Introduction: Current guidelines for the management of acute gallstone pancreatitis recommend cholecystectomy as definitive treatment during primary admission or within 2 weeks of discharge, with the aim of preventing recurrent pancreatitis. However, cholecystectomy during the inflammatory phase may increase surgical complication rates. This study aimed to determine whether adherence to the guidelines prevents recurrent pancreatitis while minimising surgical complications.

Methods: Multi-centre review of seven UK hospitals, indentifying patients presenting with their first episode of gallstone pancreatitis between 2006 and 2008.

Results: A total of 523 patients with gallstone pancreatitis were identified, of which 363 (69%) underwent cholecystectomy (72 during the primary admission or within 2 weeks of discharge; 291 following this). Overall, 7% of patients had a complication related to cholecystectomy of which a greater proportion occurred when cholecystectomy was performed within guideline parameters (13% vs 6%; \( p = 0.07 \)). 11% of patients were readmitted with recurrent pancreatitis prior to surgery, with those undergoing cholecystectomy outside guideline parameters being most at risk (\( p = 0.006 \)).

Conclusion: This study suggests cholecystectomy within guideline parameters significantly reduces recurrence of pancreatitis but may increase the risk of surgical complications. A prospective randomised study to assess the associated morbidity is required to inform future guidelines.
Introduction

Acute pancreatitis is a growing burden for health services, with hospital admission rates in the UK rising from 4.9 per 100,000 population in the 1960s, to 20.7 per 100,000 by 2000.1–3 Gallstones are the underlying cause of acute pancreatitis in 35–40% of these admissions.4,5 Definitive management of gallstone pancreatitis requires cholecystectomy to prevent further attacks, with endoscopic biliary sphincterotomy being used for cases where surgery is deemed unsafe or is otherwise not feasible.6 The on-going debate over optimal timing of cholecystectomy is whether to ensure complete recovery from the acute inflammatory phase7,8 or to prevent recurrent attacks of acute pancreatitis by undertaking early surgery.9

A recent systematic review suggested that interval cholecystectomy after mild gallstone pancreatitis is associated with a high risk of readmission for recurrent biliary events, with recurrence estimated to occur in 9% of patients prior to interval cholecystectomy.10 The authors stated that index cholecystectomy appeared safe, with no difference in operative complications, conversion rate or mortality when compared to delayed surgery. However, the lack of quality publications was acknowledged with only 9 small studies meeting their criteria from some 38 reviewed studies (8 cohort studies (range 19–281 patients, median 131) and one single-centre randomised trial of 50 patients).

Currently guidelines on management of gallstone pancreatitis are based on these small studies.11–13 The British Society of Gastroenterologists (BSG) and the American Gastroenterological Associations (AGA) advise that all patients, regardless of severity, who are suitable for surgery should undergo cholecystectomy during the index admission, or if not feasible within 2 weeks (BSG), or no later than 2–4 weeks (AGA) of discharge.14,15 These guideline-defined parameters only equate to a consensus of opinion and highlight the need for large, high quality multicentre studies to ensure the recommended practice minimises surgical complications and prevents further episodes of pancreatitis.

The aim of this study was to determine whether cholecystectomy performed during the index admission, or within 2 weeks of discharge, prevents recurrent gallstone pancreatitis and minimises surgical complications.

Methods

A pilot study was carried out at 3 of centres for a one-year period, with 96 patients identified, 19 of which had undergone definitive management within 2 weeks of discharge. It was therefore predicted that over 500 patients would be identified by reviewing seven centres over 3 years, allowing for 100 patients receiving definitive management within 2 weeks of discharge.

Patients presenting with a first episode of gallstone pancreatitis between 1st January 2006 and 31st December 2008 at seven hospitals within the West Midlands, UK were identified, initially from hospital coding records using International Classification of Diseases Revision 10 codes K85 and K86.1, before screening by inclusion and exclusion criteria.16

Inclusion and exclusion criteria

To be included, patients had to satisfy all of the following inclusion criteria: (1) first presentation of pancreatitis; (2) elevated amylase of ≥500 IU/l (normal upper limit at participating hospitals ranged from 100 to 150 IU/l); (3) radiological evidence of gallstones within the gallbladder up to six months prior to or within 2 weeks following the date of admission. Any patient with either (1) a previous history of pancreatitis (either documented or from a previously raised amylase at any time point); (2) a history of alcohol excess (acute or chronic); (3) diagnosed with pancreatitis secondary to endoscopic retrograde cholangiopancreatography (ERCP), were excluded.

The main endpoints for this study were biochemical recurrent pancreatitis and surgical complications in those who underwent cholecystectomy. Unplanned readmissions and total length of stay were considered secondary endpoints. C-reactive protein (CRP) of >150 mg/l within 48 h of admission was used as a surrogate marker for severity of pancreatitis.14,17

Data collection

Data were collected by reviewing medical records and computer-based hospital systems using a standardised electronic proforma. Approval was gained from the local audit department at each site with individual patients being assigned a code to preserve anonymity. Data collected included: age, gender, definitive procedures (ERCP or surgical intervention), surgical complications, in-hospital mortality and recurrent pancreatitis (pre- or post-cholecystectomy), defined as a discrete episode of pain consistent with a history of pancreatitis with associated raised amylase, not in continuity with the initial presentation. The length of hospital admissions and the timing of definitive procedures were documented, as were any re-admissions occurring up to 31st August 2010 used as the guillotine point at the start of the data collection period.

Statistical analysis

Continuous data are presented as median and interquartile range (IQR) with differences between groups assessed using the Mann–Whitney U test. Categorical data were tested using the χ² test or Fisher’s exact test as appropriate. Patients who underwent a cholecystectomy as part of another surgical procedure were excluded from analysis of the outcomes of the surgical procedure. Data were analysed using SPSS 18.0 (SPSS Inc., Chicago, Illinois).

Results

Some 523 patients were identified at the 7 hospitals with a first admission of biliary pancreatitis between January 2006 and December 2008. Admissions per hospital ranged from 34 to 141 with a median of 75 admissions during the study period. The final outcome of all patients is shown in Fig. 1 with demographic and clinical characteristics shown in Table 1.
There were 18 in-hospital deaths during the index admission (median age of 78.5 (70.75–82.5) years). Fifteen patients had not undergone management of their gallstones; two had undergone ERCP; one patient died following open necrosectomy (with cholecystectomy) during the first week of admission and was excluded from further analysis. On a subsequent admission, one further death was recorded secondary to recurrent pancreatitis. This patient had been previously deemed unfit for intervention. There were no deaths in patients undergoing cholecystectomy as their planned treatment for pancreatitis.

Management

A total of 421 (80%) patients underwent a definitive biliary procedure: 363 (69%) underwent cholecystectomy; 164 (31%) underwent ERCP; for 58 (11%) this was their only intervention; 93 (18%) had no definitive treatment during the follow up period (Fig. 1). Seventy-two patients (20%) underwent cholecystectomy during the index admission or within 2 weeks of discharge, 291 patients (80%) underwent cholecystectomy more than two weeks after the first episode of gallstone pancreatitis.

Some 351 patients (97%) underwent a laparoscopic procedure, 23 (7%) of which were converted to an open cholecystectomy. One (1%) conversion occurred in 68 patients undergoing laparoscopic cholecystectomy within 2 weeks, as compared to 22 (8%) in the 283 after 2 weeks of discharge (p = 0.094) (Table 2).

Of the 12 (3%) patients who underwent a planned open procedure, 4 (5%) were performed during index admission or within 2 weeks of discharge compared to 8 (3%) during a subsequent admission.

Across hospitals, a similar rate of cholecystectomy was observed (65–73%, p = 0.89) but compliance with guidelines ranged significantly from 4.5% to 45% (p < 0.001). There was no correlation between hospital volume and guideline compliance.

Patients who underwent early cholecystectomy were much more likely to have an on-table cholangiogram (OTC) performed intra-operatively, whereas those with a delayed procedure were more likely to have an MRCP performed pre-operatively (p < 0.001) (Table 2).

Table 1 – Demographic data.

<table>
<thead>
<tr>
<th></th>
<th>All* (523)</th>
<th>Cholecystectomy** (363)</th>
<th>ERCP only (58)</th>
<th>No treatment (93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>63 (47–75)</td>
<td>58 (43–69)</td>
<td>80 (67.5–84)</td>
<td>75 (60–83)</td>
</tr>
<tr>
<td>Sex male:female</td>
<td>1:1.8</td>
<td>1:2.0</td>
<td>1:1.4</td>
<td>1:1.6</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>101 (23–211)</td>
<td>91 (18–207)</td>
<td>144 (44–215)</td>
<td>150.5 (66–242)</td>
</tr>
<tr>
<td>Total length of stay in days</td>
<td>9 (6–17)</td>
<td>9 (6–17)</td>
<td>12 (7–27)</td>
<td>9 (5–20)</td>
</tr>
<tr>
<td>Mortality</td>
<td>18 (3.5%)</td>
<td>0 (0.0%)</td>
<td>2 (3.4%)</td>
<td>15 (16.1%)</td>
</tr>
</tbody>
</table>

ERCP = endoscopic retrograde cholangiopancreatography; CRP = C reactive protein.

* 8 patients lost to follow up.
** One patient died following open necrosectomy 7 days from admission and was excluded from the cholecystectomy group.
Overall, 7% (26/363) of patients had a complication in relation to their cholecystectomy. The biliary complications were five bile leaks, one case of dehydration secondary to T-tube drainage and two common bile duct (CBD) injuries; one being repaired during the initial surgery, with the other requiring a further operation. Of the biliary complications 2 (3%) occurred within the guidelines and 6 (2%) after 2 weeks of discharge ($p = 0.661$). Five patients (2%) developed post-operative pancreatitis, 3 cases in the patients managed within the guidelines ($p = 0.055$), with no retained stones being identified in these patients.

The remaining complications were three respiratory tract infections, one case of adult respiratory distress syndrome (ARDS), one myocardial infarction, three surgical site infections, one small bowel injury which was repaired at the time of surgery and two cases where further surgery was required (bleeding and internal herniation).

Surgical complications were categorised for analysis using the Clavien–Dindo classification (Table 3).18,19 No patients had a Grade V complication. A larger percentage of grade I/II complications occurred when cholecystectomy was performed within the defined guideline parameters ($p = 0.024$); there was a trend towards more complications overall in the early management group, but this did not reach significance (Table 4).

When the cholecystectomies were split into groups of 50 (±10) patients by time performed in relation to the primary admission (Fig. 2), the unadjusted rate of complications was highest in surgery performed within the index admission and up to 2 weeks from discharge, but lowest within for those performed within four to seven weeks from discharge.

### Table 2 – Patient demographics in relation to timing of cholecystectomy.

<table>
<thead>
<tr>
<th>Timing of laparoscopic cholecystectomy in relation to time of discharge</th>
<th>Overall (364)</th>
<th>Within 2 weeks (72)</th>
<th>After 2 weeks (291)</th>
<th>p Value$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58 (43–69)</td>
<td>55 (34–68)</td>
<td>58 (45–70)</td>
<td>0.075$^a$</td>
</tr>
<tr>
<td>Male</td>
<td>34% (124)</td>
<td>33% (22)</td>
<td>34% (102)</td>
<td>0.672</td>
</tr>
<tr>
<td>CRP$^d$</td>
<td>91 (18–207)</td>
<td>121 (17–227.5)</td>
<td>80 (18–207)</td>
<td>0.484$^a$</td>
</tr>
<tr>
<td>CRP &gt; 150 mg/l$^d$</td>
<td>37% (120/326)</td>
<td>42% (27/64)</td>
<td>35% (93/262)</td>
<td>0.386</td>
</tr>
<tr>
<td>Index admission LOS</td>
<td>6 (4–11)</td>
<td>7 (5–13)</td>
<td>6 (4–10)</td>
<td>0.076$^a$</td>
</tr>
<tr>
<td>Total LOS</td>
<td>9 (6–17)</td>
<td>7 (5–13)</td>
<td>9 (6–17)</td>
<td>0.096$^a$</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRCP</td>
<td>35% (128)</td>
<td>11% (8)</td>
<td>43% (120)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ERCP</td>
<td>29% (106)</td>
<td>27% (20)</td>
<td>31% (86)</td>
<td>0.571</td>
</tr>
<tr>
<td>Median time to cholecystectomy</td>
<td>81 (35–162)</td>
<td>7 (3–10)</td>
<td>103 (51–176.5)</td>
<td>–$^a$</td>
</tr>
<tr>
<td>OTC</td>
<td>13% (47)</td>
<td>30% (22)</td>
<td>9% (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conversion to open$^b$</td>
<td>7% (23/352)</td>
<td>2% (1/68)</td>
<td>8% (22/284)</td>
<td>0.094</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-admission prior to cholecystectomy</td>
<td>18% (66)</td>
<td>4% (3)</td>
<td>22% (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent pancreatitis</td>
<td>11% (40)</td>
<td>5% (4)</td>
<td>12% (34)</td>
<td>0.099</td>
</tr>
<tr>
<td>Peri-operative complications</td>
<td>7% (26)</td>
<td>13% (9)</td>
<td>6% (17)</td>
<td>0.070</td>
</tr>
<tr>
<td>Post-operative pancreatitis</td>
<td>2% (6)</td>
<td>3% (2)</td>
<td>1% (3)</td>
<td>0.289</td>
</tr>
</tbody>
</table>

LOS – length of stay; CRP – C-reactive protein; MRCP – magnetic resonance cholangiopancreatography; ERCP – endoscopic retrograde cholangiopancreatography; OTC – on-table cholangiogram.

- Not performed.
- Excludes 12 patients undergoing planned open surgery.
- P value calculated using Fishers exact or chi squared test as appropriate unless indicated. P values less than 0.05 were classed as significant and are highlighted in bold.
- CRP not available in 38 cases.
- Mann–Whitney U test.

### Table 3 – The Clavien–Dindo classification of surgical complications.17,18

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions, including wound infections opened at the bedside.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs (excluding antiemetics, electrolytes and analgesics). Blood transfusions and total parental nutrition are also included.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication ± requiring intensive care management</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient</td>
</tr>
</tbody>
</table>

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Recurrent pancreatitis

In total, 55 (11%) patients had a second episode of pancreatitis. Second episodes occurred a median of 44 (10–191) days from discharge; 16 (29%) cases occurred within 2 weeks of discharge from their index admission.

Of the 306 patients who were discharged and readmitted for cholecystectomy, 37 (12%) suffered a recurrent attack of pancreatitis prior to operation; 9 of these patients had a second attack within 2 weeks and this included 2 patients who were managed within the guidelines (Table 5). For patients undergoing cholecystectomy outside the guidelines, the risk of pancreatitis recurrence was significantly increased (p = 0.006). 5 patients had postoperative recurrent pancreatitis.

Unplanned readmissions

The overall proportion of patients experiencing unplanned readmission was 18% but there was a significant difference between those undergoing surgery within 2 weeks of discharge (4%) and those waiting longer than two weeks (22%) (p = 0.001) (Table 2).

Length of stay

There was not a significant difference in the median total inpatient length of stay in those who underwent cholecystectomy within index admission (7.5 days, p = 0.277), but for those who were operated on during the same admission or within 2 weeks of discharge, the overall length of stay was reduced to 7 days (p = 0.050) as compared to those who underwent surgery after these guideline defined parameters (9 days) (Table 2).

Those patients who had a recurrent episode of pancreatitis had a significantly shorter inpatient stay of 5 (3–9) days during their subsequent admission (p < 0.001).

Discussion

The timing of biliary surgery in patients with acute gallstone pancreatitis remains a contentious issue. This is the largest multicentre cohort study to report on outcomes following definitive treatment of biliary pancreatitis and shows a wide variation in clinical practice across the seven centres studied.
In this study group, no major consequences of delay in performing cholecystectomy were identified, despite 80 per cent being managed outside of current guidelines; this lack of compliance with current guidelines is consistent with recently published national data on the subject.\textsuperscript{13} No deaths occurred in patients who underwent early or delayed surgery with the rate of peri-operative complications being lower in those undergoing delayed cholecystectomy.

Recurrent pancreatitis rates have been quoted as being as high as 18\%\textsuperscript{20} in patients awaiting intervention after gallstone pancreatitis and 8.5\% in patients post-cholecystectomy with either retained or primary bile duct stones.\textsuperscript{21} In our study 12\% of patients awaiting cholecystectomy were readmitted with recurrent pancreatitis which is similar to the 9\% identified in a recent meta-analysis.\textsuperscript{10} However, 7\% (5) of those patients who underwent an operation within the guidelines also had a recurrent episode; two pre- and three post-operatively. This indicates there is a risk of a second episode regardless of timing of surgery. It is important to note that previous work has shown that the first episode of pancreatitis confers the greatest risk with subsequent readmissions having a lower mortality.\textsuperscript{22} This is reflected in our study, with the median additional length of stay in patients readmitted being 5 days and no deaths reported as a result of recurrent pancreatitis due to delay in intervention.

Those undergoing cholecystectomy after the index admission had a higher rate of conversion. This may be due to case selection, such as a higher rate of open procedures being selected during the index admission, or surgeon experience or variation in threshold for converting. A previous study indicated that early cholecystectomy may be more technically challenging.\textsuperscript{23}

The incidence of major complications such as common bile duct (CBD) injury or bile leak is in keeping with other reports.\textsuperscript{24,25} Although the operative complication rate in those undergoing cholecystectomy during index admission was twice that of the delayed group, the numbers are small. Those studies focussing on the value of early cholecystectomy in biliary pancreatitis have not reported peri-operative complications in their cohort,\textsuperscript{21,26–28} except conflicting findings from It\textsuperscript{28} with greater morbidity in the later group and McCulloch\textsuperscript{29} who also found a trend towards an increased complication rate following early cholecystectomy.

Of those patients within our study population undergoing cholecystectomy, 73 (20\%) underwent surgery within current BSG guidelines; the majority of patients being treated outside the recommended timeline, which is also reflected in other studies.\textsuperscript{21,29–31} All hospitals in this study fell short of the recommendations, although practice did vary considerably. Factors such as use of OTC or MRCP were significantly linked with the timing of cholecystectomy. Variation in local practice to select a preoperative MRCP to confirm the bile duct was clear of gallstones rather than using intra-operative OTC, may have been a factor in delaying patients out with the guidelines. Severity as either assessed by absolute value of CRP or by those who had a CRP of greater than 150 mg/l had no effect on the selection of timing of operation. This poor compliance would suggest adequate systems are not currently in place to manage all patients within the guidelines, or the guidelines are being disregarded by clinicians. Either way, the group selected for delayed surgery did not appear to be at increased risk in terms of recurrent pancreatitis, post-operative complications or mortality. This would suggest delaying surgery may be a satisfactory treatment option for selected patients. A prospective, randomised study of cholecystectomy for pancreatitis would be justified by these findings.

The primary shortcoming of this study is the retrospective design utilised. We attempted to mitigate against this by analysing across multiple sites over three years. Electronic admissions, episode and follow-up data have made this retrospective analysis more reliable over recent years as witnessed by an overall loss to follow-up rate in this cohort of 8\% (1.5\%). We did not attempt to collect detailed information on patient comorbidities in order to simplify and homogenise data collection, although this information would have subsequently been useful to verify similarity between patient groups undergoing early or late intervention. In terms of follow-up, we are confident that all major post-operative complications, readmissions and deaths have been identified within the presenting hospital, but we cannot control for patients who may have attended a different hospital after their index gallstone pancreatitis admission. The amylase cut off level of 500 IU/l, higher than conventional guidance\textsuperscript{14} was chosen to exclude any patients who may have had equivocal diagnoses at the time of presentation, which would have otherwise diluted the dataset. An accepted limitation of this policy is that some patients with a mild form or delayed presentation of true gallstone pancreatitis may have been missed.

This study identified that operative complications were lowest between 4 and 7 weeks from discharge, having been at their highest within the index admission up to 2 weeks after discharge (Fig. 2). Complications rise from 12 weeks after discharge onward. Therefore, whilst there is no obvious detrimental effect of delaying surgery beyond 2 weeks of discharge, there is no conferred benefit of delaying definitive management after 12 weeks, and therefore operating within 3 months of admission may reduce readmission and recurrent biliary events whilst reducing operative risk.

Despite the majority of patients being managed outside of the national guidelines, no deaths or other serious sequelae were identified relating to this. Patients whose definitive treatment is delayed may be readmitted pre-operatively with recurrent biliary events, but this only marginally affects the total length of stay. An association was found between early surgical intervention and an increased complication rate. A

\begin{table}
\centering
\begin{tabular}{|l|c|c|}
\hline
 & Number of patients & Percentage of readmissions \\
\hline
All readmitted & 66 (22\%) & \\
Gallstone pancreatitis & 37 (12\%) & 56 \\
Biliary colic/cholecystitis & 21 (7\%) & 32 \\
Jaundice & 2 (1\%) & 3 \\
Pseudocyst & 2 (1\%) & 3 \\
Other (see text) & 4 (1\%) & 6 \\
\hline
\end{tabular}
\caption{Reasons for first unplanned readmission prior to cholecystectomy.}
\end{table}

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prospective study is clearly required to define the optimum time for intervention but this study indicates there is little disadvantage in delaying cholecystectomy beyond index admission in the majority of patients.

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REFERENCES