Indication and Timing of Cholecystectomy in Acute Biliary Pancreatitis - Systematic Review

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ABSTRACT: Acute biliary pancreatitis (ABP) poses significant challenges in determining the optimal timing and approach for cholecystectomy, particularly in mild, moderately severe, and severe forms. This article reviews the existing literature on cholecystectomy timing and its impact on outcomes in ABP. A systematic literature search yielded 41 relevant articles from PubMed and Scopus databases. In mild ABP, early cholecystectomy within 72 hours of onset is increasingly favoured due to reduced technical difficulty and lower risk of recurrent pancreatitis. Conversely, delayed cholecystectomy, although traditionally practiced, may lead to higher recurrence rates and prolonged hospital stays. For moderate severe ABP, evidence remains limited, but early cholecystectomy appears to decrease hospital stay without increasing perioperative complications. In severe ABP, consensus suggests delaying cholecystectomy until peripancreatic collections resolve, typically 6 to 10 weeks post-onset, to minimize surgical morbidity. The role of endoscopic retrograde cholangiopancreatography (ERCP) alongside cholecystectomy remains contentious, with guidelines recommending its use in specific scenarios such as cholangitis or biliary obstruction. However, routine ERCP in mild ABP lacks robust evidence and may increase complications. Challenges persist regarding the management of residual choledocholithiasis post-ABP, highlighting the need for improved diagnostic criteria and management protocols. Overall, this review underscores the evolving landscape of cholecystectomy timing in ABP and provides insights into current best practices and areas for future research.

KEYWORDS: Acute, biliary, pancreatitis, cholecystectomy, ERCP.

Introduction

Acute pancreatitis is a common diagnosis in the surgical and gastroenterological departments, with an incidence of up to 45 cases per 100,000 people [1].

Stone migration is the most common etiological factor for acute pancreatitis, with up to 20% of all cases of acute biliary pancreatitis being severe forms [2].

For all these cases, removing the underlying factor i.e. cholecystectomy would therefore be the most logical and straightforward solution as recurrent attacks can prove to be more severe and life threatening.

In general, the indication for surgery in acute biliary pancreatitis (ABP) has changed dramatically over the last 3 decades, due to better understanding of the surgical and disease-related pathophysiological changes associated with ABP and the widespread adoption of new approach techniques, such as laparoscopy, computed tomography (CT) guided percutaneous access, and endoscopic ultrasound-guided drainage.

Based on the severity of the disease, the 2012 revision of the Atlanta Classification distinguishes between 3 types of pancreatitis: mild, moderately severe, and severe forms [3].

It also differentiates between two evolutive phases: early, in which the systemic inflammatory response syndrome occurs as consequence of local pancreatic injury, and late, occurring only in moderately severe and severe acute pancreatitis.

The severity stratification is important for both prognostic and therapeutic reasons, as it allows to evaluate the potential risks and to initiate the proper treatment.

The mild form, usually corresponding to interstitial edematous pancreatitis, will resolve in 7 to 10 days, as it does not associate local or systemic complications, usually offering a window of opportunity for the surgical management of the etiologic factors of ABP.

Moderately severe pancreatitis is considered in case of local complications or transient organ failure (<48h), while the severe form of pancreatitis involves persistent organ failure, thus making emergency surgery more probable while also increasing the surgical morbidity and mortality.
Material and Methods

In order to find the highest level of evidence, we conducted a systematic research of the literature of two databases (PubMed and Scopus), using the following key words: “gallstone pancreatitis” or “biliary pancreatitis” or “acute pancreatitis”.

Regarding the level of evidence, the following articles were prioritized: clinical trials, meta-analysis, systematic reviews and randomized controlled trial.

The search yielded a total of 2104 articles (683 from PubMed and 1421 from Scopus), out of which 283 duplicates were removed.

After article screening 1751 articles were excluded due to wrong population, Non-English language, wrong topic.

A number of 70 articles were retrieved for full-text assessment.

After additional exclusion, 41 articles were included in the review (Figure 1).

Figure 1. Flow-chart containing article selection process.
Cholecystectomy and mild biliary pancreatitis

One point of divergence is the timing of the procedure, with literature evidence and guidelines advocating for cholecystectomy during the same admission.

However, these recommendations are not commonly put in practice as they are in obvious contrast with the traditional attitude.

For example, of more than 25,000 patients acutely admitted to hospitals in England with gallstone-related disease, only 14.7% had cholecystectomy performed during the same admission, while in US only 57% of patients admitted for ABP had index cholecystectomy [4].

Likewise, more than 75% of patients admitted in Dutch hospitals with mild biliary pancreatitis underwent cholecystectomy a median of 6 weeks after discharge [5].

The traditional surgical dogma supports conservative treatment for 2 weeks before undergoing cholecystectomy for a variety of reasons.

Arguably, delayed cholecystectomy may offer more time for a detailed examination while making intraoperative main bile duct exploration unnecessary.

In the same time, by delaying the surgical procedure it can avoid the overlap of acute inflammatory state and may offer time to relieve edema and adhesions.

However, during the last two decades, a growing number of studies and guidelines lowered these concerns, emphasizing the advantages of early cholecystectomy in mild biliary pancreatitis [6,7].

Numerous authors argued that surgery within 72 hours of onset is less difficult because the separation planes still offer evident anatomical landmarks.

Moreover, as time passes, the technical difficulty of the surgical procedure usually increases, together with the risk of stone migration [8,9].

For instance, Ito et al. observed an increased risk of recurrence within 2 to 4 weeks after discharge following ABP, with a 12.5% of recurrences within 1 week, 31.3% within 2 weeks, and 50% within 4 weeks [10].

Likewise, Bakker et al. observed a significantly increased risk of recurrent biliary events following delayed cholecystectomy after mild ABP.

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy appears to lower the incidence of recurrent pancreatitis but has no impact or even increases the risk for other biliary events [5,10].

In a more recent study, Senol et al. analysed the surgical outcomes in early (less than 2 weeks) versus late cholecystectomy (more than 2 weeks) for non-severe ABP patients [11].

In case of same-admission cholecystectomy, the mean time to surgery was 1.7 weeks compared to 6.7 weeks for delayed procedure.

Difficult dissection was observed in 13.95% of early cholecystectomy cases, as opposed to 20.51% for late procedures, with longer operative time in case of delayed cholecystectomy but with similar conversion rates and morbidity.

The mean hospital stay was 10 days in the early cholecystectomy group compared to 17 days in the delayed group, while 17.9% cases in the late cholecystectomy group had gallstone-related diseases requiring readmission after the initial episode of ABP.

Currently most guidelines support the use of index laparoscopic cholecystectomy as early as the second hospital day if the patient is clinically improving [12,13].

Moreover, the general opinion is not to postpone cholecystectomy for more than 14 days, due to the increased probability of recurrent biliary events [14].

This surgical attitude allowed for a significant decrease in the overall hospital costs while diminishing the risk for recurrent pancreatitis [15].

Moderate Severe biliary pancreatitis

There are few articles investigating the role and timing of cholecystectomy in moderate severe acute pancreatitis, as most studies only evaluate the mild and severe forms of ABP.

In a recent randomized controlled trial (RCT), Dawoodabadi et al. assessed the optimal moment for laparoscopic cholecystectomy in moderate ABP [14].

No differences in peri-operative complications, conversion rate, procedure time were observed between early (<48 h) and delayed (>1 week) cholecystectomy.

The only notable difference was the significant decrease in hospital stay for early cholecystectomy.

The study suffered from some randomization issues, most notable one being the inclusion of mild biliary pancreatitis cases in the general analysis.

In another RCT, Jee et al., 72 patients with mild to moderate biliary pancreatitis were
randomized to either early or delayed cholecystectomy.

Similar perioperative morbidity, conversion rates were observed between groups, and at a significantly lower rate of recurrent biliary events was noted in the patients undergoing early cholecystectomy [16].

Again, the inclusion of mild biliary pancreatitis cases in the general analysis was a distorting factor that may have altered the overall results.

However, this common approach for mild and moderate forms of ABP may have a plausible explanation because after 48 hours, in case of favourable clinical evolution, both entities tend to behave similarly and, to a point, become indistinguishable entities.

Moreover, even the Atlanta Classification acknowledges the difficulties in distinguishing between the two forms of pancreatitis, especially during the initial phase [3].

The real differences that truly differentiate the surgical approach between different types of ABP reside in the presence of peripancreatic collections.

**Severe acute pancreatitis**

The surgical attitude in general, and the indication for cholecystectomy, in particular in cases with severe acute pancreatitis is an even more challenging topic, as severe acute pancreatitis is a life-threatening disease with high hospital mortality of up to 14% [17].

Therefore, the selection of the optimal timing for surgery is critical, as the associated risk of elective surgery—i.e. cholecystectomy—would further increase the morbidity and mortality due to the intense inflammatory changes and fluid collections that are common finding in severe ABP [18].

Opting for early cholecystectomy in these cases would lead to a higher risk for contamination of the peripancreatic collections during the surgical procedure and would unnecessarily increase the incidence of complications, especially the septic ones.

Thankfully, the surgical dogma and current protocols seem to converge on a common conclusion, namely that in acute biliary pancreatitis with peripancreatic fluid collections, cholecystectomy should be delayed until the early inflammatory episode will phase out and the fluid collections will stabilize or resorb [19].

These recommendations are also applicable to laparoscopic surgery, leading to a lower complication rate of less than 11% for delayed surgery, compared to as much as 44% in case of early cholecystectomy [20].

Unfortunately, there is surprisingly little evidence concerning the optimal timeframe for cholecystectomy in severe ABP.

Hughes et al. tried to address this aspect in a systematic review including 11 guidelines, out of which only 4 indicated a specific interval for cholecystectomy of more than 6 weeks.

Although the indication for delayed surgery was based on the statistically significant decrease in morbidity and mortality rates, the quality of evidence for these recommendations was poor [21].

The recent multicentric prospective cohort study of Hallensleben et al. which included 248 patients from 27 Dutch hospitals with biliary pancreatitis and a CT severity score of more than 2 investigated the optimal time for acute cholecystectomy.

The results were rather predictable, showing that the best moment for cholecystectomy after necrotising ABP should not exceed 8 weeks after discharge, if no peripancreatic collections are identified, as the risk of recurrent pancreatitis is significantly lower at this interval.

Likewise, the risk of recurrent biliary events is diminished when cholecystectomy is performed at no more than 10 weeks after discharge. Interestingly, the complication rate of cholecystectomy does not appear to decrease over time [22].

Based on these facts, the current clinical evidence suggests that cholecystectomy should be postponed until the peripancreatic collections resolve or, if the collections persist, after no less than 6 weeks [23].

**ERCP and cholecystectomy**

The role and timing of ERCP as an addition to cholecystectomy in ABP is still a matter of debate.

Generally, routine use of ductal imaging in mild gallstone pancreatitis is controversial, as most studies suggest that in case of patients with low risk for choledocholithiasis direct evaluation of the common bile duct may be safely overlooked when cholecystectomy is considered [2,10].

Moreover, it seems that routine intraoperative cholangiography should not be routinely performed in patients with mild ABP and normalizing bilirubin levels [24].

However, there are certain authors who suggest non-invasive routine common bile duct (CBD) evaluation should be encouraged after mild acute biliary pancreatitis.
Some even argued that intraoperative cholangiography (IOC) should be the investigation of choice in such cases [25].

Despite some recent evidence pointing that in case of ABP and cholangitis urgent (<24 h) and early (24-72 h) ERCP does not offer significant differences in terms of length of hospitalisation, healthcare costs, and mortality, all available guidelines still recommend urgent ERCP and biliary drainage in the first 24 hours [26].

For patients with ABP and ongoing biliary obstruction the current indication is that ERCP and ES should be performed within the first 72 hours.

No current guideline advice for routine ERCP during ABP if neither cholangitis nor ongoing main bile duct obstruction are diagnosed.

However, it should be noted that cholecystectomy remains a crucial element in the therapeutic algorithm for mild ABP even in the presence of cholangitis or biliary obstruction, since an increased risk for other biliary complications has been observed when only ERCP and sphincterotomy were performed during the index admission.

Several studies analysing early versus delayed cholecystectomy after ERCP and ES for mild ABP showed a significantly increase in biliary complication and readmission rate associated with delayed cholecystectomy [27-20].

Although no consensus exists on this topic, the conclusion of most studies investigating the timing of cholecystectomy after endoscopic sphincterotomy is that early surgery (less than 14 days after ES) seems to be indicated not only in mild ABP but also in most cases of choledocolithiasis [30-32].

The results of the EMILY trial would clarify the impact of ES and delayed cholecystectomy in mild ABP [33].

On the contrary, the use of ES and interval cholecystectomy in severe ABP may be a reasonable option to index cholecystectomy, but the level of evidence concerning this topic is still low [34,35].

However, ES per se only decreases the recurrence rate of ABP but it does not seem to reduce the incidence of recurrent biliary events in necrotic ABP, and should be used alone only in those patients that are non-candidates for cholecystectomy [22,34,36].

Another point of debate is the opportunity of ERCP and ES in case of predicted severe ABP without cholangitis or common bile duct obstruction, as initial studies were unable to draw clear conclusions on this topic [37].

However, a more recent multicentric RCT (APEC study) did not observed a reduction of major complications or mortality, compared with conservative treatment for those undergoing urgent ERCP with sphincterotomy compared to routine ERCP [38].

Based on these evidences in case of predicted severe ABP the role of ERCP should be limited to selected patients with cholangitis or main bile duct obstruction.

Cholecystectomy and residual choledocolithiasis

As the risk for residual CBD stones after ABP remains high, several controversies arise regarding the method of choice for diagnosis and, more importantly, the timing for both diagnosis and treatment.

Although the indication for endoscopic stone extraction remained unchallenged, both the European Society of Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE) issued updated guidelines for managing suspected choledocholithiasis, with supposedly increased predictive power [39,40].

The improvements are not spectacular, as suggested by the recent meta-analysis of Wang et al., with best qualifiers for potential choledocholithiasis being stones found during transabdominal ultrasonography, cholangitis, and total bilirubin above 4mg/dl associated with CBD dilatation of more than 6mm [41].

Another debatable issue is the viability of these criteria for cholecystectomized patients, as some modest evidence indicate that the dilatation of CBD is not a predictor for choledocolithiasis in this category of patients [42].

Given the clear indications for cholecystectomy in mild ABP, this aspect should be more thoroughly investigated.

However, even current guidelines may warrant some revisions in order to offer better predictive power over the presence of main bile duct stones, as a growing body of evidence indicate that there is significant discordance between the recommended diagnostic and therapeutic protocol of these guidelines, and the actual management of patients with choledocolithiasis [42].

Moreover, the diagnostic accuracy of these guidelines remains relatively low, especially for intermediate risk patients [43].

The EAST multicenter study, involving 844 prospectively identified patients from 12 medical centers in United States, indicated that nearly 45% of patients with suspected choledocholithiasis...
had a different management than the current SAGES and ASGE recommendations [44].

In a prospective study on 256 patients with suspected CBP stones, the presence of biliary pancreatitis was a strong predictor against the existence of a retained CBD stone [45].

However, the performance of the probability criteria for CBD lithiasis in this study was modest, with an accuracy of 59.0% for the high-risk cases and 41.0% for the moderate-risk patients.

Another non-randomized prospective study of Gomez-Torres et al. evaluating the use of magnetic resonance cholangiopancreatography (MRCP) and intraoperative cholangiography (IOC) in patients with mild ABP reported a low positive predictive value (PPV) and sensibility of the individual predictors of choledocholithiasis proposed by ASGE [25].

For example, a distended common bile duct of more than 6mm presented a sensitivity of just 33% and a PPV of 9%, while the total bilirubin level of more than 1.8mg/dl had a positive PPV of 7% and a sensitivity of 67%.

Moreover, only 20% of the patients at high risk for choledocholithiasis had main bile duct stones discovered during MRCP or IOC.

Several issues may arise from these observations, such as the need for better prognostic factors or a wider indication of main bile duct imaging, other than abdominal ultrasound, in suspected cases of choledocholithiasis after an episode of ABP.

Conclusions

In mild acute gallstone pancreatitis, laparoscopic cholecystectomy should be performed during index admission, while in severe pancreatitis cholecystectomy should be delayed until local complications have resolved or between 6 to 10 weeks after the onset of ABP.

ERCP is recommended in case of cholangitis or CBD obstruction associated with ABP, or after the resolution of the current episode of ABP, as an elective procedure.

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Conflict of interests

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References


