2022) [28]	cross-sectional (cohort-type accuracy study); retrospective	Germany	89	57.67 [c]	CECT, PC drainage, EUS-guided FNA	Alb; BUN; Ca; Crea; CRP; HCT; IL-6; PCT	AUC; ROC; Se; Sp	within 48 h	N/A
Zheng et al. (2011) [30]	cross-sectional (cohort-type accuracy study); prospective	China	30	55.5 [c]	CECT, US- or CT-guided FNA	CRP; IL-6, PCT; sTREM-1; TNF-alpha; WBC	AUC; NPV; PPV; ROC Se; Sp	72 h	N/A

a = median; b = range; c = mean; d = standard deviation; N/A = not applicable; Alb = albumin; AUC = area under the ROC curve; BUN = blood urea nitrogen; Ca = calcium; CECT = contrast-enhanced computed tomography; Crea = creatinine; CRP = c-reactive protein; D-dim = D-dimer; EUS = endoscopic ultrasound; FNA = fine needle aspiration; GCSF = granulocyte colony-stimulating factor; HCT = hematocrit; h = hours; IL-6 = interleukin-6; LDH = lactate dehydrogenase; NPV = negative predictive value; PCT =

procalcitonin; PC = percutaneous; PLT = platelet; PPV = positive predictive value; ROC = receiver operating characteristic; Se = sensitivity; sICAM-1 = soluble intercelluar adhesion molecule-1; Sp = specificity; sTREM-1 = soluble triggering receptor expressed on myeloid cells; TNF-alpha = tumor necrosis factor-alpha; US = ultrasound; WBC = white blood cell; † = study included only in a systematic review.

8.1.3. Poor Predictive Value of CRP, PCT, and WBC Alone Within 72 h of Admission in ANP

A subgroup analysis was conducted based on the timing of the index test. In five studies, the index test was performed within the first 72 hours after admission (55-58, 63). Our findings showed that within the first 72 hours after admission, the pooled AUC was 0.69 (95% CI: 0.62–0.76) for CRP, 0.69 (95% CI: 0.60–0.78) for PCT, and 0.61 (95% CI: 0.47–0.75) for WBC (Figures 2–4).

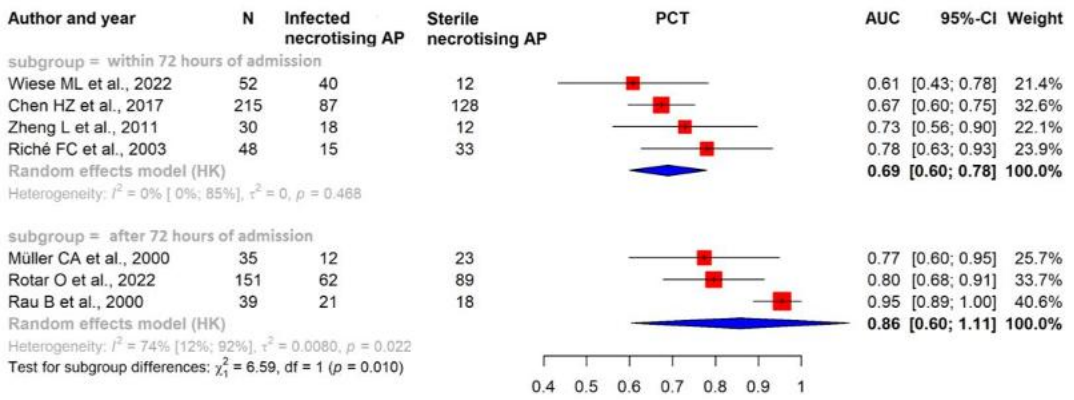


Figure 2. Diagnostic accuracy of PCT for predicting INP (68)

Forest plot illustrating the area under the receiver operating characteristic curve (AUC) of PCT for differentiating infected from sterile necrotizing pancreatitis. Subgroup analyses are presented according to the timing of PCT measurement (within 72 hours of hospital admission and after 72 hours, examining a two-week period of the disease). Within the first 72 hours, PCT demonstrated limited discriminatory ability (pooled AUC 0.69, 95% CI 0.60–0.78). After 72 hours, PCT showed improved predictive performance (pooled AUC 0.86, 95% CI 0.60–1.11). AP: acute pancreatitis; AUC: area under the ROC curve; CI: confidence interval; h: hours; INP: infected necrotizing pancreatitis; PCT: procalcitonin.

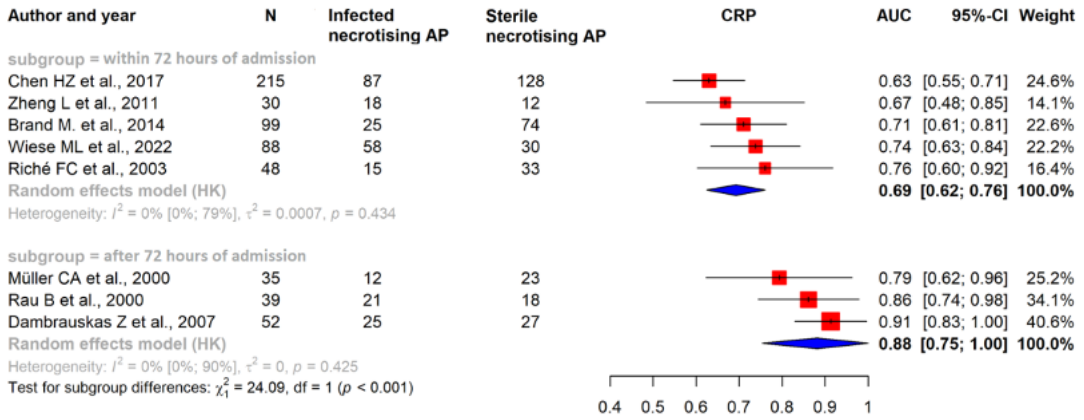


Figure 3. Diagnostic accuracy of CRP for predicting INP (68)

Forest plot showing the AUC of CRP in distinguishing infected from sterile necrotizing pancreatitis, stratified by timing of CRP assessment. When measured within 72 hours of admission, CRP demonstrated poor predictive value (pooled AUC 0.69, 95% CI 0.62–0.76). In contrast, CRP measured after 72 hours showed good diagnostic performance (pooled AUC 0.88, 95% CI 0.75–1.00). AP: acute pancreatitis; AUC: area under the ROC curve; CI: confidence interval; CRP: C-reactive protein, h: hours; INP: infected necrotizing pancreatitis.

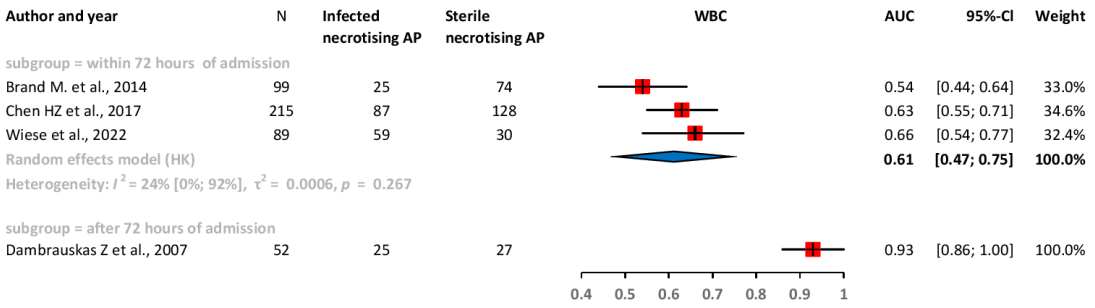


Figure 4. Diagnostic accuracy of WBC for predicting INP (68)

Forest plot presenting the AUC of WBC for identifying infected necrotizing pancreatitis. When assessed within 72 hours of admission, WBC demonstrated poor discrimination (pooled AUC 0.61, 95% CI 0.47–0.75). Limited data were available for measurements obtained after 72 hours, precluding pooled analysis for this subgroup. AP: acute pancreatitis; AUC: area under the ROC curve; CI: confidence interval; h: hours; INP: infected necrotizing pancreatitis; WBC: white blood cell count.

8.1.4. CRP and PCT Levels After 72 h of Admission Demonstrate Good Predictive Value in ANP

Beyond 72 hours after admission, in studies evaluating at least a two-week disease course, CRP demonstrated an elevated pooled AUC of 0.88 (CI: 0.75–1.00), while PCT showed

a pooled AUC of 0.86 (CI: 0.60–1.11), indicating good predictive value (Figures 2 and 3) (49).

8.1.5. Risk of Bias Assessment

The QUADAS-2 assessment indicated that the included studies were of moderately high quality.

8.1.6. Certainty of Evidence

The certainty of evidence from our analysis was rated as low, mainly due to imprecision indicated by wide CIs. This imprecision introduces uncertainty in the estimates and may affect the overall confidence in the findings.

8.1.7. Publication Bias and Heterogeneity

Funnel plot analysis was not feasible due to the limited number of studies. Heterogeneity among the subgroups was not significant.

8.2. Study II.

8.2.1. Basic characteristics of AP

In total, 101 cases from 14 countries and 19 centers were included in the analysis. Basic characteristics are presented in Figure 5.

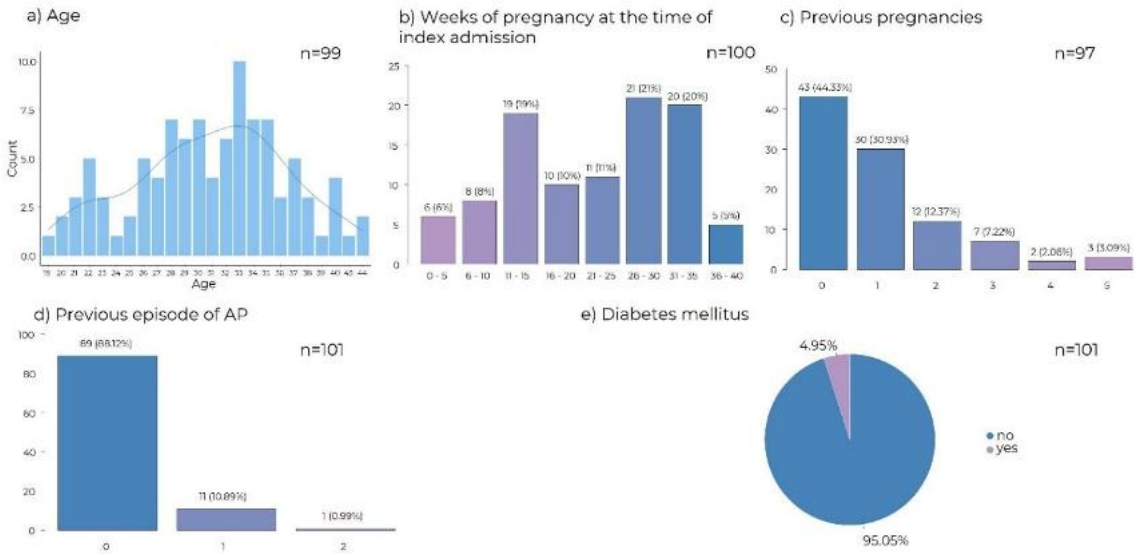


Figure 5. Characteristics of Pregnant Women with Acute Pancreatitis (1)

Demographic and clinical characteristics of pregnant women diagnosed with AP, including age (a), gestational week at admission (b), number of previous pregnancies (c), number of previous AP episodes (d), and presence of diabetes mellitus (e).

AP - Acute Pancreatitis

The median patient age was 31 years (Q25-75, 27–35), and 44% of patients were in their first pregnancy. The median gestational age at presentation was 25 weeks (Q25-75 14–31). Regarding disease severity, 86% (n=87/101) had mild AP, 9% (n=9/101) had moderate AP, and 5% (n=5/101) had severe AP. Coexisting conditions included cholecystitis in 14% (n=14/101), cholangitis in 7% (n=7/101), both conditions in 3% (n=3/101), and peritonitis in 1% (n=1/101). The median length of hospitalization (LOH) was six days (Q25-75 4–9.5) (Figure 6), and the one-year readmission rate was 17% (n=16/95). Cholecystectomy was performed in 29 patients during pregnancy and in 49 postpartum, with most postpartum procedures scheduled within the first three months after delivery.

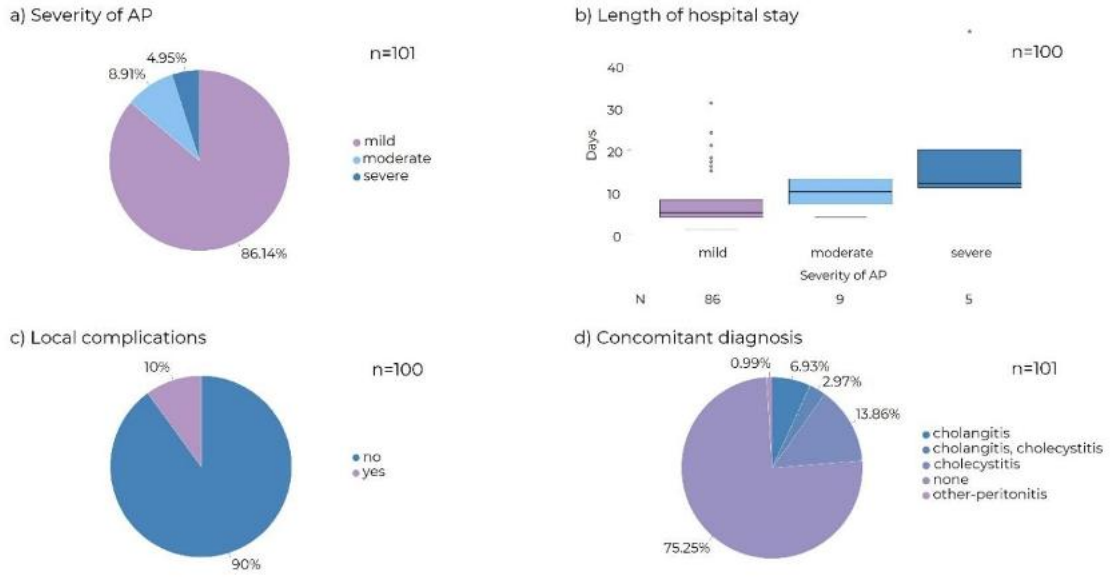


Figure 6. Acute Pancreatitis Characteristics (1)

Details on the clinical course of AP during pregnancy, including severity classification (a), length of hospital stay (b), occurrence of local complications (c), and concomitant diagnoses (d).

AP - Acute Pancreatitis

Antibiotic therapy was used in 30% of cases (n=30/99) during hospitalization. Regarding nutritional support, 69% of patients received no enteral nutrition (n=68/99), while 23% received oral feeding (n=23/99), 7% nasogastric feeding (n=7/99), and 1% nasojejunal feeding (n=1/99) (Figure 7).

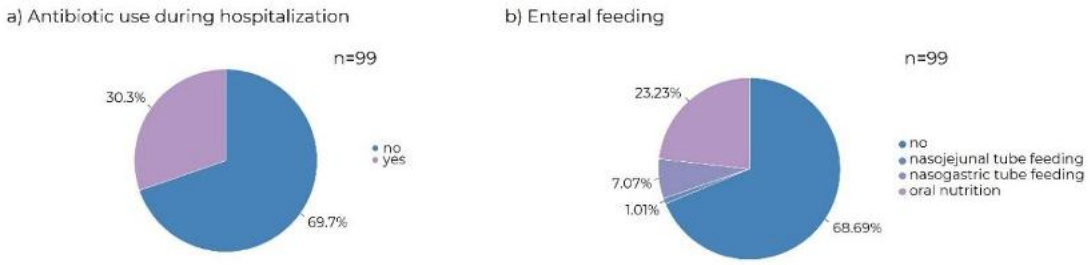


Figure 7. Therapy during Acute Pancreatitis (1)

Use of antibiotics during hospitalization (a) and administration of enteral feeding (b) in pregnant patients with AP.

A prior history of symptomatic cholelithiasis was reported in 37% of patients (37/100), with 11 of these (34%) experiencing an episode within six months before their pancreatitis (Figure 8).

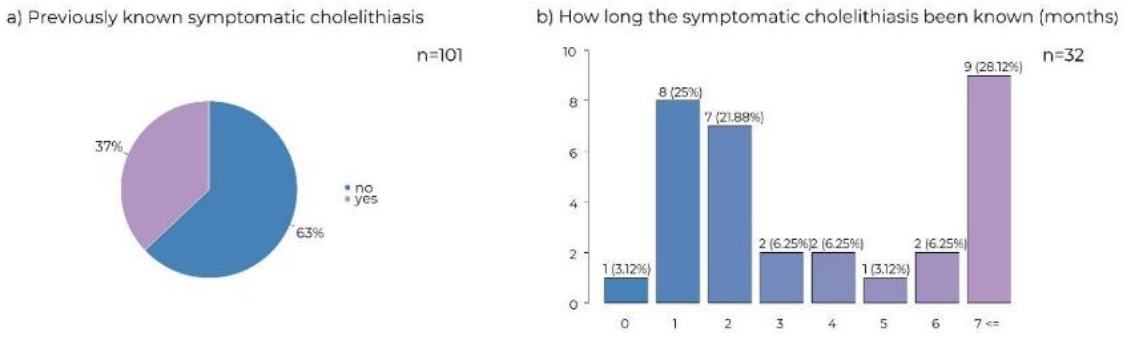


Figure 8. Symptomatic cholelithiasis (1)

Prevalence (a) and duration (b) of previously known symptomatic cholelithiasis in women who developed acute biliary pancreatitis during pregnancy.

Choledocholithiasis was present in 23% of patients (23/97), and 67% had multiple gallstones. Gallstones or sludge were identified in all 101 patients: in 97 cases (96%) via imaging, in 2 cases (2%) during ERCP, and in 2 cases (2%) during surgery. ERCP was performed in 22 patients, of whom 16 (73%) had choledocholithiasis, and 9 (41%) had cholangitis (Figure 9).

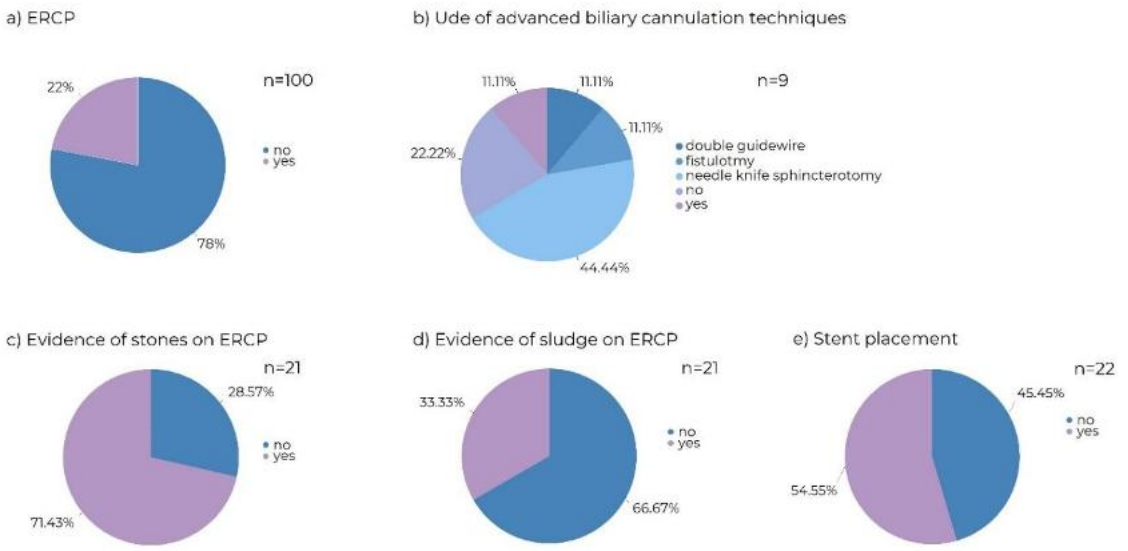


Figure 9. Endoscopic therapy during hospitalization (1)

ERCP performed (a), use of advanced biliary cannulation techniques (b), presence of stones (c) and sludge (d) on ERCP, and biliary stent placement (e). ERCP - Endoscopic retrograde cholangiopancreatography

Fetal mortality occurred in 6.2% (n=6/97), including five events before or during the 20th week of gestation and one that occurred postnatally. Preterm birth was recorded in 12% of pregnancies (n=10/83). Premature rupture of membranes occurred in 4 cases (n=4/83), with no cases of amniotic infection or HELLP syndrome (n=0/83 and n=0/100). No maternal deaths were observed (n=0/101).

8.2.2. Effectiveness and safety of cholecystectomy in mild biliary AP

Among patients with mild biliary pancreatitis, 17 underwent cholecystectomy during pregnancy, while 50 were treated conservatively. None of the patients who had surgery

experienced readmission for biliary complications within one year (0%, n=0/17), compared with 24% (n=12/49; p=0.027) in the non-surgical group. Readmissions were most frequently due to recurrent AP (n=8/48) or to cholecystitis or cholangitis (Figure 10).

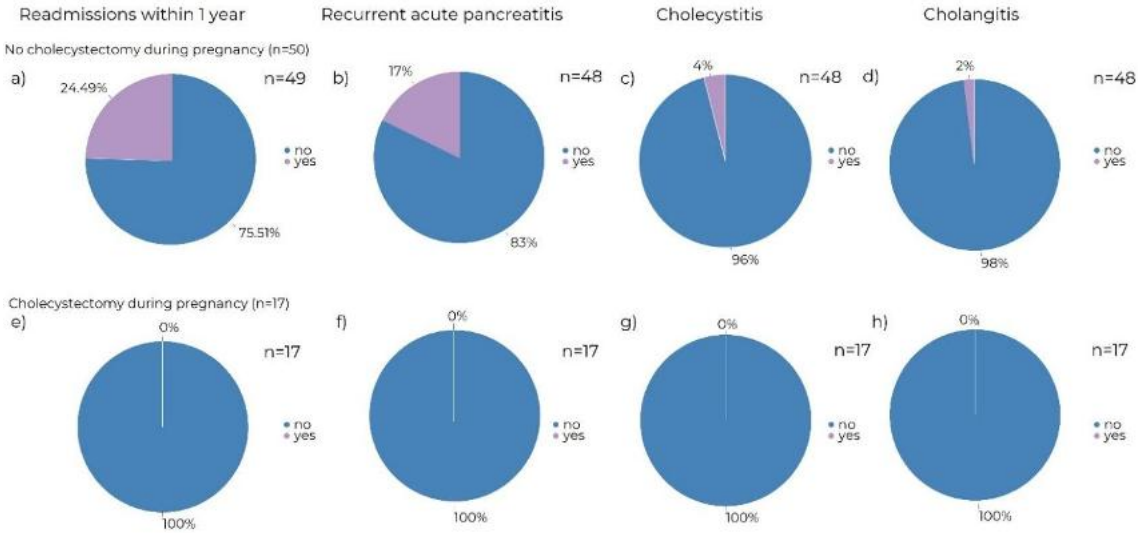


Figure 10. Readmissions after mild biliary pancreatitis during pregnancy with or without cholecystectomy (1)

Readmission rates after mild biliary pancreatitis within one year (a), recurrent pancreatitis (b), cholecystitis (c), and cholangitis (d) in women without cholecystectomy during pregnancy. Readmission rates after mild biliary pancreatitis within one year (e), recurrent pancreatitis (f), cholecystitis (g), and cholangitis (h) in women with cholecystectomy during pregnancy. Statistical analysis was performed using Fisher's exact test for readmission within one year (p = 0.027) and for recurrent AP (p = 0.094). AP: acute pancreatitis

Preterm birth rates did not differ between patients who underwent cholecystectomy and those managed conservatively (7.1%, n=1/14 vs. 11%, n=5/45; p>0.999). Neonatal intensive care admission was slightly less frequent in the cholecystectomy group (0%, n=0/13) compared with the non-surgical group (2.5%, n=1/42; p>0.999). Although fetal loss appeared marginally higher among patients who underwent surgery (18%, n=3/17 vs. 2%, n=1/49; p=0.050), all cases occurred following first-trimester cholecystectomy (Figure 11). Median age was comparable between the surgical and non-surgical groups [33 (31–34) vs. 30 (26–33) years; p=0.154]. In contrast, gestational age at presentation was significantly lower in the cholecystectomy group [15 (8–26) weeks] than in the

conservative group [26 (17–31) weeks; p=0.008]. The length of hospitalization was similar, with median stays of 6 days (Q25–75: 4–8) and 5 days (Q25–75: 3–6), respectively (p = 0.341).

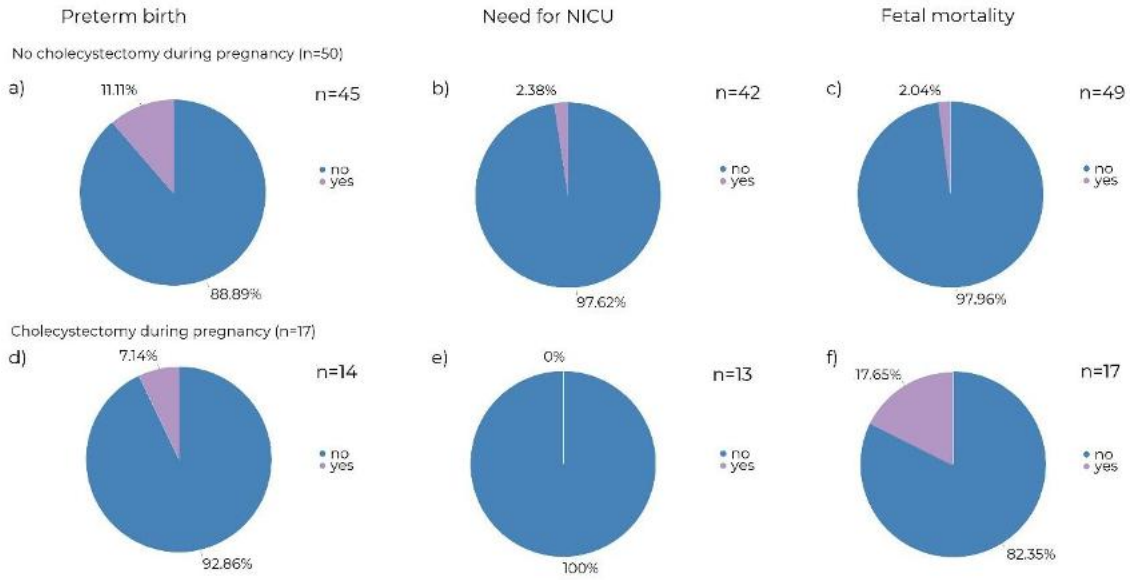


Figure 11. Outcome of pregnancy with mild biliary pancreatitis during pregnancy with or without cholecystectomy (1)

Preterm birth (a), NICU admission (b), and fetal mortality (c) in women after mild biliary pancreatitis, without cholecystectomy during pregnancy. Preterm birth (d), NICU admission (e), and fetal mortality (f) in women after mild biliary pancreatitis, with cholecystectomy during pregnancy. Statistical analysis was performed using Fisher's exact test for preterm birth (p > 0.999), for NICU admission (p > 0.999), and for fetal loss (p = 0.050).

NICU – neonatal intensive care unit

Among patients with mild biliary pancreatitis, intraoperative complication rates did not differ between those undergoing cholecystectomy during pregnancy and those operated on postpartum (12%, n=2/17 vs. 10%, n=3/30; p>0.999). Postoperative complications were likewise comparable (0%, n=0/17 vs. 0%, n=0/30; p>0.999) (Figure 12). These results indicate that cholecystectomy performed in the second or third trimester is a safe and effective approach for preventing biliary complications in mild AP. Nonetheless,

safety in the first trimester remains unclear, as all fetal losses associated with surgery occurred during this period.

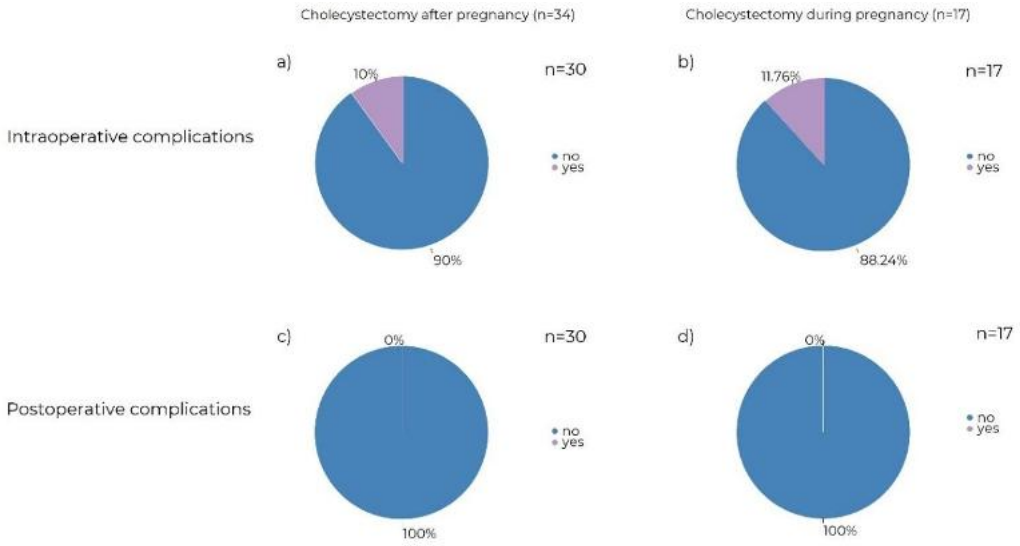


Figure 12. Surgical complications after mild biliary pancreatitis (1)

Intraoperative complications (a) and postoperative complications (b) in women undergoing cholecystectomy after pregnancy following mild biliary pancreatitis. Intraoperative complications (c) and postoperative complications (d) in women undergoing cholecystectomy during pregnancy following mild biliary pancreatitis. Statistical analysis was performed using Fisher's exact test for intraoperative complications ($p > 0.999$) and for postoperative complications ($p > 0.999$).

8.2.3. ERCP in patients with biliary pancreatitis

ERCP was performed in 22 patients: 40.9% (n = 9/22) had choledocholithiasis, 36.4% (n = 8/22) had both choledocholithiasis and cholangitis, and 4.5% (n = 1/22) had cholangitis alone. Readmission rates (23%, n=5/22 vs. 15%, n=11/72; p=0.517), fetal loss (9.1%, n=2/22 vs. 5.4%, n=4/74; p=0.618), and preterm birth (5.9%, n=1/17 vs. 12%, n=8/65; p=0.677) did not significantly differ between patients who underwent ERCP during pregnancy and those who did not (Figures 13–14).

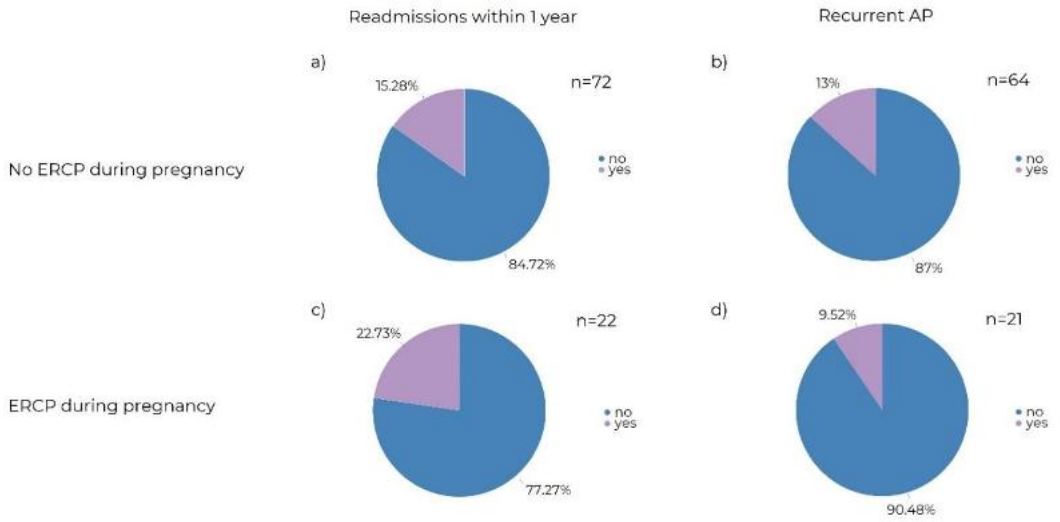


Figure 13. Readmissions after biliary pancreatitis during pregnancy with or without ERCP during pregnancy (1)

Readmission rates after biliary pancreatitis within one year (a), recurrent pancreatitis (b) in women without undergoing ERCP during pregnancy. Readmission rates after biliary pancreatitis within one year (c), recurrent pancreatitis (d), in women undergoing ERCP during pregnancy. Statistical analysis was performed using Fisher's exact test for readmission within one year ($p = 0.517$) and for recurrent AP ($p = 0.705$).
AP - Acute Pancreatitis
ERCP - Endoscopic retrograde cholangiopancreatography

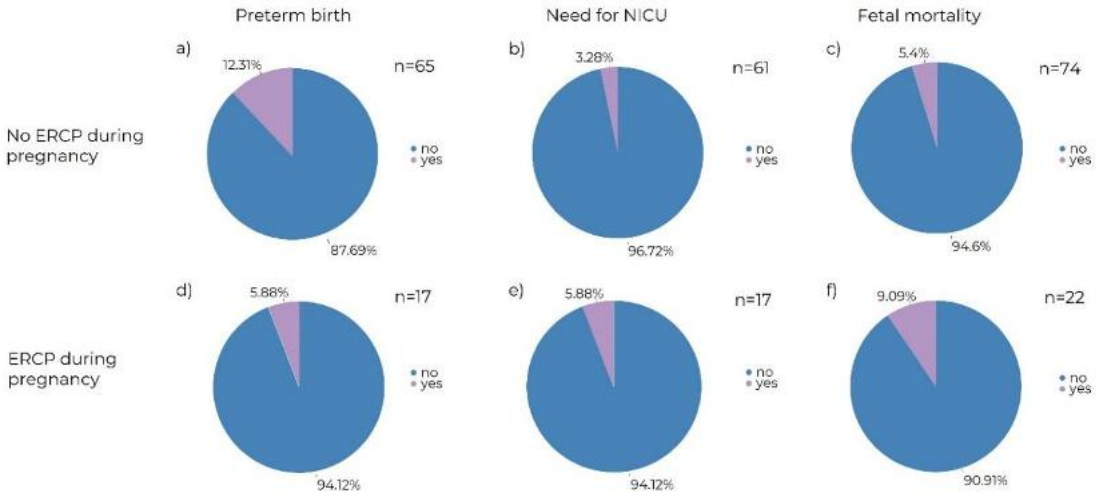


Figure 14. Pregnancy outcomes after biliary pancreatitis during pregnancy with or without ERCP during pregnancy (1)

Preterm birth (a), NICU admission (b), and fetal mortality (c) in women after biliary pancreatitis, without ERCP during pregnancy. Preterm birth (d), NICU admission (e), and fetal mortality (f) in women after biliary pancreatitis, with ERCP during pregnancy.

Statistical analysis was performed using Fisher's exact test for preterm birth (p = 0.677), for NICU admission (p = 0.527), and for fetal mortality (p = 0.618).
ERCP - Endoscopic retrograde cholangiopancreatography
NICU - neonatal intensive care unit

Of the two fetal losses in the ERCP group, one occurred in a patient with severe AP and abdominal compartment syndrome, and the other took place in the first trimester after discharge, with no apparent connection to AP or the procedure. Gestational age tended to be lower among patients who underwent ERCP [19 (Q25-75 11, 27) vs. 25 (Q25-75 14,31) weeks; p=0.221]. Post-ERCP pancreatitis was reported in one patient (n=1/22), while no other complications, such as bleeding or perforation, were observed (n=0/22). These data support the safety of ERCP during pregnancy when indicated.

8.2.4. Effectiveness and safety of cholecystectomy compared to ERCP

In the subgroup analysis comparing ERCP and cholecystectomy performed during pregnancy, no significant differences were observed in readmission rates (5%, n=1/21 vs. 27%, n=4/15; p=0.138), preterm birth (6%, n=1/17 vs. 8%, n=1/12; p>0.999), or fetal mortality (14%, n=3/22 vs. 7%, n=1/15; p=0.633) (Figure 15-16). Gestational age at presentation was comparable between the two groups [15 (Q25–75 8–22) vs. 17 (Q25–75 11–29) weeks; p=0.287]. Cholecystectomy was performed during pregnancy in seven of the 22 patients who underwent ERCP; these cases were excluded from the subgroup analysis to avoid overlap between treatment categories.

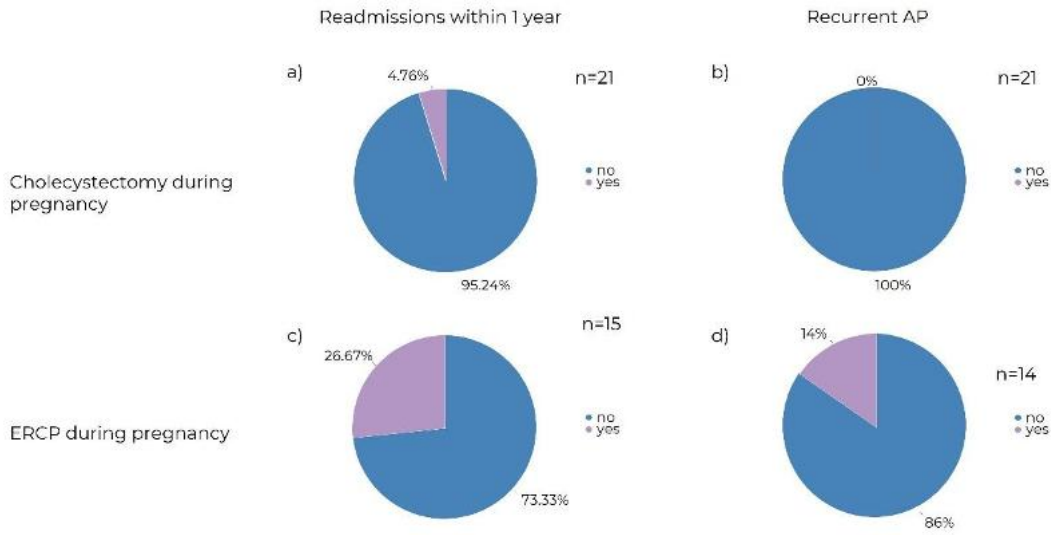


Figure 15. Readmissions after biliary pancreatitis during pregnancy with cholecystectomy or with ERCP during pregnancy (1)

Readmission rates after biliary pancreatitis within one year (a), recurrent pancreatitis (b) in women undergoing cholecystectomy during pregnancy. Readmission rates after biliary pancreatitis within one year (c), recurrent pancreatitis (d), in women undergoing ERCP during pregnancy. Statistical analysis was performed using Fisher's exact test for readmission within one year ($p = 0.138$) and for recurrent AP ($p = 0.148$).
AP - Acute Pancreatitis
ERCP - Endoscopic retrograde cholangiopancreatography

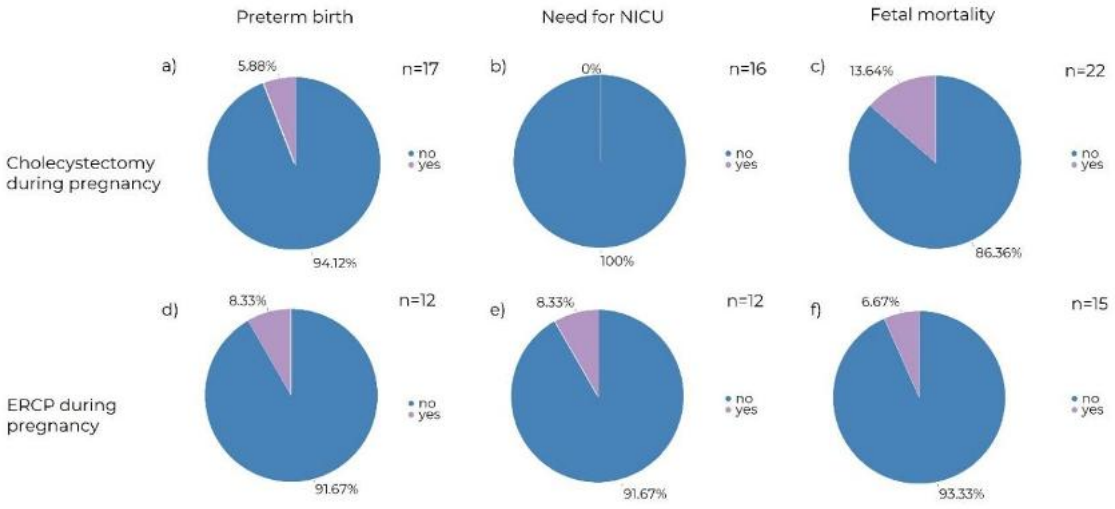


Figure 16. Pregnancy outcomes after biliary pancreatitis during pregnancy with cholecystectomy or with ERCP during pregnancy (1)

Preterm birth (a), NICU admission (b), and fetal mortality (c) in women after biliary pancreatitis, with cholecystectomy during pregnancy. Preterm birth (d), NICU admission

(e), and fetal mortality (f) in women after biliary pancreatitis, with ERCP during pregnancy. Statistical analysis was performed using Fisher's exact test for preterm birth ($p > 0.999$), for NICU admission ($p = 0.429$), and for fetal mortality ($p = 0.633$).
ERCP - Endoscopic retrograde cholangiopancreatography
NICU – neonatal intensive care unit

9. DISCUSSION

9.1. Summary of findings, international comparisons

Our first study showed that the predictive accuracy of CRP and PCT for infection in necrotizing pancreatitis varies according to the stage of the disease. During the initial three days following admission, CRP, PCT, and WBC had low predictive accuracy for infection, which is consistent with the observations of Párniczky et al. (27, 49). However, after the first three days of admission and when assessed over a disease course of at least two weeks, CRP and PCT demonstrated good predictive accuracy for infection (50). Tracking these biomarkers over time through repeated assessments may be crucial for improving diagnostic reliability.

PCT, the inactive 116–amino acid propeptide of calcitonin, rises markedly within 2–4 hours in the setting of severe systemic inflammation or bacterial infection, while exhibiting only minimal elevation during viral infections. In contrast, CRP and WBC levels rise more gradually, reaching their peak around 36 hours after endotoxin exposure. CRP is an acute-phase protein that requires more than 72 hours to reach its peak concentration. Earlier studies have demonstrated its value in predicting the severity of AP, with pancreatic necrosis being strongly associated with CRP levels above 150 mg/L within the first 72 hours (13, 69, 70). PCT release is triggered by microbial antigens and inflammatory cytokines, including IL-1β, TNF-α, and IL-6 (71, 72). After surgery, PCT may rise transiently for 12–24 hours but returns to baseline within 48 hours in the absence of infection. In contrast, CRP and WBC levels can remain elevated for a longer period postoperatively, irrespective of infection status (73). The PROCAP randomized trial, conducted at a single center, utilized a PCT-guided algorithm with a threshold of 1 ng/mL to direct antibiotic therapy. The study demonstrated a significant reduction in antibiotic prescriptions when the PCT algorithm was applied, effectively limiting unnecessary antibiotic use without increasing infection rates or prolonging hospital stay (74). The trial's findings underscore the value of incorporating biomarkers, such as PCT, into clinical decision-making to optimize management and improve outcomes in INP. Generally, antibiotic initiation is advised when PCT levels are above 0.5 ng/mL, and it is strongly recommended when levels exceed 1.0 ng/mL (71). Another study reported that

an inability to lower PCT to less than 60% of its initial value within seven days of intervention predicted higher mortality (75).

A previous systematic review identified PCT as the most reliable indicator of INP (76). Chen et al. reported that PCT could reliably predict infection within the first 48 hours. his may be explained by the tertiary care environment in which the study was conducted, characterized by a high proportion of critically ill patients at elevated risk for infection (56). The included studies lacked follow-up data, limiting the evaluation of long-term outcomes and the identification of delayed complications. Additionally, differences in threshold values prevented the pooling of sensitivity and specificity for CRP and PCT. This challenge was further exacerbated by the small number of eligible studies, which precluded quantitative aggregation.

Systemic inflammation is believed to play a central role in the development of organ dysfunction, with cytokines serving as key regulators of the inflammatory cascade. IL-6, a proinflammatory cytokine released by multiple cell types in response to tissue injury and stimuli such as TNF-α and IL-1β, promotes the hepatic synthesis of acute-phase proteins, including CRP. IL-6 levels rise markedly on the day of admission in necrotizing and SAP, making it a strong early marker for severity assessment and prediction of organ failure (58, 77). Elevated IL-6 concentrations have been observed in both SNP and INP (65).

TNF-α and sICAM were assessed as potential indicators of INP; however, neither showed adequate predictive performance (58, 65). One study also assessed G-CSF based on earlier reports suggesting that low levels might be associated with a higher risk of infection. In contrast, the study found that G-CSF concentrations were slightly increased in INP and did not prove to be a useful diagnostic marker (59, 78).
In individual studies, STREM-1 and presepsin (soluble CD14-ST) demonstrated AUC values of 0.792 and 0.956, respectively (57, 60). Presepsin has recently emerged as a promising biomarker for early infection detection and is increasingly recognized for its role in identifying sepsis and predicting disease severity (79). Furthermore, hypoalbuminemia was identified as a predictor of INP in one study and is already

recognized as a dose-dependent risk factor for organ failure, local complications, and malnutrition in AP (55, 80).

Elevated serum LDH, a marker of cellular injury, has been strongly associated with SAP and is considered a sensitive indicator of pancreatic necrosis, yet its capacity to predict IPN achieved an AUC of only 0.77 (67, 81). Notably, when LDH was combined with lymphocyte levels during the late phase of AP, the AUC improved substantially to 0.94 (67). As markers of perfusion and volume status, HCT, BUN, and creatinine have been linked to the severity and mortality of AP (82). Although HCT demonstrates poor predictive ability for INP, both creatinine and BUN correlate with IPN and are integrated into prognostic scoring models (55, 56).

Chen et al. evaluated the combined diagnostic performance of PCT, CRP, HCT, and BUN during the first 48 hours of admission (56). Similarly, Wiese et al. proposed a prediction model incorporating creatinine, CRP, albumin, and alcoholic etiology; these scoring systems outperformed single laboratory parameters in terms of ROC and AUC values (55). In a meta-analysis, Tran et al. further showed that patients with severe or necrotizing pancreatitis were more likely to develop IPN if pancreatic necrosis exceeded 50%, enteral feeding was delayed, or invasive mechanical ventilation was required (83). These observations highlight the usefulness of a comprehensive predictive strategy for identifying infected necrosis (84, 85).

In our second study, a retrospective multicenter cohort analysis, we found that pregnant patients who underwent cholecystectomy following a mild biliary episode of AP had lower one-year readmission. Nearly all readmissions were attributed to symptomatic gallbladder disease, most commonly recurrent pancreatitis. Although preterm birth rates did not differ significantly between groups, a modest increase in fetal loss was observed among patients who underwent surgery during pregnancy.

Our findings align with previous research demonstrating that conservative management of symptomatic gallbladder disease during pregnancy is associated with higher rates of hospital readmission and adverse pregnancy outcomes (86, 87). Luthra et al. reported that

ERCP reduced the likelihood of early readmission by 60%, and that performing cholecystectomy during the same admission further decreased the risk by 85% (87). Similarly, Hedström et al. found that 56% of pregnant patients initially managed nonoperatively for gallbladder disease required surgical intervention within two years postpartum (88). Jorge et al. also observed that women with uncomplicated symptomatic cholelithiasis who do not undergo surgery during pregnancy frequently need postpartum cholecystectomy, often following at least one hospitalization for recurring symptoms (30). In our cohort, 43.48% of patients had a prior episode of symptomatic cholelithiasis, including 21 individuals with symptoms within six months before hospitalization for AP, underscoring the value of elective cholecystectomy before pregnancy in symptomatic patients to prevent recurrent biliary events. Multiparity, a known risk factor for cholelithiasis, was present in 57.14% of cases (33).

Most episodes of AP occur during the second and third trimesters, likely due to physiological changes that promote gallstone formation, which increases substantially after the first trimester. Elevated intra-abdominal pressure may further contribute to this risk (89). Additionally, the presence of multiple small gallstones is a known risk factor for developing AP (90). The distribution of disease severity and the clinical course observed in our cohort resembled those typically reported in the non-pregnant population, suggesting that pregnancy does not substantially alter the overall outcome of AP. In our study, 30.3% of patients received antibiotics—most often due to concurrent conditions (24.75%)—which aligns with the considerable international variability (31–82%) in antibiotic prescribing for AP (27). Mortality associated with AP has decreased over recent decades in the general population, with approximately 80% of cases remaining mild (91). A recent meta-analysis by Hughes et al. similarly showed that maternal mortality in pregnant patients with AP is comparable to that of the general population. In contrast, fetal mortality, although slightly improved, remains high at 12.6% (35). For context, the fetal mortality rate in the European Union in 2021 was 2.3 per 1,000 births among the general population (92).

Our analysis did not demonstrate a statistically significant difference in fetal loss between patients managed surgically and those treated conservatively during pregnancy.

Nonetheless, a non-significant trend toward increased fetal loss in the first trimester was observed, which may reflect insufficient statistical power due to the limited sample size. An alternative explanation is supported by prior studies showing that AP occurring at earlier gestational stages is associated with higher fetal mortality rates (93, 94). Consistently, a recent meta-analysis reported fetal mortality rates of 20.9% in the first trimester, compared with 12.4% and 12.0% in the second and third trimesters, respectively (35). Furthermore, it should be acknowledged that baseline miscarriage rates in the general population are highest in the first trimester, affecting approximately 12–15% of recognized pregnancies before 20 weeks of gestation (95).

Laparoscopic cholecystectomy is regarded as a safe option for treating symptomatic gallbladder disease during any trimester of pregnancy; however, the second trimester is generally considered the safest period, as organogenesis has been completed and the uterus is not yet large enough to limit surgical visualization (96, 97).

Some studies have reported higher rates of fetal loss and preterm birth associated with third-trimester cholecystectomy. In contrast, others have found similar preterm birth rates when comparing surgical and conservative management approaches (88, 98-101). Hantouli et al. observed that, when outcomes were analyzed by gestational trimester and compared with non-operative management, cholecystectomy during pregnancy was associated with lower rates of fetal loss and preterm delivery (102).

ERCP is regarded as a safe procedure during pregnancy when performed in high-volume tertiary centres by a multidisciplinary team (103). In our cohort, ERCP was primarily undertaken for well-defined indications, such as cholangitis or choledocholithiasis, and sphincterotomy was performed in nearly all cases. However, this approach did not significantly reduce readmission rates or recurrent pancreatitis compared with surgical management. Consistent with the findings of the APEC trial, Schepers et al. demonstrated that urgent ERCP does not improve outcomes in patients with gallstone pancreatitis in the absence of cholangitis, supporting a more selective use of ERCP during pregnancy (104). Although pregnancy has been identified as an independent risk factor for PEP, this association remains debated (103, 105). Earlier studies reported higher PEP rates—Tang

et al. observed an incidence of 16%—whereas more recent data, including a nationwide registry study by Hedström et al., reported no cases (106, 107). In our study, post-ERCP pancreatitis occurred in only one patient.

9.2. Strengths

9.2.1. Study I.

A key strength of our study is the strict adherence to our pre-registered protocol, which ensured methodological rigor and transparency. Additionally, unlike previous systematic reviews, we performed subgroup analyses based on the timing of laboratory parameter measurements (76).

9.2.2. Study II.

The BORN study provides robust, multidisciplinary, real-world data on the management of biliary AP during pregnancy, drawing from an international, multicenter cohort. Importantly, the study offers valuable insights into maternal, fetal, and neonatal outcomes associated with cholecystectomy and ERCP during pregnancy, addressing a significant gap in the existing literature.

9.3. Limitations

9.3.1. Study I.

Our study is mainly limited by the relatively few eligible studies and considerable heterogeneity in study designs and patient cohorts. Variations in disease onset and severity further restrict the applicability of the findings to broader clinical populations. Moreover, some included studies were of low quality. Due to inconsistent and occasionally missing threshold values, we were also unable to propose a standardized cutoff for predicting infection.

9.3.2. Study II.

The retrospective design of the study inherently carries a risk of unmeasured confounding, and relevant factors such as comorbidities, socioeconomic status, nutritional status, anesthesia techniques, and variations in obstetric management may not have been fully captured. Given the international and multicenter nature of the study, heterogeneity in

surgical timing, ERCP protocols, and supportive obstetric care may also have influenced outcomes. In addition, only short-term neonatal outcomes were reported, and data on long-term infant health and developmental outcomes were not available. Although this cohort includes a relatively large number of cases for this rare condition, the overall sample size remains limited, reducing statistical power and restricting the ability to detect small but clinically relevant differences. While a randomized controlled trial could theoretically provide higher-level evidence, conducting such a study in pregnant patients would be ethically and practically challenging, given concerns regarding maternal - fetal safety and informed consent in this vulnerable population.

10. CONCLUSIONS

10.1. Study I.

During the first 72 hours after hospital admission CRP and PCT perform poorly as predictors of infection; however, their predictive accuracy improves substantially after this period, reaching levels suitable for clinical application.

10.2. Study II.

Cholecystectomy performed during the second or third trimester is a safe and effective intervention to prevent recurrent biliary events in pregnant patients with mild biliary pancreatitis, whereas its safety in the first trimester remains unclear due to limited evidence and a possible increased risk of fetal loss. ERCP is safe throughout pregnancy, but it does not significantly reduce readmission rates.

11. IMPLEMENTATIONS FOR PRACTICE

11.1. Study I.

CRP and PCT show potential as biomarkers to support appropriate antibiotic decision-making in the late phase of AP.

11.2. Study II.

Our findings support cholecystectomy during the second and third trimesters as a safe and effective strategy to prevent recurrent biliary events in pregnant patients with mild biliary AP. First-trimester surgery should be considered cautiously and reserved for selected cases following multidisciplinary evaluation. ERCP should be restricted to clear indications, such as cholangitis or persistent biliary obstruction, and performed in specialized centers, as routine use does not reduce readmissions. Multidisciplinary, individualized decision-making is essential to optimize maternal and fetal outcomes and to reduce unnecessary variation in clinical practice.

12. IMPLEMENTATION FOR RESEARCH

12.1. Study I.

Future studies with larger cohorts and extended follow-up are required to validate further and refine the predictive utility of CRP, PCT, creatinine, BUN, presepsin, and albumin for identifying IPN. Additionally, the development of a composite scoring system integrating multiple biomarkers with clinical factors - such as imaging findings and patient characteristics - may substantially improve prediction accuracy.

12.2 Study II.

Future research should address two major gaps. Prospective studies with larger cohorts are necessary to better characterize the risk of fetal loss related to first-trimester surgical intervention, accounting for gestational age and disease severity. Furthermore, longitudinal studies evaluating long-term maternal and neonatal outcomes after intra-gestational cholecystectomy are essential.

13. IMPLEMENTATION FOR POLICYMAKERS

13.1. Study I.

For policymakers, these findings underscore the need to support the development of evidence-based diagnostic pathways for IPN, including the integration of validated biomarkers into clinical guidelines. Investment in multicenter studies and standardized data reporting would help generate the robust evidence required to refine prediction models for infected necrosis.

13.2. Study II.

Our findings underscore the need for more precise, evidence-based policy guidance on the management of biliary AP during pregnancy. Policymakers should support the inclusion of trimester-specific recommendations for cholecystectomy in clinical guidelines, recognizing its safety and effectiveness in the second and third trimesters. Policies should also promote a restrictive, indication-driven use of ERCP during pregnancy, limited to cases of cholangitis or persistent biliary obstruction and performed in specialized, high-volume centers. Ultimately, fostering multidisciplinary care pathways and supporting international data collection initiatives will be crucial in reducing practice variability and enhancing maternal and fetal outcomes.

14. FUTURE PERSPECTIVES

Future research should focus on prospective studies aimed at identifying early and reliable markers of infection in AP, including the integration of artificial intelligence–based tools to support timely diagnosis and individualized decision-making. Such approaches may help identify patients who truly require antibiotic therapy and determine the optimal duration of treatment, thereby reducing unnecessary antibiotic exposure. Additionally, prospective, multicenter studies are needed to better define the optimal timing of cholecystectomy across pregnancy trimesters, with particular emphasis on accurately quantifying fetal risks associated with first-trimester surgery. Future studies should incorporate long-term maternal and neonatal follow-up to assess developmental outcomes beyond the perinatal period. These future directions will support the development of evidence-based guidelines and facilitate more individualized, safe, and effective management strategies for patients with AP.

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DOI: 10.3390/ijms25021273

IF: 4,9

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GASTROENTEROLOGY 165: 3 pp. 682-695. (2023)

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IF: 25.7

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UNITED EUROPEAN GASTROENTEROLOGY JOURNAL 11: 8 pp. 767-774. (2023)

DOI: 10.1002/ueg2.12402

IF: 5.8

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Discharge protocol in acute pancreatitis: an international survey and cohort analysis

SCIENTIFIC REPORTS 13: 1 Paper: 22109, 10 p. (2023)

DOI: 10.1038/s41598-023-48480-z

IF: 3,8

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Metabolic-associated fatty liver disease is associated with acute pancreatitis with more severe course: Post hoc analysis of a prospectively collected international registry
UNITED EUROPEAN GASTROENTEROLOGY JOURNAL 11: 4 pp. 371-382. (2023)

DOI: 10.1002/ueg2.12389

IF: 5.8

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Alcohol consumption and smoking dose-dependently and synergistically worsen local pancreas damage

GUT 71: 12 pp. 2601-2602. (2022)

DOI: 10.1136/gutjnl-2021-326853

IF: 24.5

17. ACKNOWLEDGEMENTS

I would like to sincerely thank my supervisors, Prof. Péter Hegyi and Dr. Alexandra Mikó, for their invaluable guidance and support throughout this work. Prof. Hegyi, I am deeply thankful for your dedication, motivation, and brilliant ideas, which consistently inspired my scientific thinking and shaped the direction of this research. Dr. Mikó, your patience, kindness, and thoughtful guidance provided constant encouragement and greatly contributed to the successful completion of this project.

I am especially grateful to my methodology supervisor, Dr. Eszter Szalai, whose exceptional expertise in research methodology and outstanding time management skills were instrumental to this work. Your structured approach and clarity greatly enhanced both the quality and efficiency of my research.

I would also like to thank Dr. Bálint Erőss for his continuous support in both my scientific development and clinical training during my residency. Your guidance and mentorship significantly influenced my professional growth.

I appreciate all my collaborators who contributed to this work, whether through scientific input, clinical support, or constructive discussions.

Finally, I am profoundly grateful to my family for their unwavering support and love. I also wish to thank my friends and colleagues for their encouragement, understanding, and support throughout this journey.