Title:
Days of symptoms and days of hospital admission before surgery do not influence the results of cholecystectomy in moderate acute calculous cholecystitis

Authors:
Jaume Tur-Martínez, Alfredo Escartin Arias, Pablo Muriel, Marta González, Elena Cuello, Ana Pinillos, Helena Salvador, Jorge Juan Olsina

DOI: 10.17235/reed.2020.7405/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
OR 7405

Days of symptoms and days of hospital admission before surgery do not influence the results of cholecystectomy in moderate acute calculous cholecystitis

Jaume Tur-Martínez, MD; Alfredo Escartín, MD, PhD; Pablo Muriel, MD, Marta González, MD; Elena Cuello, MD; Ana Pinillos, MD; Helena Salvador, MD, PhD; Jorge Juan Olsina, MD, PhD.
General Surgery Department. IRBLleida-University. University Hospital Arnau de Vilanova. Lleida. Spain.

Correspondence:
Jaume Tur-Martínez, MD
General Surgery Department - Hepatobiliopancreatic Surgery Unit
University Hospital Arnau de Vilanova
Av. Alcalde Rovira Roure, 80, 25198 Lleida, Spain
Email: jaume.tur.martinez@gmail.com
ORCID: 0000-0002-1936-5881

ABSTRACT

Background and Aims
Early cholecystectomy is the gold standard treatment for acute calculous cholecystitis (AC), although for grade II, many surgeons still prefer delayed cholecystectomy, to avoid surgical complications. The aim of this study is to analyze postoperative morbidity and mortality for Tokyo Guidelines grade II AC treated with cholecystectomy, taking in to account the days of symptoms and the days since hospital admission.

Materials and Methods
Unicentre, retrospective study based on a prospective database. Patients with grade II AC treated with cholecystectomy were selected. Patients were analyzed according to Days of Symptoms (DS) and Days of Hospital Admission (DHA) until cholecystectomy.
Patients were subdivided in: < 3 days, 3-5 days, >5 days. Univariant and multivariant analysis for morbidity and mortality. Categorical variables were compared using chi square or Fischer's exact test. Continuous variables were compared using the Mann Whitney U test. Level of statistical significance was set at p < 0.05.

Results
998 patients with AC diagnoses were included; 567 with grade II AC; 368 treated with cholecystectomy. Nearly 90 % were treated laparoscopically; 48.1 % were operated the same day of emergency admission. For DS and DHA there were no statistical differences for severe postoperative complications, although a greater number of complications were detected in >5 DS (p: 0.32) and >5 DHA (p: 0.00). Statistically differences were found in DS for mortality (p:0.04). Postoperative length of stay was longer for >5 DHA cholecystectomies, (p > 0.05). No differences for hospital readmission.

Conclusion
Regardless of DS or DHA until cholecystectomy, do not exist statistically significant differences related to severe postoperative complications, length of stay or mortality.

Keywords
Acute cholecystitis, Acute moderate cholecystitis, laparoscopic cholecystectomy, Tokyo guidelines, Acute calculous cholecystitis, postoperative complications.

INTRODUCTION
Emergent cholecystectomy is the gold standard treatment for acute calculous cholecystitis (AC)(1). Controversy exist around the best moment for surgical treatment according to days of symptoms(2), although it seems that early surgical(3–8) treatment is becoming more frequent (9).
In the last Tokyo Guidelines published in 2018(9), supported treatment for grade I and II AC is early cholecystectomy. For grade III AC the guideline offers different options
according to the performance status of the patient and previous comorbidities. In grade II AC, although exist evidence that supports early cholecystectomy as the best treatment(10), at daily clinical practice, many surgeons prefer to do a delayed definitive treatment, to avoid surgical complications because these kind of patients can have local complications (gangrenous cholecystitis, abscess, perforation) and often present with various days of symptoms (>72 hours). Moreover, some authors have previously published worst outcomes after 48h of admission(11).

The aim of this study is to analyze postoperative morbidity, mortality and length of stay for Tokyo Guidelines grade II AC treated with cholecystectomy, taking in to account the days of symptoms and the days since hospital admission before surgery.

**Material and Methods**

Unicentre, retrospective study based on a prospective electronic database, including patients older than 18 years old, admitted to the service of General Surgery at a tertiary level hospital, with the diagnosis of AC, since 1st of January 2010 until 31st of December 2015.

Because of the retrospective character of the study, informed consent was not necessary. This study was approved by the Institutional Research Ethics Committee.

Exclusion criteria: patients with acute acalculous cholecystitis, AC as secondary diagnosis, other associated biliary events (acute cholangitis, acute pancreatitis, preoperative choledocholithiasis diagnosis) or active gastrointestinal neoplasia.

The following data were collected: age, gender, past medical history, American Society Anaesthesiologists (ASA) classification, days of symptoms until emergency consulting, days of symptoms (DS) and days of hospital admission (DHA) until cholecystectomy, severity of cholecystitis according to 2018 Tokyo guidelines(12), type of treatment (antibiotics, cholecystectomy, cholecystostomy), surgical approach (open or laparoscopy), postoperative complications and its severity according to Clavien-Dindo classification(13), length of stay (LOS) in days, 30-days postoperative readmission and 30-day mortality.

Postoperative complications were considered as any medical or surgical event occurred during the first thirty postoperative days.
The diagnosis was based on a blood test with hemogram, liver enzymes, inflammatory markers and coagulation test. Abdominal ultrasound was performed to all patients and if the diagnosis was unclear, an abdominal CT or cholangio-MRI was performed. Severity of AC was defined based on the 2018 Tokyo Guidelines criteria(9,12): **Grade I AC** does not meet the criteria for “grade II” or “grade III” AC. **Grade II AC** is associated with any one of the following conditions: (1) elevated WBC count (> 18,000/mm³), (2) palpable tender mass in the right upper abdominal quadrant, (3) duration of complaints > 72 hours, (4) marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). **Grade III AC** is associated with dysfunction of any one of the following organs/systems: (1) cardiovascular dysfunction: hypotension requiring treatment with dopamine ≥ 5 mg/kg per minute, or any dose of norepinephrine, (2) neurological dysfunction: decreased level of consciousness, (3) respiratory dysfunction: PaO₂ /FiO₂ ratio < 300, (4) renal dysfunction: oliguria, creatinine > 2.0 mg/dL, (5) hepatic dysfunction: PT international normalized ratio > 1.5, (6) hematological dysfunction: platelet count < 100,000/mm³.

Patients were operated independently by the on call team or by de hepatobiliary pancreatic surgery team.

Between all patients with diagnosis criteria of AC and fulfill the inclusion criteria, we focused on patients with AC grade II treated with cholecystectomy. All other patients were excluded.

This group of patients was analyzed according to days of symptoms (DS) until the surgical procedure and according to days of hospital admission (DHA) until surgery. At both analysis the cohort was divided in: < 3 days, 3-5 days, >5 days.

Because of the retrospective character of the study, a preliminary calculation of the number of patients needed to be included could not be realized. This way, taken into account the high prevalence of the illness as well as previous studies, we considered that an initial cohort of nearly 1000 patients and a subgroup of nearly 400 patients, could be enough to achieve a statistical power of at least 80 %.

An univariant analysis for morbidity and mortality was performed, taking into account the whole sample. A multivariant analysis was performed for variables clinically
relevant or with a \( p \) value < 0.2; Odds Ratio (OR) and 95 \%\ confident interval were provided. Categorical variables were compared using chi square or Fischer's exact test. Continuous variables were compared using the Mann Whitney U test. Level of statistical significance was set at \( p < 0.05 \). SPSS program version 19.0 (IBM Co Armonk, NY, USA) was used for statistical results.

**RESULTS**

A total of 998 patients were included with AC diagnose; 567 were classified as grade II AC. Of this group, 368 patients were treated with cholecystectomy and this is the ongoing cohort for analysis (Figure 1).

The cohort was analyzed twice: according to DS and to DHA. In both analyses there was a predominance of males and in both groups patients older than 80 were around 20 \% (33 and 37 patients for <3 days and 3-5 days in DS; 75 and 4 patients for <3 days and 3-5 days in DHA), except in the subgroup of >5 DS and DHA, which represents 13.6 \% (11 patients) and 40 \% (2 patients), respectively.

**Days of symptoms analyses**

There are no statistical differences between the subgroups of days in reference to ASA, previous biliary events or associated choledocholithiasis (Table 1).

Most of the patients (97.3 \% - 358 patients) were treated with cholecystectomy as first line treatment. Nearly half of our patients were operated at the moment they consulted to the emergency room (47.3 \% - 174 patients), while the other part was operated before third day of hospital admission and during the first five days of symptoms.

In the subgroup of >5 days, 11.1 \% (9 patients) cholecystectomy was performed as second option treatment because of failure of antibiotics, been this difference statistical significant between the other two subgroups. Open surgeries were mainly done in the >5 days subgroup (12.3 \% - 45 patients). The laparoscopic conversion rate was higher in the 3-5 and > 5 days subgroups, without statistical significance. The main reasons for conversion were technical difficulty to complete cholecystectomy. The number of postoperative complications was greater in the > 5 days subgroup, although
the severity of the complications was higher in the 3-5 days subgroup, without statistical significance. Mortality was registered in only 3 patients in the <3 days subgroup. There were no statistical differences according to length of stay: 5.2 days (1-36), 5.5 days (1-24) and 6.1 days (1-21) for > 3 DS, 3-5 DS and > 5DS, respectively (p: 0.4). Hospital readmission was more frequent in the 3-5 days subgroup, being statistical differences with the other two subgroups.

**Days of hospital admission analyses:**

In the DHA analyses (Table 2), differences were found for ASA classification, being more common ASA 3 in the >5 days subgroup. Cholecystectomy was the first line treatment in most of patients, except in 4 patients in subgroup 3-5 days, were antibiotic treatment was chosen. Most of cholecystectomies were performed by laparoscopic approach, without statistical differences between the subgroups. The conversion rate to open surgery from laparoscopy was statistically higher in the >5 days subgroup and as in the other group of patients, the main reasons for conversion were technical difficulty to complete cholecystectomy. There were no statistically differences for severe morbidity (Clavien-Dindo >II) or mortality, but it seems to be a higher number of postoperative complications in the >5 days subgroup. The LOS was longer (p< 0.05) in patients operated with more DHA: 5.3 days (1-36), 8.16 days (3-18) and 15.8 days (9-21), for < 3 DHA, 3-5 DHA and > 5 DHA, respectively. A longer LOS was found for patients operated after 3 DHA, but this data must be taken with care, because in those patients the surgery was performed after hospital admission. In this case, an analysis of postoperative length of stay was performed, showing longer stay for > 5 DHA, without statistically significance: 4.8 days (1-36), 4.89 days (1-13) and 6.4 days (3-12), for < 3 DHA, 3-5 DHA and > 5DHA, respectively.

There were no differences for hospital readmission.

As shown in Table 3, most of the patients (72.8 % - 268 patients) were operated the same day of emergency admission, being laparoscopic cholecystectomy first line of treatment.

If we take into account all patients, more than 90 % (340 patients) where operated by laparoscopic approach, with a conversion rate less than 10 % (31 patients) (Table 1...
We want to highlight that patients with >5 DS experienced less laparoscopic approach, being about 87.7 % (71 patients) with a conversion rate of 7.1 % (5 patients). This conversion rate is justified because of intraoperative difficulties that could not be resolved laparoscopically.

With reference to postoperative complications, we observed that in patients with >3 DHA, the number of postoperative complications increases (p: 0.9); in patients with > 5 DHA, also increases until 20 % (1 patient), without statistical significance (Table 1 and 2). It should be noted that in patients with >5 DHA, cholecystectomy was not the first line treatment and was performed as a rescue treatment; this group of patients represents a small cohort, so data must be analyzed carefully.

Severity of postoperative complications was not enhanced when patients were operated before 5 DHA, while after 5 DHA the severity seems to increase, without statistical significance (p: 0.9). This phenomenon could be explained by the fragmentation of the groups, which produce a reduction in sample size of each subgroup.

The main postoperative biliary complications were registered: 4 biliary leaks through the cystic stump, which were treated with Endoscopic-Retrograde Cholangiopancreatography (ERCP) and plastic stenting; 1 biliary leak throw the cystic stump which required surgery because of biliary peritonitis; 1 main bile duct stenosis treated with a biliary stent; 1 main bile duct injury which required right hepatectomy with hepatico-jejunostomy and 1 biliary leak because of a Luschka channel treated with surgery. All these data means a 2.18 % of biliary complications secondary to cholecystectomy, while surgical bile duct injury represents only 0.27 %. These results adjusts to the results of other groups published recently(14).

Mortality was registered in 3 patients, all of them in the subgroup of <3 DS and < 3 DHA. The first patient had previous chronic renal failure with peritoneal dialysis and presented a renal decompensation with a consecutive multi-organ failure. The second patient suffered an acute respiratory failure secondary to a bronchoaspiration and the third patient was the patient with a surgical injury of bile duct, which required a right hepatectomy and hepatico-jejunostomy, requiring polytransfusion because of an intraoperative bleeding and presenting in the postoperative course a multi-organ
refractory failure. Probably in the first 2 patients, their preoperative comorbidities conditioned the postoperative course. Instead, in the last case mortality can be directly related to the surgery. Because of the fragmentation of the sample of patients with grade II AC into different subgroups, it could be difficult to obtain parameters that significantly influences morbidity and mortality. This way, an univariant and multivariant analysis for morbidity and mortality has been realized taking into account the whole cohort of patients with diagnoses of AC, to achieve more relevant data (Table 4). As shown in table 4, severe cholecystitis (OR 7.22, 95%CI [3.62-14.38], p < 0.001) and conversion to open surgery (OR 5.68, 95% CI [2.74-11.77], p < 0.001) were the main risk factors for severe morbidity (Clavien-Dindo > II). Moreover, previous morbidity (OR 6.4, 95%CI [1.4-29.3], p: 0.017) and grade III cholecystitis were the most relevant risk factors for mortality.

DISCUSSION
In patients with AC grade I (mild) 2018 Tokyo guidelines(12), it seems that days of symptoms are not too much relevant, because as it is an incipient process without local complications, surgery usually is safe and with a very low risk of postoperative complications.
On the other hand, severe AC (grade III) will need different types of treatment (antibiotic alone, cholecystectomy or cholecystostomy), depending on the hemodynamic situation of the patient, performance status and associated morbidity(9). Although the gold standard treatment for AC seems to be cholecystectomy(9), the best moment for it, is still in doubt in daily clinical practice. Many studies are written about it, but the problem is that some authors bases on days of symptoms while others bases on days of hospital admission(15), so this makes difficult to compare results. Some meta-analysis(3) mix both results and compare them, but in our opinion, they are not comparable.
After analyzing all our data, it seems that days of symptoms and days of hospital admission does not increase severe postoperative complications or hospital admission...
and laparoscopic cholecystectomy remains as the gold standard treatment for grade II AC.

Differences in postoperative mortality was found in DS group. After analyzing carefully this data, we can see that 3 patients died in the < 3 days and as explained in the results, they were patients with previous complex co-morbidities. Moreover, those 3 patients had a mild or moderate cholecystitis, so it is clinically striking that those patients with less complex cholecystitis, had the higher mortality, so we consider this result must be taken with care.

Highlights that patients with > 5 DHA had les abdominal drainage (p:0.04). This phenomenon could be explained because most of these patients were operated by surgeons belonging to the hepatobiliary surgery unit, which usually use no abdominal drainage if no intraoperative complications occur.

Re-admission was found in the 3-5 DS sub-group with an increase in the number of postoperative complications, without statistical significance. We want to highlight that those patients with >5 DS will present with AC technically more complex, because intraoperative findings will be more difficult to solve (abscess, gallbladder perforation, gallbladder plastron...). In these cases, it is recommendable that cholecystectomy be performed by surgeons with experience in biliary surgery and advanced laparoscopy. Some of these cases with local complications, could also be treated without surgery (percutaneous drainage and antibiotic).

Apart from the benefits of early cholecystectomy, it is well known that those patients with AC which are not operated as first line treatment, will present a severe recurrence in about 20 % of cases(16), as our group has published recently, so it is important to treat as soon as possible AC.

Although this study includes an elevated number of patients, there are some limitations like the unicenter and retrospective character, and the division into subgroups which may reduce the statistical power of the results.

To conclude, this study supports no differences in severe postoperative morbidity, mortality and length of stay related to DS or DHA until cholecystectomy is performed in patients with grade II AC.
Prospective randomized trials with higher volume of patients are necessary to confirm these data.

DECLARATION OF CONFLICTING INTERESTS
Jaume Tur-Martínez, Alfredo Escartín, Pablo Muriel, Marta González, Elena Cuello, Ana Pinillos, Helena Salvador and Jorge-Juan Olsina declare that they have no conflict of interest.
AUTHOR CONTRIBUTION
All authors contributed to the study conception and design. Material preparation and data collection were performed by Ana Pinillos, Elena Cuello, Pablo Muriel and Marta González. Analysis was performed by Alfredo Escartín and Jaume Tur-Martínez. The first draft of the manuscript was written by Jaume Tur-Martínez and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

FUNDING
The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES


<table>
<thead>
<tr>
<th>Age &gt; 80 yo</th>
<th>3 ≤ days n=120</th>
<th>3-5 days n=167</th>
<th>&gt;5 days n=81</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male)</td>
<td>33 (27.5%)</td>
<td>37 (22.2%)</td>
<td>11 (13.6%)</td>
<td>0.06</td>
</tr>
<tr>
<td>ASA III-IV</td>
<td>80 (66.6%)</td>
<td>99 (59.3%)</td>
<td>43 (53.1%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes Mellitus-II</td>
<td>33 (27.5%)</td>
<td>47 (28.1%)</td>
<td>21 (25.9%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Previous biliary events</td>
<td>8 (6.7%)</td>
<td>11 (6.6%)</td>
<td>0 (0%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Associated Choledocholithiasis</td>
<td>1 (0.8%)</td>
<td>2 (1.2%)</td>
<td>2 (2.5%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Cholecystectomy Laparoscopy</td>
<td>120 (100%)</td>
<td>166 (99.4%)</td>
<td>72 (88.9%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Type of cholecystitis</td>
<td>112 (94.1%)</td>
<td>157 (94%)</td>
<td>71 (87.7%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Conversion from laparoscopy</td>
<td>6 (5.4%)</td>
<td>20 (12.7%)</td>
<td>5 (7.1%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Abdominal drainage</td>
<td>87 (72.5%)</td>
<td>120 (71.9%)</td>
<td>46 (57.5%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Type of cholecystitis</td>
<td>33 (19.8%)</td>
<td>33 (19.8%)</td>
<td>28 (35.4%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Edematous</td>
<td>82 (69.5%)</td>
<td>105 (62.9%)</td>
<td>41 (51.9%)</td>
<td></td>
</tr>
<tr>
<td>Gangrenous</td>
<td>27 (22.9%)</td>
<td>29 (17.4%)</td>
<td>10 (12.7%)</td>
<td></td>
</tr>
<tr>
<td>Perforated</td>
<td>17 (14.2%)</td>
<td>32 (19.2%)</td>
<td>18 (22.2%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Nº patients with complication</td>
<td>2 (1.7%)</td>
<td>1 (0.6%)</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Surgical injuries</td>
<td>15 (12.5%)</td>
<td>28 (16.8%)</td>
<td>9 (11.1%)</td>
<td>0.40</td>
</tr>
<tr>
<td>C-D ≥II</td>
<td>3 (2.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.04</td>
</tr>
<tr>
<td>30 days mortality</td>
<td>2 (1.7%)</td>
<td>10 (6%)</td>
<td>0 (0%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 1: Days of symptoms until cholecystectomy.
Table 4: Risk factors for mortality and morbidity (Clavien-Dindo >II) for all the cohort

Table 2. Days since hospital admission until cholecystectomy.

Table 3: Patients operated on the same day of emergency consulting (day 0).

<table>
<thead>
<tr>
<th></th>
<th>Mortality No</th>
<th>Mortality Yes</th>
<th>Multivariant analysis: OR (CI 95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=978</td>
<td>n=20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 80 yo</td>
<td>335 (34.3)</td>
<td>13 (65)</td>
<td>0.004</td>
<td>n.s</td>
</tr>
<tr>
<td>Male</td>
<td>559 (57.2)</td>
<td>15 (75)</td>
<td>0.1</td>
<td>n.s</td>
</tr>
<tr>
<td>Diabetes-II</td>
<td>256 (26.2)</td>
<td>10 (50)</td>
<td>0.017</td>
<td>n.s</td>
</tr>
<tr>
<td>Previous morbidity</td>
<td>345 (35.3)</td>
<td>18 (90)</td>
<td>0.000</td>
<td>6.4 (1.4-29.3)</td>
</tr>
<tr>
<td>Previous biliary events</td>
<td>77 (7.9)</td>
<td>4 (20)</td>
<td>0.049</td>
<td>n.s</td>
</tr>
<tr>
<td>Severe cholecystitis (grade III)</td>
<td>76 (15.0)</td>
<td>17 (85)</td>
<td>0.000</td>
<td>40.7 (11.3-146.2)</td>
</tr>
<tr>
<td></td>
<td>Morbidity (Clavien-Dindo &gt;II) No</td>
<td>Morbidity (Clavien-Dindo &gt;II) Yes</td>
<td>Multivariant analysis: OR (CI 95%)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>n=978</td>
<td>n=20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 80 yo</td>
<td>292 (33.5)</td>
<td>56 (44)</td>
<td>0.016</td>
<td>n.s</td>
</tr>
<tr>
<td>Male</td>
<td>494 (56.7)</td>
<td>79 (63)</td>
<td>0.2</td>
<td>n.s</td>
</tr>
<tr>
<td>Previous morbidity</td>
<td>293 (33.6)</td>
<td>69 (55)</td>
<td>&lt;0.001</td>
<td>n.s</td>
</tr>
<tr>
<td>Previous biliary events</td>
<td>66 (7.6)</td>
<td>15 (12)</td>
<td>0.09</td>
<td>n.s</td>
</tr>
</tbody>
</table>

yo: years old; ASA: American Society Anaesthesiologists classification; C-D: Clavien-Dindo classification

of patients diagnosed of acute calculous cholecystitis.
OR: odds ratio; CI: confidence Interval; yo: years old

Figure 1: Flow-chart. AC: Acute calculous cholecystitis.