UNIVERSITÀ DEGLI STUDI DI PAVIA

DOTTORATO DI RICERCA IN MEDICINA SPERIMENTALE

Closing the Gap Between Evidence and Practice: Underutilization of Same-Admission Cholecystectomy in Mild Acute Biliary Pancreatitis - a multicenter prospective study.

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Abstract

Background

Mild acute biliary pancreatitis (MABP) represents the most frequent form of acute pancreatitis, primarily caused by gallstones or biliary sludge. Although considered the least severe presentation, MABP carries a substantial risk of recurrence. International guidelines strongly recommend same-admission cholecystectomy (SAC) as the standard of care for MABP, supported by evidence from randomized controlled trials and meta-analyses demonstrating its efficacy and safety. Nevertheless, clinical practice often deviates from these recommendations, with interval cholecystectomy (IC)—performed weeks after discharge—remaining widely adopted. This discrepancy between evidence and practice exposes patients to preventable complications and repeated hospitalizations.

Methods

The **Cholecystectomy TIming for Mild Acute biliary Pancreatitis (CTIMAP) study** was designed as a prospective, multicenter observational investigation across 66 hospitals worldwide between June 2022 and November 2023. Adults diagnosed with MABP according to the Revised Atlanta Classification (2012) were stratified into SAC and IC groups, while a third cohort included patients who did not undergo cholecystectomy within six months. The primary endpoint was six-month readmission due to GRE. Secondary endpoints included 30-day postoperative complications, mortality, intraoperative events, bail-out procedures, operative time, postoperative length of stay (LOS), and total LOS. Data were recorded in a centralized REDCap database and propensity score weighting to minimize confounding.

Results

A total of 445 patients with MABP were enrolled, of whom 413 underwent cholecystectomy. Among

these, 235 (57%) received SAC, while 178 (43%) underwent IC; 116 patients (26% of the total cohort) did not receive cholecystectomy within six months. SAC was associated with a significantly lower risk of six-month readmission for GRE compared with IC (hazard ratio [HR] 0.26; 95% CI 0.07–0.97; p = 0.046). After propensity score weighting, the benefit of SAC was even more pronounced (HR 0.11; 95% CI 0.02–0.55; p = 0.007). Rates of postoperative complications, conversions to open surgery, bail-out procedures, and intraoperative complications were comparable between SAC and IC, confirming the safety of early intervention. While postoperative LOS was slightly longer for SAC, total hospital LOS did not differ significantly between groups. Operative times were longer for SAC, largely due to the higher frequency of concomitant intraoperative ERCP or biliary exploration.

Conclusion

The CTIMAP study provides robust, real-world prospective evidence that same-admission cholecystectomy is safe and significantly reduces the risk of recurrent gallstone-related events compared to interval cholecystectomy. Despite these advantages, SAC remains underutilized, with nearly half of patients in the study managed with IC and one-quarter not undergoing surgery at all within six months. These findings underscore the persistent evidence–practice gap in the management of MABP. Overcoming logistical barriers, standardizing protocols, and promoting adherence to guidelines are essential steps toward ensuring that a greater proportion of patients benefit from timely surgical intervention.

Introduction

1. Acute Pancreatitis: Epidemiology and Clinical Burden

Acute pancreatitis (AP) is a frequent and clinically significant gastrointestinal emergency worldwide. Its global incidence is estimated to be approximately 34 cases per 100,000 individuals per year, but considerable geographical variation exists, with rates ranging from 13 to 45 per 100,000 depending on the population studied (1). Over the past two decades, the number of hospitalizations for AP has continued to rise in many countries, reflecting not only improved diagnostic recognition but also changes in lifestyle and increasing prevalence of risk factors such as obesity, gallstones, alcohol use, and metabolic syndrome (2).

In most Western countries, gallstones and biliary sludge are the leading causes of AP, accounting for 40–70% of cases, followed by alcohol (20–30%). Other etiologies include hypertriglyceridemia, post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, drugs, autoimmune pancreatitis, and rare metabolic or structural conditions. Importantly, gallstone-related AP is more prevalent among older patients and women, while alcohol-related cases are more common in younger men (1).

Although overall mortality for AP has decreased due to advances in critical care and multidisciplinary management, morbidity remains high. Patients often require repeated hospital admissions, invasive interventions, and prolonged monitoring. In addition, AP imposes a considerable economic burden

on healthcare systems, ranking among the leading causes of emergency admissions for gastrointestinal disorders (3).

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2. Clinical Classification of Acute Pancreatitis

The Revised Atlanta Classification (2012) has provided an internationally accepted framework for defining the severity of AP. According to this classification, AP is stratified into:

- **Mild AP:** No organ failure and no local or systemic complications. This accounts for 70–80% of cases and usually has a favorable prognosis.
- **Moderately severe AP:** Transient organ failure (<48h) and/or local or systemic complications without persistent organ failure.
- **Severe AP:** Persistent organ failure (>48h), often with multiple organ dysfunction, associated with mortality rates up to 30%.

Mild acute biliary pancreatitis (MABP) is the most common presentation, and while mortality is negligible, the recurrence rate is substantial if gallstone disease is not definitively treated. Recurrent attacks increase the risk of complications and decrease quality of life, underscoring the importance of timely cholecystectomy.

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3. Pathophysiology of Gallstone-Induced Pancreatitis

The pathogenesis of biliary pancreatitis is strongly linked to the transient obstruction of the ampulla of Vater by gallstones or biliary sludge. Acosta and Ledesma first described this mechanism in 1974,

demonstrating how temporary obstruction of the common channel leads to pancreatic duct hypertension and premature activation of trypsinogen into trypsin within the pancreatic acinar cells. This initiates autodigestion and an inflammatory cascade.

The subsequent release of cytokines and inflammatory mediators such as interleukins, tumor necrosis factor-alpha, and chemokines amplifies the systemic inflammatory response. While in mild disease this cascade resolves spontaneously, in severe cases it can evolve into systemic inflammatory response syndrome (SIRS), multi-organ dysfunction, and even death. In MABP, however, the clinical concern lies not in systemic inflammation but in recurrence: unless the source of obstruction (the gallbladder) is definitively removed, patients remain at high risk for gallstone-related events (GRE) including biliary colic, acute cholecystitis, obstructive jaundice, cholangitis, and recurrent AP (4,5).

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4. Definitive Management of MABP: The Role of Cholecystectomy

Cholecystectomy remains the definitive treatment for gallstone pancreatitis. By removing the gallbladder, the source of migrating gallstones or sludge is eliminated, thus preventing recurrence. The timing of cholecystectomy, however, has been the subject of long-standing debate (6-24).

4.1 Interval Cholecystectomy (IC)

Traditionally, many surgeons favored delaying surgery for 6–8 weeks after the acute episode, adopting the strategy known as interval cholecystectomy (IC). This approach was justified by concerns that early surgery might be complicated by edema and inflammation, increasing the

technical difficulty, prolonging operative time, and raising the risk of conversion to open surgery or bile duct injury (24). Moreover, logistical constraints, particularly the limited availability of emergency operating room (OR) time, made delayed surgery more convenient in many hospitals.

4.2 Same-Admission Cholecystectomy (SAC)

In contrast, accumulating evidence (6-18) since the 2000s has demonstrated that same-admission cholecystectomy (SAC)—defined as surgery performed during the index admission for MABP—is safe and effective. SAC prevents recurrent GRE, reduces the need for readmissions, and does not increase perioperative complications. Indeed, some studies have even reported that delaying surgery beyond two weeks increases operative difficulty due to the development of adhesions and fibrosis.

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5. Evidence from Randomized Controlled Trials and Meta-Analyses

Multiple randomized controlled trials (RCTs) and systematic reviews have compared SAC with IC in patients with MABP:

- **PONCHO Trial** (8): A multicenter RCT that randomized 266 patients to SAC or IC. SAC significantly reduced recurrent gallstone-related complications with no increase in perioperative morbidity.
- **Aboulian et al., 2010** (12): Demonstrated that early laparoscopic cholecystectomy within 48h was associated with shorter hospital stay and no increase in complications.

- **Ito et al., 2008** (15): Reported that delaying surgery beyond two weeks substantially increases the risk of recurrent attacks.
- **Meta-analyses** (9,10,16,17,18,22): Consistently confirmed that SAC is superior to IC in reducing recurrence, shortening hospital stay, and preventing readmissions, with comparable complication rates.

Collectively, these studies have shifted international consensus towards recommending SAC as the preferred strategy for MABP.

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6. Current Guidelines

Several international societies have incorporated the evidence into their clinical guidelines:

- **World Society of Emergency Surgery (6):** Recommends SAC for all patients with MABP, provided there are no contraindications.
- **International Association of Pancreatology (IAP) / American Pancreatic Association (APA, 2013):** Strongly advocate early cholecystectomy.
- **American Gastroenterological Association (AGA, 2013):** Advises performing cholecystectomy during the index admission.
- **NICE Guidelines (UK):** Recommend cholecystectomy within two weeks of discharge, although real-world adherence is poor.

Despite these clear recommendations, SAC remains underutilized in daily practice.

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7. The Evidence–Practice Gap

While guidelines are unequivocal, audits and observational studies highlight a persistent gap between evidence and practice.

- In the **MANCTRA-1 audit** (19-20)**,** SAC was performed in only 29% of MABP cases worldwide.
- UK national data revealed that up to one-third of patients do not undergo cholecystectomy within one year of discharge.
- In the United States, large database analyses confirm similar trends, with delayed or absent surgery common in routine care.

The consequences are significant: patients discharged without surgery have up to a 30% risk of readmission within one year, with associated increases in morbidity, healthcare costs, and mortality.

The reasons for this underutilization are multifactorial:

1. **Logistical constraints** – lack of emergency OR availability and competing priorities.
2. **Perceived risks** – concerns among surgeons regarding operative difficulty during the acute phase.
3. **Institutional inertia** – adherence to historical practices and lack of standardized protocols.
4. **Patient-related factors** – comorbidities, late presentation, or need for preoperative optimization.

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8. Rationale for the CTIMAP Study

Given the clear evidence favoring SAC and the persistent underutilization in practice, the **Cholecystectomy TIming for Mild Acute biliary Pancreatitis (CTIMAP) study** was developed to evaluate the real-world implementation of guideline recommendations.

Unlike randomized controlled trials, which are often limited by strict inclusion criteria, CTIMAP was designed as a **prospective, multicenter, observational study** including a broad patient population across 66 centers worldwide. This design allowed the collection of robust real-world data on the adoption of SAC versus IC, clinical outcomes, and the organizational factors influencing surgical timing.

The primary objective was to assess whether SAC reduces the rate of six-month readmission for GRE compared with IC. Secondary objectives included evaluating complications, operative times, length of stay, and the proportion of patients who did not undergo surgery at all. Importantly, the study employed **propensity score weighting** to adjust for confounding, enhancing the reliability of its findings.

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9. Hypothesis and Objectives

The study hypothesis was clear:

- **Same-admission cholecystectomy reduces the risk of recurrent gallstone-related events without increasing surgical complexity or postoperative complications compared to interval cholecystectomy.**

The specific objectives were:

1. **Primary Objective** – To compare the incidence of six-month readmission for GRE between SAC and IC.
2. **Secondary Objectives** – To evaluate perioperative complications, mortality, intraoperative events, operative times, postoperative and total length of stay, and the rate of patients not undergoing cholecystectomy within six months.

By addressing both clinical outcomes and organizational barriers, CTIMAP provides novel insights into how evidence-based recommendations can be effectively translated into real-world practice.

Materials and Methods

1. Study Design

The **Cholecystectomy TIming for Mild Acute biliary Pancreatitis (CTIMAP) study** was conducted as a **prospective, multicenter, observational cohort study** designed to evaluate the real-world timing of cholecystectomy in patients diagnosed with mild acute biliary pancreatitis (MABP). Unlike randomized controlled trials, CTIMAP aimed to capture routine clinical practice across a large and heterogeneous patient population, reflecting both high-volume tertiary centers and smaller hospitals. The study was coordinated by the Fondazione IRCCS Policlinico San Matteo in Pavia, Italy, under the supervision of the World Society of Emergency Surgery, with international expansion to include 66 participating centers across Europe, Asia, Africa, and the Americas.

The rationale for an observational design was twofold: first, strong evidence from RCTs already supported same-admission cholecystectomy (SAC) as the preferred management strategy; second, a prospective cohort approach enabled evaluation of the extent to which these recommendations were being implemented in daily clinical practice, as well as identification of barriers to guideline adherence.

The study was conducted in accordance with the **Declaration of Helsinki** and Good Clinical Practice standards.

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2. Study Population

2.1 Inclusion Criteria

Eligible patients were:

- Adults aged **≥18 years**.
- Hospitalized with a confirmed diagnosis of **acute pancreatitis** according to the **2012 Revised Atlanta Classification**, requiring two of the following three criteria:
    1. Abdominal pain consistent with acute pancreatitis (acute onset of persistent, severe, epigastric pain often radiating to the back).
    2. Serum lipase or amylase activity at least three times the upper limit of normal.
    3. Characteristic findings of acute pancreatitis on cross-sectional imaging (contrast-enhanced CT, MRI, or abdominal ultrasound).
- Pancreatitis classified as **mild**, defined as the absence of organ failure and local or systemic complications.
- Etiology confirmed as **biliary**, with evidence of gallstones or sludge in the gallbladder or common bile duct.
- Informed consent provided prior to enrollment.

2.2 Exclusion Criteria

Patients were excluded if they met any of the following:

- Moderately severe or severe acute pancreatitis.
- Pancreatitis of non-biliary origin (alcoholic, hypertriglyceridemic, drug-induced, autoimmune, etc.).
- Pregnancy or lactation.
- Chronic pancreatitis.

- Active alcohol abuse.
- Inability or unwillingness to comply with follow-up.

These criteria ensured a homogeneous population focused exclusively on MABP.

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3. Study Groups and Definitions

Enrolled patients were stratified into three groups based on the timing of cholecystectomy:

1. **Same-Admission Cholecystectomy (SAC):** Laparoscopic or open cholecystectomy performed during the index admission for MABP.
2. **Interval Cholecystectomy (IC):** Surgery performed after hospital discharge, within **six months** of the index admission.
3. **No-Cholecystectomy Group:** Patients who did not undergo surgery within six months of discharge.

The distinction between SAC and IC followed the study protocol definitions. Additionally, intraoperative procedures such as ERCP or main biliary duct (MBD) exploration were recorded when performed concurrently with cholecystectomy.

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4. Study Procedures

4.1 Enrollment and Baseline Assessment

At admission, all patients were screened for eligibility. After informed consent, baseline assessments included:

- Demographic data (age, sex).
- Clinical history and comorbidities.
- Laboratory tests: complete blood count, serum lipase, liver function tests, C-reactive protein (CRP), procalcitonin (PCT), creatinine, arterial blood gases.
- Vital signs: blood pressure, heart rate, temperature, respiratory rate.
- Imaging studies: abdominal ultrasound and/or contrast-enhanced CT or MRI.
- Severity scores: **POSSUM physiological score** and **ASA classification**.
- Findings of gallstones vs biliary sludge, gallbladder wall thickening, or pericholecystic fluid.

4.2 Operative Data

For patients undergoing cholecystectomy, intraoperative details included:

- Timing (SAC vs IC).
- Surgical approach (laparoscopic vs open).
- Operative time (minutes).
- Intraoperative complications (e.g., bleeding >500 ml, bile duct injury, bowel perforation, vascular injury, anesthetic complications).
- Bail-out procedures (subtotal cholecystectomy, fundus-first technique, cholecystostomy).
- Conversion to open surgery.
- Intraoperative ERCP or biliary exploration.

4.3 Postoperative and Follow-Up Assessments

- **30-day follow-up:** Postoperative complications classified according to **Clavien-Dindo**. Specific outcomes included bile duct injury, bile leakage, wound infections, intra-abdominal abscesses, and systemic complications (respiratory, cardiac, renal, thromboembolic). Postoperative length of stay (PO-LOS) was also recorded.
- **6-month follow-up:** Conducted through outpatient visits or telephone interviews. Data included readmissions due to GRE, additional ERCP procedures, late complications, and whether the patient had undergone definitive cholecystectomy.

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5. Endpoints

5.1 Primary Endpoint

- **Six-month readmission due to gallstone-related events (GRE):** defined as recurrent biliary colic, acute cholecystitis, recurrent AP, obstructive jaundice, or cholangitis.

5.2 Secondary Endpoints

- **30-day postoperative complications** (overall and biliary-specific).
- **30-day mortality.**
- **Intraoperative complications** and need for bail-out procedures.
- **Conversion to open cholecystectomy.**
- **Operative time.**
- **Postoperative length of stay (PO-LOS).**

- **Total length of stay (T-LOS):** including index admission, subsequent hospitalization for IC, and any readmission due to GRE.
- **Proportion of patients not undergoing cholecystectomy** within six months.

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6. Data Management

All data were entered into a secure, web-based REDCap database hosted at the San Matteo Hospital, Pavia. Each center had unique login credentials and user rights, ensuring data protection and traceability. Patient identifiers were pseudonymized to comply with **GDPR regulations**. Quality checks were performed regularly, and access logs were monitored to ensure accuracy and compliance.

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7. Statistical Analysis

7.1 Descriptive Statistics

Continuous variables were summarized as median and interquartile range (IQR) or mean ± standard deviation (SD), depending on distribution. Categorical variables were presented as counts and percentages.

7.2 Comparative Analyses

- Continuous variables: **Mann-Whitney U test** (non-parametric).
- Categorical variables: **Fisher's exact test** or chi-squared test.

7.3 Primary Endpoint

The rate of 6-month readmission due to GRE after hospitalization for MABP (primary endpoint) was compared between groups using a Cox regression model; hazard ratios and 95% confidence intervals were computed (HR, 95%CI). Kaplan Meier curves by approach were plotted. Logistic and generalized linear regression models were fitted for continuous and binary secondary endpoints, respectively. Continuous variables were log transformed before entering the model. Huber-White robust standard errors were computed to account for intra-Centre correlation.

7.4 Propensity Score Analysis

To reduce variability and heterogeneity among the included patients and reduce selection bias, a logistic regression-derived propensity score was used to adjust for selection bias.

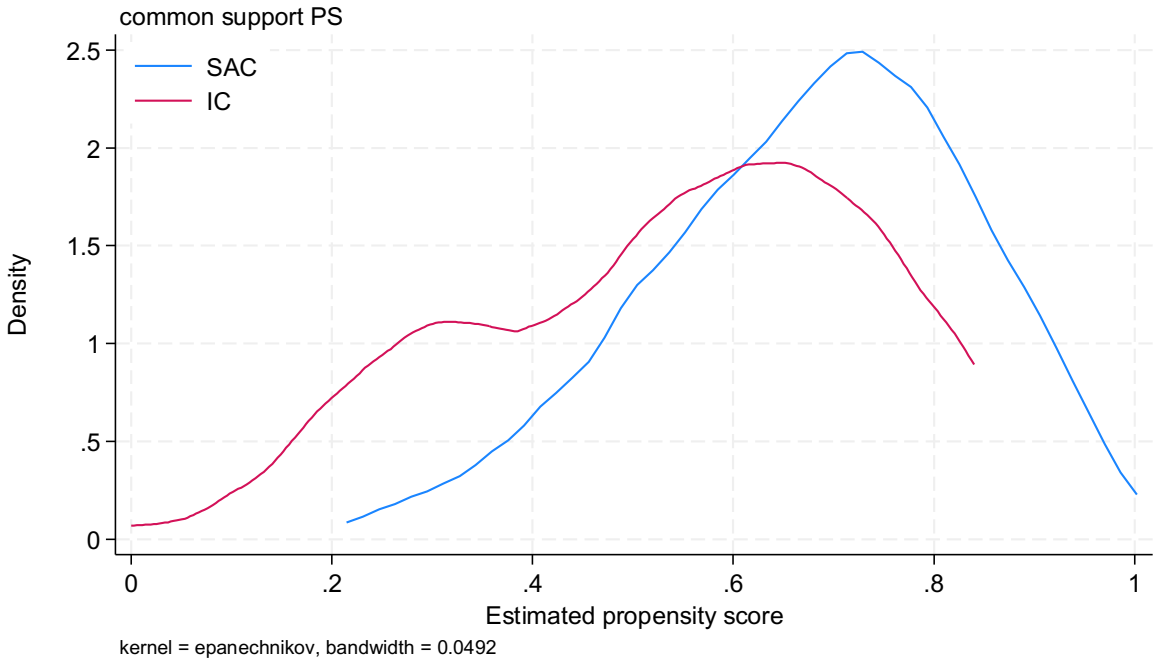
Covariates included age, sex, BMI, ASA score, POSSUM score, WBC, lipase, CRP, presence of gallstones vs sludge, gallbladder wall thickening, preoperative ERCP, and center characteristics.

- PS Overlap: Supplementary Figure 1 shows good overlap between groups after weighting.
- Balance achieved: Standardized mean differences were <0.1 for all covariates post-weighting.

This confirms the robustness of the PS-weighted results.

After PS matching 232 patients were left, with 201 available for the analysis of the primary endpoint, with a good overlap between groups. Balancing properties were satisfied.

Figure 1. PS overlap between groups



7.5 Secondary Endpoints

- Logistic regression for binary outcomes (e.g., complications, conversions).
- Generalized linear models for continuous outcomes (operative time, LOS).
- Robust standard errors were applied to account for intra-center clustering.

7.6 Sample Size Calculation

The sample size calculation for this study was based on the study by Al-Qahtani et al. (15) which reports a SAC to IC ratio of 0.45. In this study, the rate of readmissions for biliary events was 1.12% after SAC and 17.65% after CI; these correspond to an event-free survival of 0.99 and 0.82, respectively. We use da conservative approach in this observational study, with a power of 90% and a type I error of 1%. Based on these hypotheses, a ratio of SAC to IC as above, a 2-sided log rank test will be able to elicit such a difference if a total of 213 patients are enrolled (96 SAC and 117 IC), with

22 events expected.

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8. Ethical Considerations

The study protocol (version 2.0, February 2022) was approved by the **Institutional Review Board (IRB) of the coordinating center** (Fondazione IRCCS Policlinico San Matteo, Pavia, Italy) and by the **local ethics committees** of all participating institutions. Written informed consent was obtained from all patients before enrollment.

The study was conducted in accordance with the **Declaration of Helsinki**, Good Clinical Practice guidelines, and relevant national regulations. Patient confidentiality was ensured through anonymization and secure data storage. The study carried minimal additional risks since all procedures (cholecystectomy, ERCP, imaging, laboratory assessments) were part of standard clinical care

Results

1. Study Cohort

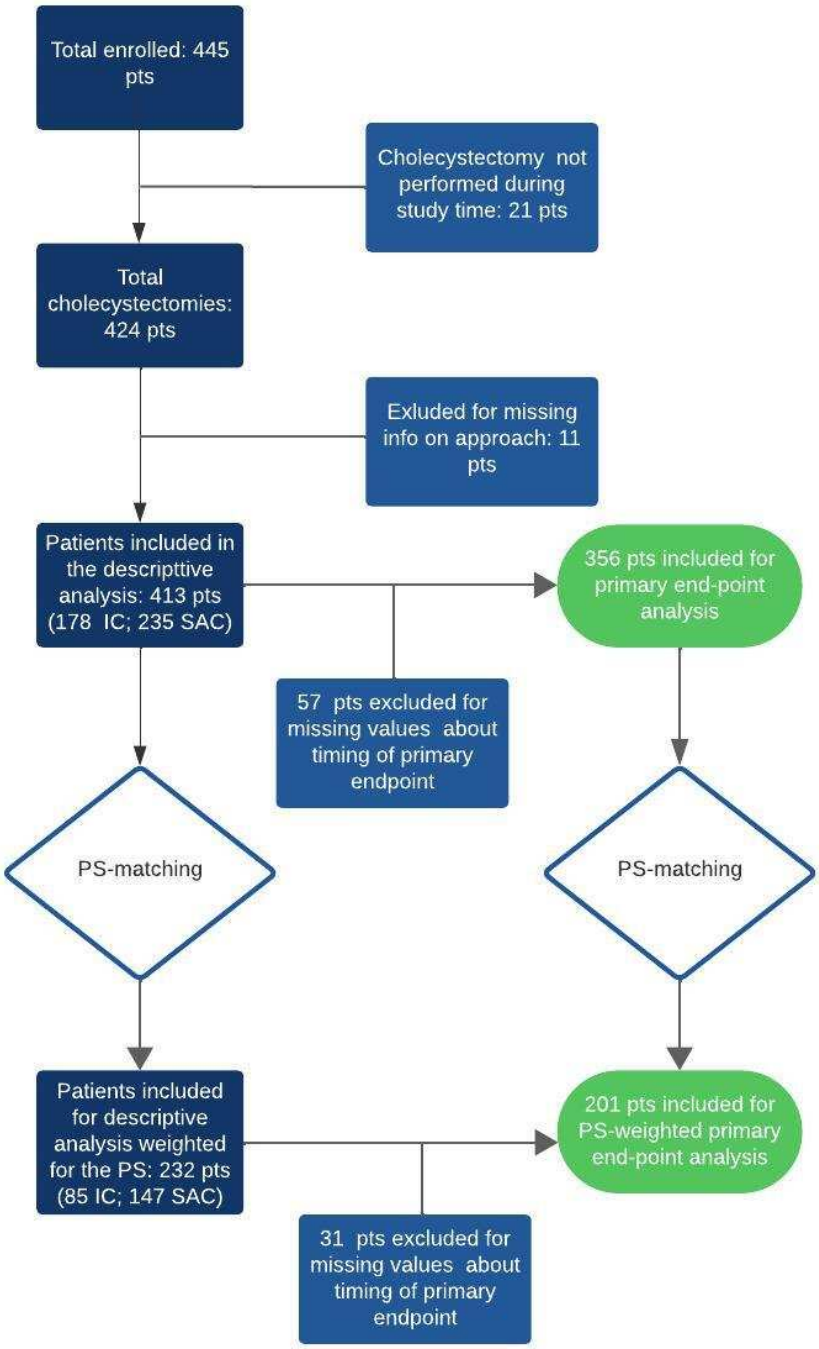
Between June 2022 and November 2023, a total of **445 patients** with mild acute biliary pancreatitis (MABP) were enrolled across **66 centers worldwide**.

Of these:

- **116 patients (26%)** did not undergo cholecystectomy within six months of the index admission.
- After excluding patients with missing data (n=11) and those lost to follow-up (n=21), the final analytic cohort included **413 patients** who underwent cholecystectomy.
- Among them:
    - **235 patients (57%)** underwent same-admission cholecystectomy (SAC).
    - **178 patients (43%)** underwent interval cholecystectomy (IC).

Figure 2 (Patients' Flowchart) summarizes patient recruitment, exclusions, and final group allocation.

Figure 2. Patients' flowchart



1.1 Baseline Characteristics

Patients' demographic and clinical characteristics are reported in **Table 1**. Key findings include:

- **Age:** Median age was 56 years in SAC vs 59 years in IC (p=0.30).
- **Sex:** Males represented 38% of SAC and 41% of IC patients (p=0.47).
- **Etiology:** Gallstones were identified in 85% (SAC) vs 91% (IC); sludge was more common in SAC (15% vs 9%).
- **Gallbladder wall thickening/pericholecystic fluid:** More frequent in SAC (57%) compared to IC (45%, p=0.021).
- **Preoperative ERCP:** Significantly higher in SAC (36% vs 24%, p=0.017).
- **Intraoperative ERCP o MBD exploration:** More frequent in SAC (8% vs 3%, p=0.033).
- **Inflammatory markers:** Median CRP was higher in IC (13.0 mg/L) vs SAC (4.0 mg/L, p<0.001).

These data reveal some heterogeneity between groups, particularly in inflammatory status, surgical risk and perioperative management.

Table 1. Patients' characteristics

Variable		IC N (%) Median (IQR) (N=178)	SAC N (%) Median (IQR) (N=235)	p-value
Sex	Male	73 (41.0)	87 (37.5)	0.477
Stones vs Sludge	Stones	158 (91.3)	198 (85.3)	0.089
	Sludge	15 (8.7)	34 (14.7)	
Thickened gallbladder wall and/or pericholecystic fluid		78 (44.8)	131 (56.5)	**0.021**
Pre-operative ERCP		42 (24.4)	83 (35.8)	**0.017**
BMI	<25	46 (29.1)	60 (26.0)	0.343
	25-30	69 (43.7)	118 (51.1)	
	>30	43 (27.2)	53 (23.0)	
ASA-score	1	49 (28.0)	79 (34.7)	0.501
	2	92 (52.6)	112 (49.1)	
	3	33 (18.9)	36 (15.8)	
	4	1 (0.6)	1 (0.4)	

Age		59.0 (44.0-70.0)	56.0 (44.0-67.0)	0.300
Were the stones in the MBD, in the gallbladder or both?	In gallbladder	126 (72.0)	154 (66.1)	0.083
	In MBD	9 (5.1)	6 (2.6)	
	In both	40 (22.9)	73 (31.3)	
WBC count		11.5 (9.0-13.7)	11.6 (9.0-13.7)	0.548
Serum lipase		832.0 (340.0-2676.0)	1067.0 (455.0-2500.0)	0.211
POSSUM-PS		17.0 (14.0-21.0)	17.0 (15.0-21.0)	**0.018**
Max PCT value		0.1 (0.1-0.4)	0.1 (0.0-0.6)	0.457
Max PCR value		13.0 (2.4-66.6)	4.0 (0.9-14.0)	**<0.001**
Intraop ERCP o MBD exploration		5 (2.8)	19 (8.1)	**0.033**

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2. Primary Endpoint: Six-Month Readmission for Gallstone-Related Events

The **primary outcome** was the rate of six-month readmission for gallstone-related events (GRE).

- **Unadjusted analysis:**
    - GRE occurred in **6 patients (2.5%)** in the SAC group vs **16 patients (9%)** in the IC group.
    - Incidence rate: 0.40 per 100 person-months (SAC) vs 1.30 per 100 person-months (IC).
    - **Hazard Ratio (HR): 0.26 (95% CI 0.07–0.97; p=0.046)**.
- **Propensity score-weighted analysis:**
    - After inverse probability weighting, SAC demonstrated a **much lower risk of GRE**.
    - **HR: 0.11 (95% CI 0.02–0.55; p=0.007)**.

Figure 2 shows the Kaplan–Meier curve of GRE-free survival for SAC vs IC. **Figure 3** displays the propensity score-weighted survival curves.

These results clearly support SAC as superior in preventing recurrent biliary events.

Figure 3. Kaplan Meier readmission for GRE – free survival

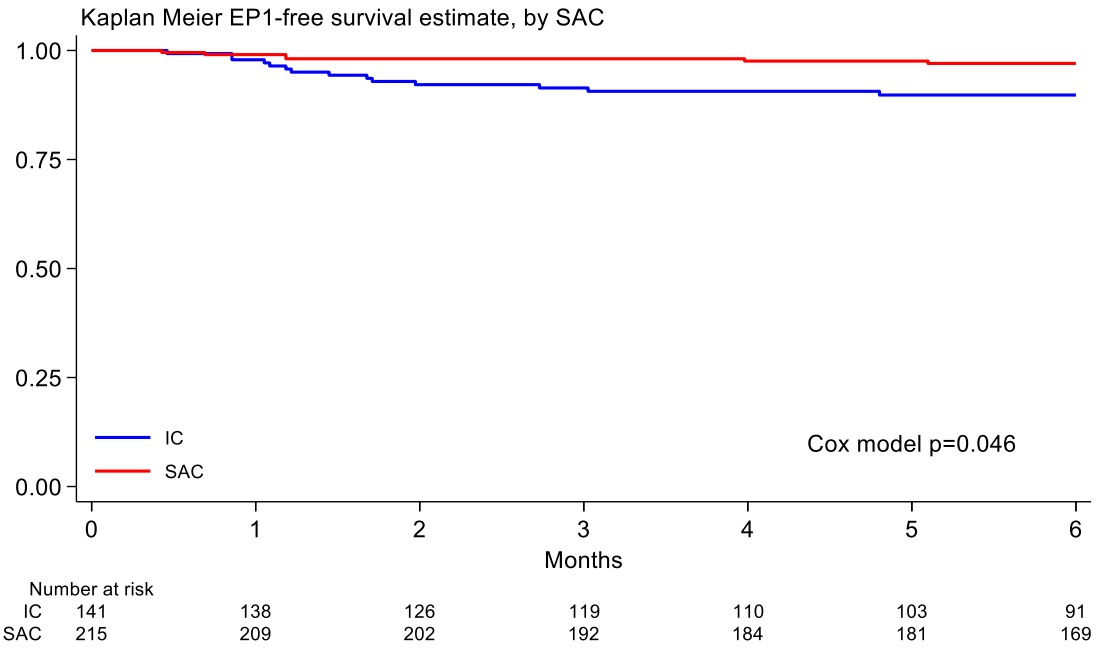
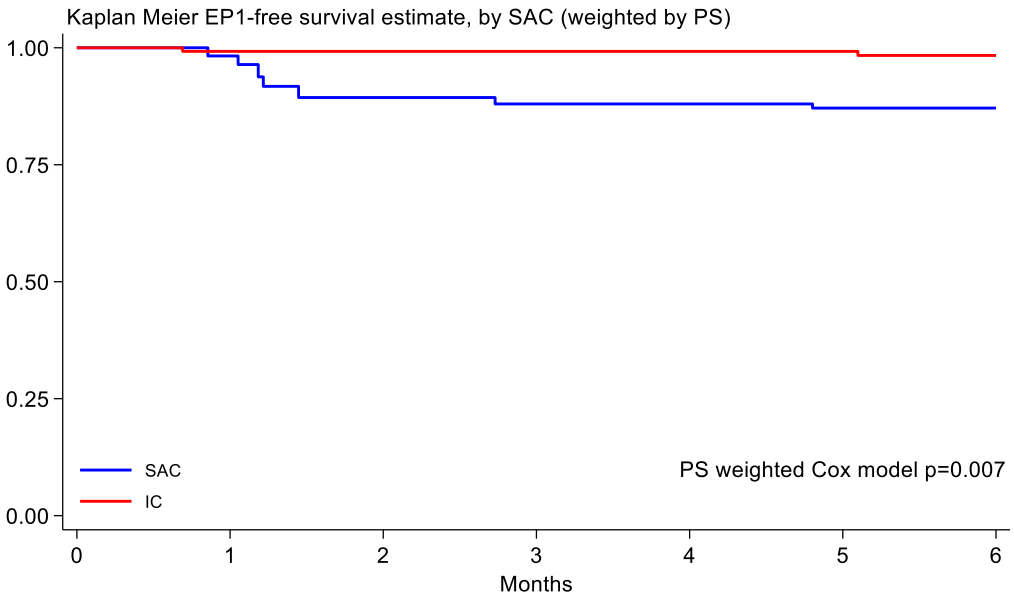


Figure 4. Kaplan Meier readmission for GRE – free survival weighted by PS



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3. Secondary Endpoints

3.1 Postoperative Complications

3.1.1 Unadjusted

- Overall 30-day postoperative complication rates were similar:
    - SAC: 8.5%
    - IC: 4.5% (p=0.20)
- Major complications (Clavien-Dindo ≥III): 2.1% (SAC) vs 1.7% (IC), not statistically significant.
- Biliary tree injuries: rare, with 1.7% in IC vs none in SAC (p=0.08).
- No 30-day postoperative mortality was observed.

3.1.2 Propensity score-weighted analysis

- Overall 30-day postoperative complication rates were similar:
    - SAC: 6.8%

    - IC: 2.4% (p=0090)
- Major complications (Clavien-Dindo ≥III): 0.7% (SAC) vs 1.2% (IC), not statistically significant.
- No Biliary tree injuries.
- No 30-day postoperative mortality was observed.

SAC did not increase perioperative risk compared to IC.

3.2 Intraoperative Outcomes

3.2.1 Unadjusted

- **Intraoperative complications:** 0.9% (SAC) vs 3.4% (IC), not significant.
- **Bail-out procedures:** 6.4% (SAC) vs 7.6% (IC).
- **Conversion to open surgery:** 3.2% (SAC) vs 2.5% (IC).

3.2.2 Propensity score-weighted analysis

- **Intraoperative complications:** 0.7% (SAC) vs 2.4% (IC), not significant.
- **Bail-out procedures:** 2.7% (SAC) vs 3.7% (IC), not significant.
- **Conversion to open surgery:** 2.9% (SAC) vs 4.0% (IC), not significant.

No significant differences were found between groups, supporting the technical feasibility of SAC.

3.3 Operative Time

*3.3.1 Unadjusted***:** Median operative time was longer for SAC (80 minutes) compared with IC (60 minutes).

3.3.2 Propensity score-weighted analysis: Difference remained significant, with SAC associated with 27% longer operative time (p=0.016).

This difference is likely attributable to the higher frequency of intraoperative ERCP and biliary exploration in the SAC group (8.2% vs 2.9%).

3.4 Length of Stay (LOS)

3.4.1 Unadjusted

- **Postoperative LOS (PO-LOS):** Median 3 days (SAC) vs 2 days (IC); SAC associated with longer PO-LOS (p=0.002).
- **Total LOS (T-LOS):** Median 12 days (SAC) vs 8 days (IC), but the difference was not statistically significant (p=0.11).

3.4.2 Propensity score-weighted analysis:

- **Postoperative LOS (PO-LOS):** Median 2 days (range 2-4) (SAC) vs 2 days (range 1-3) (IC); SAC associated with longer PO-LOS (p=0.003).
- **Total LOS (T-LOS):** Median 8 days (SAC) vs 10 days (IC), but the difference was not statistically significant (p=0.176).

Interpretation: although SAC prolongs the index admission, the total length of hospital stay does not significantly differ compared to IC, as delayed surgery entails an additional hospitalization.

Table 2. Secondary end-points

Variable	IC %	SAC %	p-value	OR (SAC vs IC)	95% CI
30-day complications	4.5	8.5	0.201	1.98	0.70-5.61
30-day major complications	1.7	2.1	0.783	1.27	0.23-6.88
Biliary tree injuries	1.7	0.0	0.08	//	//
30-day mortality	0.0	0.0	//	//	//
Intraoperative complications	3.4	0.9	0.142	0.24	0.04-1.60
Bail-out procedure	7.6	6.4	0.753	0.83	0.27-2.61
Conversion to open	2.5	3.15	0.653	1.27	0.45-3.59
	Median (IQR)	**Median (IQR)**	**p-value**	**Difference SAC-IC***	**95%CI**
Operative time	60 (50-90)	80 (60-110)	0.195	0.15 *Ratio 1.16*	-0.08-0.37 *0.92-1.45*
Post-op LOS	2 (1-3)	3 (2-5)	**0.002**	0.44 *Ratio 1.56*	0.17-0.71 *1.19-2.04*
Total LOS	12 (7-25)	8 (5-14)	0.112	-0.66 *Ratio 0.52*	-1.48-0.16 *0.23-1.17*

Table 3. PS- weighted secondary endpoints

Variable	IC %	SAC %	p-value	OR (SAC vs IC)	95% CI
30-day complications	2.4	6.8	0.094	2.55	0.82-7.96
30-day major complications	1.2	0.7	0.892	0.83	0.06-11.40
Biliary tree injuries	0.0	0.0	//	//	//
30-day mortality	0.0	0.0	//	//	//
Intraoperative complications	2.4	0.7	0.368	0.44	0.04-3.67
Bail-out procedure	3.7	2.7	0.791	0.84	0.22-3.16
Conversion to open	4.0	2.9	0.763	0.81	0.21-3.10
			p-value	**Difference SAC-IC***	**95%CI**
Operative time*	65 (45-90)	87 (60-115)	**0.016**	0.24 *Ratio 1.27*	0.05-0.43 *1.05-1.54*
Post-op LOS	2 (1-3)	2 (2-4)	**0.003**	0.50 *Ratio 1.64*	0.17-0.82 *1.19-2.26*
Total LOS	10 (7-16)	8 (5-24)	0.176	-0.19 *Ratio 0.83*	-0.46-0.09 *0.63-1.09*

3.5 Patients Without Cholecystectomy

Of the initial cohort, **116 patients (26%)** did not undergo cholecystectomy within six months. This subgroup was at particularly high risk for recurrent biliary events, highlighting a major gap in care delivery.

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6. Key Findings Summary

1. **SAC significantly reduced six-month readmissions for GRE** compared to IC, both unadjusted and after PS weighting.
2. **Safety profile was comparable**: no increase in complications, bail-out procedures, or conversions.
3. **Operative time was longer** in SAC, explained by concomitant ERCP/MBD exploration procedures.
4. **Postoperative LOS was longer** in SAC, but **total LOS was similar** between groups.
5. A **quarter of patients doesn't underwent cholecystectomy within 6 months**, highlighting underutilization of definitive treatment.

Discussion

1. Main Findings of the CTIMAP Study

The CTIMAP study provides strong prospective, real-world evidence that **same-admission cholecystectomy (SAC)** is superior to **interval cholecystectomy (IC)** for patients with mild acute biliary pancreatitis (MABP). In a cohort of 445 patients across 66 international centers, SAC was associated with a significantly lower six-month readmission rate for gallstone-related events (GRE), both in unadjusted and propensity score (PS)-weighted analyses. Importantly, the safety profile of SAC was comparable to IC, with no significant differences in postoperative complications, intraoperative events, conversions to open surgery, or mortality.

Although SAC was associated with longer operative times and a slightly prolonged postoperative length of stay (LOS), the total LOS did not differ significantly between SAC and IC, since delayed cholecystectomy requires a separate admission. Strikingly, more than one-quarter of patients does not underwent definitive cholecystectomy within six months, remaining at high risk of recurrence.

Together, these findings reinforce SAC as the optimal strategy for MABP, while highlighting persistent barriers that hinder its universal implementation.

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2. Interpretation in the Context of Existing Literature

2.1 Consistency with Randomized Controlled Trials

The results of CTIMAP align with those of multiple randomized controlled trials (RCTs). The **PONCHO trial** (8), a landmark multicenter RCT, demonstrated that SAC markedly reduced recurrent biliary complications compared to IC, without increasing surgical morbidity. Similarly, Aboulian et al. (12) showed that laparoscopic cholecystectomy performed within 48 hours was associated with shorter hospital stay, without higher operative risk.

CTIMAP confirms these conclusions in a **real-world, multicenter observational setting**, providing external validity to RCT findings. Whereas RCTs often include selected patients under tightly controlled conditions, CTIMAP encompassed diverse institutions and heterogeneous patient populations, thus reflecting clinical reality.

2.2 Evidence from Meta-Analyses

Several meta-analyses have consolidated the superiority of SAC (9,10,16,17,18,22). A 2021 systematic review by Walayat et al. (9) reported that early cholecystectomy is safe and associated with reduced operative time, shorter LOS, and fewer recurrent events. Yang et al. (16) and Lyu et al. (10) reached similar conclusions, showing no increased risk of bile duct injuries or conversions to open surgery.

CTIMAP reinforces these results but adds novel insights. Interestingly, unlike previous meta-analyses, the study observed longer operative times in SAC, likely explained by the higher frequency of intraoperative ERCP or main bile duct exploration. This nuance emphasizes that longer surgery does not necessarily reflect increased technical difficulty, but rather the need to manage concomitant biliary pathology during the acute admission.

3. Clinical Implications

3.1 SAC as the Standard of Care

The clinical message of CTIMAP is unequivocal: SAC should be considered the **standard of care** for all eligible patients with MABP. Delaying cholecystectomy exposes patients to a substantially higher risk of recurrent GRE, with potentially severe consequences such as recurrent pancreatitis or cholangitis. Moreover, each readmission translates into additional healthcare costs, repeated imaging and laboratory tests, prolonged absence from work, and reduced quality of life.

3.2 Safety of SAC

CTIMAP data confirm that SAC is **not associated with higher perioperative risk**. Complication rates, including major morbidity and biliary injuries, were comparable between SAC and IC. Even conversion to open surgery or bail-out procedures did not differ significantly. These findings should reassure surgeons concerned about technical difficulty during acute episodes. In fact, delaying surgery may paradoxically increase complexity due to post-inflammatory adhesions, as previously suggested by Da Costa et al. (8,23).

3.3 Hospital Resource Utilization

From a system perspective, the slight increase in postoperative LOS with SAC is counterbalanced by the avoidance of a second admission required for IC. CTIMAP demonstrated no significant difference in **total LOS** between strategies, reinforcing the efficiency of SAC from a healthcare utilization standpoint. This echoes results from earlier RCTs and meta-analyses that highlighted reduced cumulative hospital stay with SAC.

4. Barriers to SAC Implementation

Despite strong evidence, SAC adoption remains suboptimal, as demonstrated by CTIMAP: only 57% of patients received SAC, while nearly half underwent IC and one quarter received no cholecystectomy at all. Several barriers contribute to this persistent evidence–practice gap:

4.1 Logistical Constraints

One of the most cited obstacles is the **limited availability of operating rooms** and surgical teams. In many hospitals, emergency operating room capacity is prioritized for life-threatening cases such as perforations, bowel obstructions, or trauma, relegating SAC to elective lists. Scheduling SAC during the index admission often requires restructuring workflows and allocating dedicated slots for biliary surgery.

4.2 Perceived Surgical Risks

Although evidence consistently shows that SAC does not increase perioperative complications, many surgeons remain concerned about **operative difficulty in inflamed tissues** (24)**.** This perception persists despite data demonstrating comparable rates of complications, conversions, and bail-out procedures. Overcoming these misconceptions is essential to changing surgical culture.

4.3 Institutional Inertia

In some centers, IC remains the “default” strategy due to **historical practices** and lack of standardized local protocols. Without institutional commitment, individual surgeons may continue to delay surgery, perpetuating outdated habits.

4.4 Patient Factors

Patient comorbidities, late presentations, or lack of preoperative optimization can also contribute to delays. In certain cases, clinicians may prioritize stabilization of other medical conditions before scheduling surgery, inadvertently increasing the risk of recurrence.

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5. Strategies to Bridge the Gap

Addressing these barriers requires interventions at multiple levels:

5.1 Optimizing Resource Allocation

Hospitals should establish structured scheduling systems that allocate dedicated operating room slots for conditions that are not true emergencies but cannot be postponed to elective lists—so-called semi-urgent procedures such as same-admission cholecystectomy (SAC). Integrating these semi-urgent slots alongside other urgent surgeries could ensure timely access to care, reducing preventable readmissions..

5.2 Education and Training

Educational programs are essential to dispel the misconception that SAC is technically riskier. Continuous professional development, surgical workshops, and dissemination of evidence through conferences and peer-reviewed publications can reinforce guideline-based practices.

5.3 Standardized Protocols

Institutions should adopt **standardized clinical pathways** for the management of MABP, emphasizing SAC as the routine approach. Multidisciplinary collaboration between surgeons, gastroenterologists, emergency physicians, and anesthesiologists is critical for consistent implementation.

5.4 Data-Driven Advocacy

Regular audits of institutional data can demonstrate the benefits of SAC in reducing readmissions and cumulative hospital stay. Publishing and disseminating local success stories can motivate wider adoption and encourage healthcare administrators to allocate resources accordingly.

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6. Strengths of the CTIMAP Study

Several strengths make CTIMAP a valuable contribution to the literature:

1. **Large sample size**: Over 400 patients across 66 centers, ensuring generalizability.
2. **Prospective design**: Minimizes recall bias and improves data quality compared to retrospective studies.
3. **International participation**: Increases external validity across diverse healthcare systems.
4. **Propensity score adjustment**: Enhances robustness by reducing confounding and balancing baseline differences.
5. **Comprehensive endpoints**: Including clinical outcomes, operative details, and resource utilization.

7. Limitations of the CTIMAP Study

Despite its strengths, several limitations must be acknowledged:

- **Observational design**: Residual confounding cannot be completely excluded, even after PS adjustment.
- **Heterogeneity between centers**: Differences in resources, surgical expertise, and institutional protocols may influence outcomes.
- **Surgeon discretion**: Timing of cholecystectomy was determined by attending surgeons, introducing potential selection bias.
- **Missing data**: A small proportion of patients were excluded due to incomplete records.
- **Follow-up limited to six months**: Longer-term outcomes, including recurrence beyond six months, were not assessed.

These limitations should be considered when interpreting the findings.

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8. Future Perspectives

The CTIMAP study raises important questions for future research and policy:

1. **Implementation Research** – Evaluating how to translate evidence into routine practice, including interventions such as dedicated OR slots, care bundles, and fast-track pathways.
2. **Integration with ERCP Timing** – Understanding the optimal sequencing of ERCP and cholecystectomy, particularly in patients with choledocholithiasis.

3. **Health Policy Interventions** – National health systems could incentivize adherence to SAC protocols through performance indicators, reimbursement models, or accreditation standards.
4. **Long-Term Follow-Up** – Future studies should evaluate outcomes beyond six months, including recurrence at 12–24 months and long-term quality of life.

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9. Overall Message

The CTIMAP study confirms that **same-admission cholecystectomy is safe, effective, and underutilized**. The clinical superiority of SAC over IC is no longer in doubt; the remaining challenge is ensuring that these findings are consistently applied in real-world practice.

Bridging the evidence–practice gap requires **organizational changes, education, and resource allocation**. By prioritizing SAC for MABP, healthcare systems can prevent recurrent complications, reduce unnecessary hospitalizations, and improve patient outcomes.

Conclusion

Mild acute biliary pancreatitis (MABP) is the most common form of acute pancreatitis and, although associated with low mortality, it carries a substantial risk of recurrence and gallstone-related events (GRE) if not definitively treated. Cholecystectomy represents the cornerstone of management, yet the optimal timing of surgery has long been debated.

The CTIMAP study, a large prospective multicenter observational investigation, provides compelling real-world evidence supporting **same-admission cholecystectomy (SAC)** as the preferred management strategy for MABP. Compared with interval cholecystectomy (IC), SAC was associated with a significantly lower risk of six-month readmission for GRE, without an increase in postoperative complications, intraoperative risks, or mortality. Although SAC was linked to longer operative times and a slightly prolonged postoperative hospital stay, total length of stay was not significantly different from IC.

Importantly, CTIMAP also revealed that SAC remains underutilized: nearly half of patients were still managed with IC, and one quarter of patients did not undergo definitive surgery at all within six months. This evidence–practice gap highlights a major challenge in contemporary surgical care—translating established evidence into routine practice. The reasons for this gap are multifactorial, including perceived surgical risks, logistical constraints, institutional inertia, and patient-related factors.

The implications of these findings are twofold. Clinically, they reaffirm that SAC is safe and effective, and its adoption should be standard practice to minimize preventable morbidity. From a healthcare systems perspective, they underscore the need for organizational and policy interventions aimed at

overcoming barriers to implementation. Strategies such as dedicated operating room slots for conditions that are not true emergencies but cannot be postponed to elective lists, standardized institutional protocols, surgeon education, and continuous audit of outcomes are essential steps toward ensuring adherence to guideline-based care.

In conclusion, the CTIMAP study bridges a critical gap between evidence and practice by demonstrating that SAC not only improves patient outcomes but also represents an efficient use of healthcare resources. To optimize the management of MABP, it is imperative that surgical communities and healthcare institutions embrace SAC as the default strategy. By doing so, the preventable burden of recurrent gallstone-related complications can be significantly reduced, improving patient safety, quality of care, and overall healthcare efficiency.

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