MANAGEMENT OF ACUTE CHOLECYSTITIS IN A MEDIUM-SIZED CENTRE

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Management of acute cholecystitis in a medium-sized centre

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Gràcies a la Laia Falgueras per fer possible aquest treball.
1. ABBREVIATIONS

γGTP  Gamma-glutamyltransferase
AAC  Acalculus acute cholecystitis
AC  Acute Cholecystitis
AG  Acute Cholangitis
ALP  Alkaline Phosphatase
ALT  Alanine Aminotransferase
AST  Aspartate Aminotransferase
CT  Computerized tomography
OC  Open Cholecystectomy
LC  Laparoscopic Cholecystectomy
OR  Other researcher
CRP  C Reactive Protein
MR  Main researcher
MRI  Magnetic Resonance Image
RUQ  Right upper quadrant
STD  Upper range standard values
SD  Standard deviation
US  Ultrasounds
T-Bil  Total bilirubin
TG  Tokyo Guidelines
WBC  White blood count
2. ABSTRACT

Title: Management of acute cholecystitis in a medium-sized centre
Authors: Adrià Costa, MS; Laia Falgueras, MD.

Background: Cholelithiasis is a frequent gastrointestinal disease, and acute cholecystitis (AC) is one of its most frequent complications. Before Tokyo Guidelines (TG) for AC management, no consensus on how to diagnose and treat these patients was established. Despite having a low mortality rate, a meta-analysis reported a 3% of mortality before guidelines implementation. After TG, no studies clarified its improvement in terms of mortality and only few were carried out. Those studies demonstrated only a reduced length of stay in comparison. Authors concluded that further studies are needed. Additionally, no studies collecting AC data were found in our region. Finally, due to its chronic condition, cholelithiasis is a high burden disease all over, and AC management is expensive as well. This study may have an economic impact if it reveals that we could be more efficient treating these patients. Thus, this study pretends to analyse how our medium-sized centre manages AC, to compare our results with those obtained during pre-TG era, to create a large data base and finally to know which impact had TG on AC management.

Objective: This study aims to find the mortality rate of patients diagnosed and treated of AC according to TG recommendations at General Surgery department of our centre. We expect a 2.5% mortality rate, demonstrating a better survival rate than before TG era. Length of stay and surgical-related complications will be also evaluated.


Methods: We will need a sample of 82 patients if we expect a 2.5% of mortality rate. Non-probabilistic, consecutive method of recruitment will be used. TG diagnostic criteria will be applied for these patients and they will be categorized into three severity groups with different treatment per each one. Statistical analysis will be adjusted by possible confounding variables.

Keywords • acute cholecystitis • mortality rate • criteria • hospital stay • sequels
3. BACKGROUND

Gallbladder stones disease, also known as cholelithiasis, is a common, chronic and recurrent hepatobiliary disease. Due to an impaired cholesterol metabolism and reduced gallbladder motility - among other factors - gallstones are formed in the gallbladder or in the bile ducts. Even though it is present worldwide, its prevalence varies by region\cite{10,11}. In Western countries it has a prevalence of 7.9\% in men and 16.6\% in women\cite{8}, with a lower rate in Asian and African countries. As a result of its chronic and recurrent status, it has an economic impact and a sustainable burden, becoming one of the most expensive diseases among gastroenterology pathologies, exceeding 5 billion dollars in the United States\cite{10}.

As above-commented, women suffer more from this disease as female gender is one of the main risk factors to develop gallstones, especially during fertile age and pregnancy, when gallbladder evacuation is impaired. However, high prevalence has been observed among cirrhotic men as well. The bile excretion to the duodenum is reduced by age due to motility’s reduction, becoming a common disease especially in the elderly. Obesity also implies an impaired cholesterol metabolism, involving a high prevalence in those patients. Drugs - like oestrogens - , diet or genetic factors are also known as risk factors to develop gallstones\cite{10,11}.

The composition of gallstones varies: cholesterol stones are up to 75\% of the total, followed by pigment stones (less than 30\% of cholesterol in their composition) and mixed stones. Once the gallstone is formed, it may shrink, grow or remain the same size for decades. It may have a widely range of on-set presentation, and many patients (up to 80\%) will not experience any symptom through their lives\cite{10}. Normally, it presents with abdominal discomfort and indigestion, but those symptoms are weakly specific and both symptoms can be seen in other gastrointestinal diseases. It is not unusual that the first diagnosis is made by chance during any other image exploration.
of the abdomen, such as a CT scan or US imaging. Among all the patients suffering from gallstone disease, only 3-6% will develop further complications, such as acute cholecystitis, acute cholangitis, jaundice and pancreatitis[15]. Amongst all of the complications that these patients can suffer, acute cholecystitis is the most common and one of the most frequent diseases among gastrointestinal-related attended visits to our emergency department. AC is an acute inflammatory disease of the gallbladder after obstruction of the cystic duct. Up to 1-3% of patients with abdominal pain can be account for AC, and around 10% of patients with symptomatic gallstones will develop AC during their life, being both more common and severer with age (20.9% above 50 years)[8,10].

Up to a 90% of the cases of AC are related with gallstones, known as cholecystolithiasis[18], but other causes may develop it as well: helminthic infection (ascariasis) is one of the most frequent causes of AC in developing countries. AIDS is also a risk factor as long as patients suffering from AIDS usually have abnormal liver functions - i.e. AF is elevated in blood tests - and dilatation of cystic is observed by US and CT scans. Drugs may be involved in some AC such as oral contraceptives, though its relation is discussed, ceftriaxone (only during treatment due to augmented precipitated calcium salt in bile) and fibrates[8,11,21]. Finally, acalculous acute cholecystitis (AAC) is also an acute condition involving gall bladder inflammation but its causes are completely different from those of calculous AC. Normally, it’s due to a local ischemia of the gall bladder in elderly or severe injured patients with other illness. Diabetes and myocardial infarction have been proved as causes of AAC and especially patients who are admitted to ICU for over a long period tend to develop this condition[8,27].

Once a stone is impacted on the neck of the gallbladder, it goes through different phases if treatment is not rapidly applied: till day four, only oedema is visible in its
walls, evolving to haemorrhage and necrosis of the wall and vascular thrombosis after 96 hours of the on-set. After seven days, suppurated cholecystitis and pericholecystic abscesses are present, increasing its mortality\textsuperscript{[17]}. Advanced phases are avoidable with early detection using image techniques, proper physical exploration and a administrating a correct treatment, saving a high amount of money in further procedures\textsuperscript{[8]}. Yet, they can be lethal when severe.

Further complications may occur: perforation of the gallbladder, biliary peritonitis and biliary fistula to the duodenum, Mirizzi Syndrome\textsuperscript{1} - though infrequent - and gallstone ileus, causing mechanical obstruction at the ileocecal valve\textsuperscript{[1,8,21]}, resulting in a higher mortality.

AC prognosis may vary depending on its severity\textsuperscript{[4]} though mild and moderate cases have low mortality rate. Elderly patients and those with comorbidities tend to have higher mortality than healthy, young patients\textsuperscript{[17]}. AG findings on a AC patient are considered as bad prognosis factors\textsuperscript{[15]}. Postoperative infections were the main cause of death after surgery before 1980 such as ascending cholangitis, hepatic abscess and sepsis. Nowadays, mortality has decreased since the proper use of antibiotics and general supportive care was established\textsuperscript{[9,24,26]} and these patients have the same expectancy of life as other patients have.

For decades, AC diagnosis has been established by clinical findings, local and systemic inflammatory signs and laboratory tests\textsuperscript{[8,25]}. Its typical presentation is constant pain for hours and tenderness in the RUQ, normally with a previous history of pain on the same region. Murphy’s sign\textsuperscript{2} may be present in these patients whereas blood tests show elevated PCR, elevated WBC and fever. None of them were completely specific of AC,

\textsuperscript{1} Mirizzi Syndrome: Obstruction of common hepatic duct due to an impacted stone in Hartmann’s pouch
\textsuperscript{2} Murphy sign: Inspiration interruption by pain or palpation in RUQ
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and some of them may be present in other acute abdominal causes that have to be ruled out. After new image techniques utilisation, such as high-resolution CT scan and US scan, it was far easier to diagnose a gall bladder dysfunction. Actually ultrasound scanning became a fast, non-expensive choice for these patients upon their arrival at emergency department\(^2,8\). Even though it is an observational-dependent technique, it is really useful to observe pericholecystic fluid (fluid around the gall bladder), distended gall bladder wall and oedema. CT scan may be used to rule out other acute abdomen causes in uncertain diagnosis. Despite having these techniques, no radiology criteria were established to properly diagnose acute cholecystitis, leading every centre to use their own criteria.

Before the publication of Tokyo Guidelines in 2007, there was weak consensus on diagnosing criteria and treatment of acute cholecystitis for the above-mentioned\(^3,6,19,25\). There were no international standards of managing these common acute pathologies: open cholecystectomy used to be the best procedure to solve the condition after the acute phase\(^20,26,28\). Actually, most of studies regarding AC have always carried out in a different way that we are proposing: to prove out whether LC was better than OC, which has been the gold standard lately\(^9,14,20,26,28\). LC proved to reduce the mortality and length of stay by itself due to a smaller wound (as the intraabdominal procedure is the same for both OL and LC\(^7,24\). Overall, about 20% of patients with AC need emergency surgery, especially when their condition is deteriorated and generalised peritonitis or emphysematous cholecystitis are present\(^3,5,17\). Percutaneous cholecystostomy has been proposed as a minimally invasive procedure in moderate and severe cases. Those patients have a higher risk from major surgery and they need to solve the acute phase before to undergo to laparoscopy. It has been evidenced that this procedure may reduce mortality\(^7,9\).
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To settle down universal criteria and management, experts of Japanese Hepatobiliary Association proposed an international consensus in 2005: the Japanese clinical guidelines for acute cholecystitis and acute cholangitis\(^{[19]}\). Then, in further revisions, they published Tokyo Guidelines in 2007, reaching an 84'9\% of sensitivity in diagnosing AC and becoming the international reference ever since\(^{[2]}\). However, potential shortcomings were present according to some authors so these guidelines needed further evidence\(^{[6]}\). Thus, they carried out a new study in order to upgrade the Tokyo guidelines, publishing TG 2013\(^{[2,3]}\).

They finally proposed high sensitive diagnosing criteria for AC using clinical features, blood test data and image findings. To reach that high sensitivity of diagnosing AC, they excluded patients with AG findings or other causes of AC, i.e acalculous cholecystitis, which is not taken into consideration in their publication either.

**Table 1 Diagnostic criteria of AC. Adapted from \(^{[2]}\)**

<table>
<thead>
<tr>
<th>A. Local signs of inflammation</th>
<th>B. Systemic signs of inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Murphy’s sign</td>
<td>1) Fever (&gt;37'5(^\circ)C)</td>
</tr>
<tr>
<td>2) RUQ mass / pain / tenderness</td>
<td>2) Elevated CRP ((\geq 3)mg/dl)</td>
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<tr>
<td></td>
<td>3) Abnormal WBC count</td>
</tr>
</tbody>
</table>

**C. Imaging findings characteristic of AC\(^*\)**

**Definite diagnosis:**

1) One item in A and one item in B are positive
2) C confirms the diagnosis when AC is suspected clinically

\(^*Imaging\ finding\ of\ AC:\

**US:**
- Sonographic Murphy sign
- Thickened gallbladder wall
- Enlarged gallbladder
- Incarcerated gallstone
- Sonolucent layer in the gallbladder wall, striated intramural lucencies and Doppler signals

**MRI:**
- Pericholecystic high signal
- Enlarged gallbladder
- Thickened gallbladder wall

**CT:**
- Thickened gallbladder wall
- Pericholecystic fluid collection
- Enlarged gallbladder
- Linear high-density areas in the pericholecystic fat tissue
- Non-visualized gallbladder with normal uptake and excretion of radioactivity
- Rim sign (augmentation of radioactivity around the gallbladder fossa)
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Furthermore, they divided AC into 3 sub-grades depending on its severity - mild, moderate and severe.\(^2,4,19\). It is all summed up in Table 2.

**Table 2 AC Grades of Severity Criteria. Adapted from [2]**

<table>
<thead>
<tr>
<th>Grades</th>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>Moderate -</strong></td>
<td>3 Whenever it is accompanied by any one of the following conditions:</td>
</tr>
<tr>
<td><strong>Grade II AC</strong></td>
<td>- Elevated WBC count (&gt;18000/mm(^3))</td>
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<tr>
<td></td>
<td>- Palpable tender mass in RUQ</td>
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<td></td>
<td>- Duration of complaints &gt; 72h</td>
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<td></td>
<td>- Marked local inflammation: Biliary peritonitis Pericholecystic abscess,</td>
</tr>
<tr>
<td></td>
<td>Hepatic abscess, Gangrenous cholecystitis, Emphysematous cholecystitis</td>
</tr>
<tr>
<td><strong>Severe - Grade</strong></td>
<td>Whenever it is accompanied by dysfunctions in any one of the following</td>
</tr>
<tr>
<td><strong>III AC</strong></td>
<td>organs / systems:</td>
</tr>
<tr>
<td></td>
<td>- Cardiovascular dysf. (hypotension requiring treatment with dopamine or</td>
</tr>
<tr>
<td></td>
<td>dobutamine)</td>
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<tr>
<td></td>
<td>- Neurological dysf. (decreased level of consciousness)</td>
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<tr>
<td></td>
<td>- Respiratory dysf. (PaO(_2)/FiO(_2) ratio &lt;300)</td>
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<tr>
<td></td>
<td>- Renal dysf. (oliguria, creatinine &gt; 2.0 mg/dl)</td>
</tr>
<tr>
<td></td>
<td>- Haematological dysf. (platelet count &lt; 100.000/mm(^2))</td>
</tr>
<tr>
<td><strong>Mild - Grade I</strong></td>
<td>When AC does not meet any of the above mentioned criteria (grade II or</td>
</tr>
<tr>
<td><strong>AC</strong></td>
<td>grade III)</td>
</tr>
</tbody>
</table>

Likewise, they established a pattern of treatment. Whereas antibiotics and general supportive care (intravenous rehydration fluid therapy, PPIs\(^3\), anticoagulants and analgesia) were applied to every grade, specific treatment was proposed for each grade of severity\(^4\).

Each option of treatment is chosen depending on patient’s condition, number of hours since the onset, blood parameters and so on. Whereas percutaneous cholecystostomy is preferable for those patients with comorbidities, early laparoscopy before the first

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\(^3\) PPIs: Proton-pump inhibitor

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72hrs is the best surgical choice, as it is associated with less complications, reduced length of stay and less risk of conversion to open laparotomy\textsuperscript{[18]}.

To sum up all of the treatment options, a flowchart (Figure 1) from TG13 is provided.

**Figure 1 Treatment options according to Grade and Response\textsuperscript{[12]}**

As an international consensus, it helped to settle knowledge and to start a common way to manage these pathologies. Further studies are still needed to assess whether the survival rate following these guidelines improved or not. Only few studies were published after the consensus so we do not have post-Tokyo 2013 data to compare with yet. A Japanese author weakly evidenced that only days of hospitalisation were reduced after guidelines, but concluded that further studies to evaluate a large series of patients were needed, also to prove a reduced mortality\textsuperscript{[13]}. For that reason and to make a good comparison between before and after TG publication, we had to focus on
Kimura’s meta-analysis data which studied large series of patients[^16]. It will be our data reference. We agreed its mortality rate obtained were a good standard to compare our results with.

As above mentioned, Kimura et al published in 2013 a collection data of patients diagnosed and treated of acute cholecystitis from 1958 to 2009, before the implementation of TG (see Annex 1)[^16]. Logically, we had to focus on the newest studies as good references as both the surgical treatment and the conservative management of these patients evolved considerably since 1958. The newest studies got a mortality rate between 0% and 3%[^16]. That value is an average of individually obtained in each group of severity (mortality was far higher in group 3 patients than in mild - moderate group).

To better understand how it is possible to get a 0% mortality rate in such an acute condition, we revised those studies: we found out that their sample selection was quite restricted and they only selected the better patients for studying. Actually, it was the main bias of that study.

We considered that 3% should be our reference number, and we expect a reduced mortality rate with this study. We want to prove that TG recommendations have improved this outcome and they are useful and helpful for physicians to handle this condition worldwide.

What studies did prove was that the diagnosing accuracy using TG 2013 were far higher than without them[^3].
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Something that attracted our attention was that there were not any studies evaluating these outcomes in our centre, neither in Spain. So we had not data of how we treated these patients and, specifically, how TG would have improved AC management in our department. This project also aims to collect more data about AC patients in our medium-sized centre, becoming one of the first hospitals to start a data base, along with Tarragona’s Hospital Joan XIII, who recently started a multi-centric study to recollect data of AC. Unfortunately, we do not have their results yet. Additionally, as it is a common and chronic disease the total burden spent on it is really high\(^8,10\). Based on last year prevalence data of our centre, we treated 84 AC with an average of 7’65 days of hospitalisation per each patient. According to ICS financial department, every day of hospitalisation costs 557€ (including treatments such as antibiotics, general supportive care and personnel), daily hepatobiliary blood test costs 47’85€ and Ultrasound scan, 62€. In case an abdominal CT would be needed to rule out other diagnoses of acute abdomen, it costs 95€. Leaving aside which grade the patient is categorized into, those costs are equal for each patient. Then, in case a percutaneous cholecystostomy would be necessary, total price is raised in 145€. Finally, for those who have to undergo to a laparoscopic cholecystectomy, this procedure is rated in 5548€ (no conversion to OL data is available).

With a mean of 7’65 days in our in-patient clinic (with general supportive care and antibiotics, fluids, drugs), our patients will need at least a US scan to be diagnosed, one pre-surgery blood test (supposing an invasive treatment is needed) and at least two post-surgery/treatment blood tests to check if condition is improving. In case they undergo to surgery - and no further complications after the early laparoscopic cholecystectomy appear - the total cost of their stay is 10,014’6€. In that price, we assumed diagnosis was fully accurate since the first moment using TG. We could have got to rule out other diagnosis with a CT scan, diagnosed that acute abdomen wrongly,
or to face complications during hospitalisation.

Everything results in more days of hospitalisation, more blood test and maybe other procedures. Overall, the total cost could have been much higher. Taking into account we treated 84 patients with AC last year, the total burden spent on it was 841,226€. Neither complications nor readmissions were contemplated.

Furthermore, as these procedures are not risk free patients may develop potentially complications. These complications may be related with previous comorbidity of our patients or surgery-related[17]. For instance, one of the surgical complications - even more frequent with LC than OC - is the biliary tract lesion. It is not frequent (0.4% to 0.6% of total LC) but it has an important reduction of health quality[23]. Thus, we pretend to collect all of the data regarding complications during the days of hospitalisation, and we will describe them using Dindo-Clavien Classification for Surgical Complications (see Annex 2)[22]. We aim to be more conscious of all possible complications in order to increase our caring towards these patients.
4. JUSTIFICATION

We consider this study as the initial tool to evaluate how have been implemented the international guidelines recommendations for an AC and how our department is managing that pathology. With this study we will highlight what we do correctly and especially what we can improve in further patient management.

Our first aim is to demonstrate that TG are useful for physicians and if they made an improvement to get better outcomes since its publication. Therefore, we may point whether we are following correctly TG or not (in terms of diagnosis and treatment).

Achieving better outcomes values is not our only aim nowadays. The total burden spent on this condition in our centre is really high, as we have seen before. An improvement of resources management is a latter aim if we found out that we could be as good as we can at managing AC but also doing it with a better resources handling.

Additionally, we pretend to describe the most frequent complications our patients suffer during hospitalisation. Having a complete list of most prevalent complications may change our point of view of AC. In case most of the complications appeared the first hours or days of the hospitalisation - i.e. grade 3 patients -, we should improve our caring towards them during that time and also apply an exhaustive monitoring at special units (UPIC)\(^4\) trying to prevent those possible complications, resulting in reduced morbidity, better quality of life and less budget.

Therefore, being one of the first studies in our region to evaluate those outcomes, we may set a national precedent to encourage other departments to start other projects as well, comparing and sharing our results in further national congresses.

Our last aim is to excel in AC patient management. We may start new projects as clinical protocols together with emergency department or radiology department, compare results worldwide and be a national reference in its management.

\(^4\) UPIC: Unitat polivalent d’alta intensitat de cures
5. BIBLIOGRAPHY


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6. HYPOTHESIS

Patients diagnosed and treated of acute cholecystitis as TG recommends have lower mortality than those who were not managed following these guidelines.

7. OBJECTIVES

7.1 Main objective

This study aims to find the mortality rate of patients diagnosed and treated of acute cholecystitis according to TG recommendations at General Surgery department of our centre in order to compare these results with those obtained from other studies before TG implementation[16].

7.2 Secondary objectives

- To evaluate the length of stay of these patients at our department and compare that outcome with other studies.
- To describe a list of the surgical-related complications our patients suffer during their hospitalization using Dindo-Clavien classification (see Annex 2)[22].

8. METHODS

8.1 Study Design

It will be a cross-sectional study executed at a medium-sized centre, Hospital Universitari Doctor Josep Trueta in Girona.

8.2 Participants

Patients admitted to Hospital Universitari Doctor Josep Trueta in Girona, from February 2016 to February 2017 with diagnosis of acute cholecystitis (Table 1) evaluated by an on-call surgeon or resident of general surgery department.
8.3 Sample size

Patients diagnosed with AC are our reference population. Assuming an alpha risk of 0.05 and a precision of +/- 0.005 units for an estimated proportion of 0.025, our sample size is calculated to be of 83 patients (It has been anticipated a dropout of 10%). We estimated this sample size using an online tool - Granmo® Calculator- taking into consideration that we treated 84 patients with AC last year. For that reason, we will have to spend 12 months collecting our sample.

8.4 Sample collection

A non-probabilistic consecutive method of recruitment will be used. On-call surgeons/residents of general surgery department will collect the data, who will also give proper information to the patient or his/her relatives about the study and its importance, the data confidentiality and the voluntary aspect of it (see Annex 3.1 and 3.2), inviting them to participate.

Surgeons will recollect data after 24hrs upon patient’s arrival (those who die within the 24th hour will not be included) using the case report form (see Annex 4); after discharge (to describe complications, if any) and after 30 days of the onset to register whether he or she needed readmission within a month. We consider that readmission after a month will not be related with the acute episode.

Inclusion and exclusion criteria will be applied for those patients (see Table 3). Only those who come directly to our hospital will be part of our study as clinical management may differ from one centre to another, and we only want to evaluate how our centre is managing AC. Among exclusion criteria, patients diagnosed with acute cholangitis will not be included in our study. AG management differs from AC, and its mortality is higher than AC patients. It is true that some patients come with
features of both conditions at the same moment. These patients will not be included neither, as we want to focus only on acute cholecystitis management and their results. Also, malignancy of biliary related structures is out of our interest as some procedures cannot be applied to these patients.

**Table 3 Inclusion and Exclusion criteria used in our sample collection**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients who came to our centre directly, not referred.</td>
<td>1. <strong>Death</strong> during the first 24hrs since the moment the patient came to the emergency department and is diagnosed with acute cholecystitis</td>
</tr>
<tr>
<td></td>
<td>2. Laboratory data: abnormal liver function tests Jaundice, T-Bil&gt;= 2 (mg/dL)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>ALP (IU) &gt; 1.5 x STD</em></td>
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<td></td>
<td><em>yGTP (IU) &gt; 1.5 x STD</em></td>
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<td></td>
<td><em>AST (IU)&gt; 1.5 x STD</em></td>
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<tr>
<td></td>
<td><em>ALT (IU) &gt; 1.5 x STD</em></td>
</tr>
<tr>
<td>3. Biliary dilatation, either observed with US or CT Scan</td>
<td>3. Biliary dilatation, either observed with US or CT Scan</td>
</tr>
<tr>
<td>4. Evidence of stricture, stone or stent in the biliary tract</td>
<td>4. Evidence of stricture, stone or stent in the biliary tract</td>
</tr>
<tr>
<td>5. Diagnosis of AAC</td>
<td>5. Diagnosis of AAC</td>
</tr>
<tr>
<td>6. Known or suspected cephalic pancreatic malignancy</td>
<td>6. Known or suspected cephalic pancreatic malignancy</td>
</tr>
<tr>
<td>7. Known or suspected biliary tract malignancy</td>
<td>7. Known or suspected biliary tract malignancy</td>
</tr>
<tr>
<td>8. ASA PS ≥ 5</td>
<td>8. ASA PS ≥ 5</td>
</tr>
<tr>
<td>9. &gt;7 days of the onset</td>
<td>9. &gt;7 days of the onset</td>
</tr>
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</table>
9. VARIABLES AND MEASUREMENTS

9.1 Independent variables

First of all, an on-call surgeon or resident will evaluate the patient at emergency department and decide whether he or she fulfils the diagnosing criteria of AC (Table 1). Secondly, patients will be classified in three groups (grade I, II and III) according to the severity grading in the Tokyo guidelines criteria using Table 2. These patients will be classified upon their arrival with the help of blood test performed at emergency department (CPR, WBC count), vital signs recollected by an emergency nurse (as temperature ≥37.5°C), US findings and physical examination (RUQ mass/pain/tenderness and Murphy sign) by on-call surgeon. If there is any doubt with correct diagnosis, a CT should be performed. Once classified, specific treatment will be administrated by surgeon (Figure 1).

Antibiotics and general supportive care will be used in every group. We expect to find different mortality rate depending on the grade, with a higher mortality in grade 3 - the most severe. This variable is defined as nominal, categorical variable.

9.2 Dependent variables

Our main outcome is Mortality, a categorical nominal dichotomous variable. We defined it as death past >24hrs since the first moment a surgeon visits the patient. It will be calculated as a percentage and we expect a different percentage in each group (higher percentage in grade 3). It will be recollected by the responsible surgeon who will write it down on the form (Annex 4).

A secondary dependent variable will be also recorded: Length of stay, a discrete quantitative variable, it will be calculated with the mean ± SD of the days our patients are hospitalized at our department. Finally, another secondary dependent variable will be recorded: types of surgical complications during hospitalisation, a categorical
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qualitative variable. It will be categorized into 5 groups (from I to V) according to Dindo-Clavien\(^{[22]}\). Different percentage is expected per each grade of severity.

**9.3 Co-variables**

Besides this, we pretend to create a data base collecting specific information of every patient diagnosed with AC in our department for further studies.

Following variables will be also recorded using the case report form (see Annex 4):

**Sociodemographic data**

- **Gender** (Male or Female)
- **Age** (in years)

**Anthropomorphic data**

- **Weight** (kg) and **Height** (m). Both variables will be recorded with naked feet at emergency department using a calibrated scale by a nurse.
- **BMI** (kg/m\(^2\)).

**Vital signs** (data collected upon arrival at emergency department by a nurse)

- **Pulse rate** (beats per minute)
- **Respiratory rate** (number of breaths per minute)
- **Blood Pressure** (mm of Hg). It will be measured with an automatic, calibrated periodically aneroid.
- **Temperature** (grades Celsius, armpit). *Fever considered ≥ 37'5ºC*

**Local inflammatory signs** (registered by on-call surgeon/resident after physical examination)

- **RUQ mass / pain / tenderness**, recorded as presence or absence.
- **Abdominal complaints over 72h**, recorded as presence or absence.
Systemic inflammatory signs (collected by on-call surgeon/resident according to baseline blood test performed upon arrival at emergency department)

- Elevated CPR, recorded as presence or absence. Normal values of CPR in our centre are from 0-0.5 mg/dL.
- Elevated WBC count, recorded as presence or absence. Normal values of leukocytes in our centre are from 4.4-11.3 K/mcL (K as 1000 units).
- Image findings characteristics of acute cholecystitis, recorded as presence or absence.

Type of treatment used (Observation, Cholecystostomy, Cholecystectomy). Decided by the on-call surgeon/resident according to TG2013 and patient’s condition.

Switched grade to severer one, recorded as yes or not by the surgeon.

Open laparotomy conversion from a LC, recorded as yes or not by the surgeon performing the surgery.

Readmission before day 30, recorded as yes or not by the surgeon who are in charge of that patient.

American Society of Anaesthesiologists Physical Status - ASA PS -. It will be collected by the surgeon who performs the surgery, but it is assigned by operating theatre’s anaesthesiologist.

10. STATISTICAL ANALYSIS

Results of data collected will be presented as percentages for all categorical variables (gender, RUQ mass, complaints >72hrs, elevated PCR, elevated WBC count, image findings characteristics of AC, switched grade to severer one, OL conversion, readmission <30 days, ASA PS, type of treatment used and our main variables: grades of severity, mortality and type of surgical complications);
The mean ± SD will be used for discrete quantitative variables (such as pulse rate and respiratory rate) and also for continuous quantitative variables (such as days of hospitalization, age, blood pressure, height, weight, BMI, temperature) assuming all of them have a normal distribution.

To study the relation between categorical variables (grades of severity and mortality; grades of severity and types of surgical complications) a Pearson’s chi-squared test will be used. For our first secondary objective, we will compare grades of severity and days of hospitalization. As they are a categorical variable and a quantitative variable, ANOVA will be used.

In addition, as we will use qualitative variables for our main proposal and third proposal, multivariate logistic regression analysis will be performed adjusting for co-variables. General linear model adjusted for co-variables will be used for analysis between days of hospitalisation and grades of severity. Significance for all analysis will be set at a P value <0.05.

11. STRENGTHS AND LIMITATIONS

This study is merely descriptive so that there are some inherent limitations to this type of design. First of all, we cannot make any direct causal association between variables (i.e. mortality and severity grade) but we could propose further hypothesis based on this study, especially with the large database we want to create. Secondly, our centre were not collecting data about AC - neither before nor after TG publication - so we had to suppose we would have got the same mortality rate as the reference studies that we based our comparisons with. We cannot point whether we treated them better after TG recommendations or which grade of improvement made these guidelines to our centre. To obtain the most accurate value in our results, we selected patients
Management of acute cholecystitis in a medium-sized centre

according to the criteria they used in their studies.

We assumed that our population selection criteria are quite restricted, but we tried to avoid as many confounding factors as possible. It will not be as representative as we want to: some patients have a mix of clinical or laboratory findings between AC and AG. Thus, this study will be representative for pure AC patients only, but not for those who present other clinical or laboratory findings. Furthermore, the sample size of this study is not as large as others, but we pretend to create a huge data base for further studies to analyse their data. Additionally, as long as we are going to collect data from only one centre our results maybe not as representative as if we were collecting data as a multicentre study.

In order to avoid further informational bias we had various meetings discussing about the best case report form and how to collect all the data. We tried to use hard points like dichotomical objective variables. As AC is an acute condition, sometimes it is complicated to register all the data when they come to emergency department, so we accept that some data will not be completely collected. We assume that height and weight data may not be collected for every patient as it is not a daily routine in emergency department. Even though to answer our hypothesis - which is based on mortality rate - we will not face that problem as death after 24hrs is easy to register. Additionally, Hawthorne effect may be present in our study as we pretend to register how we are managing an acute condition as a department, making everyone more prone to intensify their caring towards patients.

12. ETHICAL CONSIDERATIONS

This study will be carried out accomplishing the principles of the Helsinki Declaration (last revision in 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and it will be presented to the Clinical Research Ethical Committee (CEIC) of the Hospital
Universitari Doctor Josep Trueta who will assess whether this study fulfils the required criteria for being approved. Furthermore, this study respects confidentiality issues as all of the recollected data will be treated according to the Spanish Organic Law 15/1999 de 13 de Diciembre, de Protección de Datos de Carácter Personal. According to Law 41/2002, de 14 de Noviembre, Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica, every single patient - or their relatives, in case a patient would not be able to be informed for him/herself - will be properly informed with the attached information sheet and encourage them to sign up the informed consent (see Annex 3.1 and Annex 3.2). Personal information will not appear either in the database or in the results’ discussion. Every patient will be codified on the data base to maintain their anonymity. Investigators of this study declare that there are no conflicts of interests.

13. FEASIBILITY

This study will take place in a medium-sized centre who has all the features we need to carry it out. It has a 24 hours working emergency, surgery and radiology (in case a CT would be needed) department with on-call physicians and on-call residents. Budget will not be a huge problem to carry out this study as most of the costs are due to translation, results publication and attendance to national congress to share our results with other surgeons. Furthermore, no additional tests have to be performed to register desirable data as US and blood tests are both necessary to diagnose appropriately this condition. We do not need to buy any new equipment neither. Additional personnel - except from a statistician - is not needed (on-call surgeons will recollect the data). We focused on establish narrow selection criteria and specific outcomes to avoid misunderstandings once the surgeon is asking about patient information and fulfilling the form (Annex 4).
For all above-mentioned, we considered that it is not really complicated to start this study at our department.

14. IMPACT OF THE STUDY TO THE NATIONAL HEALTH SYSTEM

We consider that AC management needs revision. We should have a proper study monitoring such variables and concluding firstly if TG recommendations were well implemented in our department and secondly if it helped us to treat better these patients. Creating a database will also help us not only to contribute to literature with evidence but also to set a precedent for further studies. From administrative and financial point of view, this study may have a positive economic impact if it determines that we managing our resources well. If we follow what evidence said about TG implementation, we should get a reduced mortality and length of stay, which it results directly in a less budget. Yet, if it determines the opposite, a full revision of TG in our department will be needed in order to get those outcomes values and finally reduce the costs.

15. WORKING PLAN

Initial Phase (Phase 0)
After bibliographic research and protocol elaboration, we will review the protocol in order to identify possible misspellings, statistical errors or other mistakes. We will present the study to the CEIC for approval.

Coordinating phase (Phase 1)
Main researcher will organise a meeting with other involved researchers of the department to explain the aims of this study. Methods and design will be discussed and MR will emphasise how to properly collect patient’s data using the case report form.
Management of acute cholecystitis in a medium-sized centre

Also, MR will assign two responsible researchers to fulfil the data base. We will have another meeting with emergency department nurses to explain them our study and to ask them to collect vital signs, height and weight of every patient with suspicion of AC.

Data Collection (Phase 1)

During 12 months, on-call surgeons and on-call residents will recollect the data of every patient that fulfils the criteria of our study. The first time they will do it will be twenty-four hours after arrival at emergency department. They will use the case report form (Annex 4) that day. At the moment of the discharge, researchers will register whether patients developed complications or not and in case they got any complication, it will be described on the form. Within the month, if a patient was readmitted to our department, researchers would also write it down on the form.

Every three months, we will organise following coordinating meetings where MS will present the updated data base to all the team to follow up.

Data analysis (Phase 2)

Statistician consultant will be clearly involved in this stage. IBM Statistical Package for the Social Sciences (SPSS) for Windows® will be used for statistical analysis.

Results interpretation, discussing and publication (Phase 3)

Everyone will be involved in this stage. Discussions among group will take place before results publication. It will take 4 months: 1 months for results interpretation and discussion, two for paper elaboration and revision and the last one to publish our paper.
**16. CHRONOGRAM**

<table>
<thead>
<tr>
<th>Months (2015)</th>
<th>September</th>
<th>October</th>
<th>November</th>
<th>December</th>
</tr>
</thead>
</table>

**PHASE 0. Researchers: Laia Falgueras and Adrià Costa**

- Bibliographic research
- Protocol Elaboration
- Identify possible errors
- Evaluate the protocol
- Present the protocol to the ethical committee

|---------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

**PHASE 1. Researchers: MR and OR**

- Team formation
- Data collection

<table>
<thead>
<tr>
<th>Months (2017)</th>
<th>March</th>
<th>April</th>
<th>May</th>
<th>June</th>
<th>July</th>
</tr>
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**PHASE 2 and PHASE 3, Researchers: MR and OR**

- Statistical analysis
- Results interpretation
- Paper elaboration and revision
- Paper publication and Results dissemination
### 17. BUDGET

<table>
<thead>
<tr>
<th><strong>Staff</strong></th>
<th><strong>Costs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Meetings &amp; Formation</td>
<td>70 €</td>
</tr>
<tr>
<td>Prints</td>
<td>20 €</td>
</tr>
<tr>
<td><strong>Subtotal:</strong></td>
<td><strong>90 €</strong></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th><strong>Statistical Analysis</strong></th>
<th><strong>Costs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>35€/hr; 3 hours per day, 2 days/week per 4 weeks</td>
<td>840 €</td>
</tr>
<tr>
<td><strong>Subtotal:</strong></td>
<td><strong>840 €</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Travel and subsistence costs</strong></th>
<th><strong>Costs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>National congress fee (RNHPBP&lt;sup&gt;5&lt;/sup&gt;, Sevilla 2015)</td>
<td>305 €</td>
</tr>
<tr>
<td>National congress accommodation</td>
<td>206 €</td>
</tr>
<tr>
<td>National congress traveling</td>
<td>200 €</td>
</tr>
<tr>
<td>International congress fee (13&lt;sup&gt;th&lt;/sup&gt; World Congress of IJHPD&lt;sup&gt;6&lt;/sup&gt;, Geneva 2018)</td>
<td>850 €</td>
</tr>
<tr>
<td>International congress accommodation</td>
<td>250 €</td>
</tr>
<tr>
<td>International congress traveling</td>
<td>250 €</td>
</tr>
<tr>
<td><strong>Subtotal:</strong></td>
<td><strong>2,061 €</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Publication</strong></th>
<th><strong>Costs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper revision</td>
<td>200 €</td>
</tr>
<tr>
<td>Paper publication (IJHPD&lt;sup&gt;7&lt;/sup&gt;)</td>
<td>450 €</td>
</tr>
<tr>
<td><strong>Subtotal:</strong></td>
<td><strong>650 €</strong></td>
</tr>
</tbody>
</table>

**TOTAL: 3,641 €**

---

<sup>5</ sup> RNHPBP2015: Reunión Nacional de la sección de cirugía Hepatobiliopancreática de la A.E.C.

<sup>6</ sup> IHPBA: International Hepato-Pancreato-Biliary Association

<sup>7</ sup> IJHPD: International Journal of Hepatobiliary and Pancreatic Diseases
### 18. ANNEX

#### 18.1 ANNEX 1

*Figure 2 Results of the AC meta-analysis by Kimura et al, adapted from [16]*

<table>
<thead>
<tr>
<th>Author</th>
<th>Period/year</th>
<th>Country</th>
<th>Subjects</th>
<th>No. of cases</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer</td>
<td>1988-1994</td>
<td>USA</td>
<td>LC</td>
<td>246</td>
<td>4.49</td>
</tr>
<tr>
<td>Ratasoff</td>
<td>1990-1991</td>
<td>USA</td>
<td>LC</td>
<td>258</td>
<td>3.36</td>
</tr>
<tr>
<td>Gagic</td>
<td>1991-1992</td>
<td>USA</td>
<td>LC</td>
<td>93</td>
<td>6.86</td>
</tr>
<tr>
<td>Girard</td>
<td>1991-1992</td>
<td>Canada</td>
<td>LC</td>
<td>1491</td>
<td>0.63</td>
</tr>
<tr>
<td>Addison</td>
<td>1992-1993</td>
<td>UK</td>
<td>LC</td>
<td>236</td>
<td>4.66</td>
</tr>
<tr>
<td>Bediiriz</td>
<td>1993-1995</td>
<td>Turkey</td>
<td>LC</td>
<td>368</td>
<td>2.72</td>
</tr>
<tr>
<td>Gharabeh</td>
<td>1994-1999</td>
<td>Jordan</td>
<td>LC</td>
<td>204</td>
<td>0.6</td>
</tr>
<tr>
<td>Russo, MW</td>
<td>1994-2004</td>
<td>USA</td>
<td>LC</td>
<td>262,411</td>
<td>0.9</td>
</tr>
<tr>
<td>Papi</td>
<td>2004</td>
<td>Meta</td>
<td>LC</td>
<td>109</td>
<td>0.26-0.6</td>
</tr>
<tr>
<td>Giger</td>
<td>2005</td>
<td>System, rev.</td>
<td>LC</td>
<td>246</td>
<td>0</td>
</tr>
<tr>
<td>Johansson</td>
<td>2002-2004</td>
<td>Sweden</td>
<td>LC</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Al Salamah</td>
<td>1997-2002</td>
<td>Saudi Arabia</td>
<td>LC</td>
<td>311</td>
<td>0</td>
</tr>
<tr>
<td>Gursamy</td>
<td>2003</td>
<td>Meta</td>
<td>LC</td>
<td>220</td>
<td>0</td>
</tr>
<tr>
<td>Bozelliino</td>
<td>2008</td>
<td>USA</td>
<td>LC</td>
<td>1408</td>
<td>3</td>
</tr>
<tr>
<td>Lee</td>
<td>2005-2006</td>
<td>USA</td>
<td>LC</td>
<td>202</td>
<td>0.4</td>
</tr>
<tr>
<td>Gakecz</td>
<td>2000-2005</td>
<td>USA</td>
<td>LC</td>
<td>859,747</td>
<td>0</td>
</tr>
<tr>
<td>Grade</td>
<td>Definition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>Intervention not under general anesthesia.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>Intervention under general anesthesia.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication (including CNS complications)* requiring IC/ICU management.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Single organ dysfunction (including dialysis).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Multiorgan dysfunction.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suffix “d”</td>
<td>If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.
Full de informació sobre l’estudi

Títol de l’estudi: Maneig de la colecistitis aguda en un centre de tercer nivell

Propòsit i objectiu de l’estudi

El seu metge l’encoratge a participar en l’estudi sobre el maneig de la colecistitis aguda ja que vostè compleix els requisits per participar-hi. Vostè serà avaluat per un cirurgià al departament d’urgències que decidirà quin és el seu diagnòstic i quin és el millor tractament per vostè. Aquest estudi pretén avaluar el maneig del nostre centre per la vostra patologia. Estem avaluant els dies d’ingrés de mitjana així com, per ser una patologia no lliure de risc, la seva mortalitat i les complicacions que se’n deriven durant la seva estada.

Procediments de l’estudi

Un cop vostè hagi estat diagnosticat de colecistitis aguda pel cirurgià de guàrdia, aquest començarà amb les mesures necessàries per tractar-lo de la millor manera possible d’acord a les guies clíniques internacionals. En cas que fos necessari un procediment invasiu, com és una cirurgia urgent o una colecistostomia percutània, se li serà practicat un estudi preoperatori per avaluar la seva patologia i poder realitzar-la amb la màxima seguretat possible. A més, se li proporcionarà en tot moment l’atenció mèdica necessària juntament amb l’equip d’infermeria fins el moment de l’alta, així com estudis de sang de rutina per valorar la seva evolució. El cirurgià enregistrarà les dades que cregui oportunes que es derivin de la seva patologia per la futura investigació científica durant el moment de l’ingrés, així com en el moment de l’alta, per recollir si vostè ha experimentat qualsevol complicació.

Inconvenients i beneficis

En cas que la nostra hipòtesis sigui correcta, els pacients tractats com ho estem avaluant tenen una supervivència major respecte aquells tractats quan no existien aquestes guies, no observant-se grans inconvenients.

Participació

Ha de comprendre que la seva participació és totalment voluntària. Si decideix no participar, això no afectarà la seva assistència mèdica. Podrà abandonar l’estudi en qualsevol moment, així com demanar d’esborrar les seves dades recollides, sense que això afecti en cap moment a la seva assistència mèdica i sense haver de donar explicacions. Se li informarà de qualsevol canvi que tingui a veure amb aquest estudi, i el cirurgià responsable pot aturar la seva participació si ho creu oportú.
18.4 ANNEX 3.2

Consentiment informat per escrit

Títol de l’estudi: Maneig de la colecistitis aguda en un centre de tercer nivell

Jo, __________________________

He llegit la fulla d’informació que se m’ha entregat
He pogut fer pregunes sobre l’estudi
He rebut la suficient informació sobre l’estudi
He pogut parlar amb el Dr ________________________

Comprenc que la meva participació en aquest estudi és totalment voluntària.

Comprenc que la utilització de les meves dades és purament per a la investigació científica
Comprenc que puc retirar-me de l’estudi:

1- Quan vulgui
2- Sense donar explicacions
3- Sense que això repercuteixi en la meva atenció mèdica

Comprenc que puc sol·licitar l’eliminació de les meves dades en qualsevol moment

__________________________  __________________________
Data  Firma pacient

__________________________  __________________________
Data  Firma del investigador
18.5 ANNEX 4

Case report form for data collection:

Gender □ Male □ Female

Death after 24 of first visit □ Yes □ No

Length of stay of _____ days

Readmission before 30 days □ Yes □ No

1. Local signs of inflammation
   □ 1.1 Murphy’s sign
   □ 1.2 RUQ mass / pain / tenderness
   □ 1.3 Duration of complaints >72h

2. Systemic signs of inflammation
   □ 2.1 Fever
   □ 2.2 Elevated CPR
   □ 2.3 Elevated WBC count
   □ 2.4 and it is > 18000 cells / mm3

3. Imaging findings characteristics of AC, observed either by surgeon or radiologist
   □ 3.1 Yes □ 3.2 No

Date of birth ___ / ___ / _____ (DD/MM/YYYY)

Age ___ years

Height ___ metres

Weight ___ kilograms

BMI ___’___ kg/m²

Vital signs at emergency department, upon arrival:

Hearth rate ___ beats per minute

Respiratory rate ___ per minute

Blood Pressure Systolic ___ mm Hg
   Diastolic ___ mm Hg

Temperature ___ ° Celsius

Treatment used:

□ Observation

□ Cholecystostomy

□ Cholecystectomy
The patient was initially diagnosed as:

- Grade III, subgrade __
- Grade II (if any of the follows are marked: 1.2, 1.3, 2.1, 2.4)
- Grade I (if none of the above is marked)

Did your diagnosis grade switched to severer grade?  

Open laparotomy conversion after LC failure was needed  

**Severe - Grade III AC**  
Whenever it is accompanied by dysfunctions in any one of the following organs / systems:

- Cardiovascular dysf. (hypotension requiring treatment with dopamine or dobutamine)
- Neurological dysf. (decreased level of consciousness)
- Respiratory dysf. (PaO2/FiO2 ratio < 300)
- Renal dysf. (oliguria, creatinine > 2.0 mg/dl)
- Haematological dysf. (platelet count < 100,000/mm2)

Define the **grade of complications (Dindo-Clavien)**

<table>
<thead>
<tr>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>Grade V</th>
</tr>
</thead>
</table>

**Surgical complications according to [22]:**

- Renal
- Cardiac
- Neurological
- Gastrointestinal
- Respiratory
- Other (such as wound infection)

Type: _____
Management of acute cholecystitis in a medium-sized centre