

# Mortality Risk Estimation in Acute Calculous Cholecystitis: Beyond the Tokyo Guidelines

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## Research Article

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# Abstract

**Background:** Acute Calculous Cholecystitis (ACC) is the second most frequent surgical condition in Emergency Departments. The recommended treatment is the Early Laparoscopic Cholecystectomy, however, the Tokyo Guidelines (TG) advocate for different initial treatments in some subgroups of patients without a strong evidence that all patients will benefit from them. There is no clear consensus in the literature about who is the unfit patients for surgical treatment. The objective of the study is to identify the risk factors for mortality in ACC and compare them with Tokyo Guidelines (TG) classification.

**Methods:** retrospective unicentric cohort study of patients emergently admitted with and ACC during January 1, 2011 to December 31, 2016. The study comprised 963 patients. Primary outcome was the mortality after the diagnosis. A propensity score method was used to avoid confounding factors comparing surgical treatment and non-surgical treatment.

**Results:** the overall mortality was 3.6%. Mortality was associated with older age ( $68 \pm$  IQR 27 vs.  $83 \pm$  IQR 5.5;  $P < 0.001$ ) and higher Charlson Comorbidity Index ( $3.5 \pm 5.3$  vs.  $0 \pm 2$ ;  $P < 0.001$ ). A logistic regression model isolated four mortality risk factors (ACME): chronic obstructive pulmonary disease (OR 4.66;95%CI: 1.7-12.8  $P=0.001$ ), dementia (OR 4.12;95%CI: 1.34-12.7  $P=0.001$ ), age  $\geq 80$  years (OR 1.12;95% CI: 1.02-1.21  $P=0.001$ ) and the need of preoperative vasoactive amines (OR 9.9;95%CI: 3.5-28.3  $P=0.001$ ) which predicted the mortality in a 92% of the patients. The receiver operating characteristic curve yielded an area of 88% significantly higher than 68% ( $P=0.003$ ) from the TG classification. When comparing subgroups selected using propensity score matching with the same morbidity and severity of ACC, mortality was higher in the non-surgical treatment group. (26.2% vs. 10.5%).

**Conclusions:** mortality was higher in ACC patients treated with non-surgical treatment. ACME identifies high-risk patients. The validation to ACME could allow us to create a new alternative guideline to TG for treating ACC.

**Trial Registration:** retrospectively registered and recorded in Clinical Trials

(NTC 0474441).

## Background

Early laparoscopic cholecystectomy is the recommended treatment for acute calculous cholecystitis (ACC)<sup>1</sup>, but mortality in severe and/or fragile patients have promoted alternative initial non-surgical treatments (NST) such as percutaneous cholecystostomy (PC) or exclusive antibiotic treatment.

ACC does not have a high mortality rate, being 0.6 %<sup>1,2</sup> overall and 6% in severe cases<sup>3</sup> according to the highly influential Tokyo Guidelines (TG).

The optimal strategy for managing non-high-risk patients with ACC is laparoscopic cholecystectomy (LC), preferably carried out within two days from hospital admission<sup>6,7</sup>. However, despite the vast number of

publications on ACC, a definite management strategy for extreme cases remains elusive. Small samples, heterogeneity in selection and diagnosis, and assorted methodology flaws combine to obscure the definition of high-risk patients who may benefit from NST.

Using TG to dictate diagnosis, assessment, and treatment of ACC, it was expected that the vital prognosis would be greatly improved. Nevertheless, the mortality of ACC is still significant, and there is an acute need to select the best strategy for high-risk patients. There is no worldwide consensus regarding who is a high-risk patient to avoid an urgent cholecystectomy when the diagnosis of ACC is established.

In the quest to define the high-risk patient, a collection of aggregate scores (APACHE, ASA<sup>9</sup>, P-POSSUM<sup>10,11</sup>, Charlson comorbidity index (CCI)<sup>12</sup>, AAST<sup>13</sup>, Frailty Score<sup>14</sup>, and one or multiple organ dysfunction<sup>15</sup> have been employed to predict mortality losing precision in the process and creating confusion of who is the patient unfit for surgery. The objective of the current study was to create a simpler and effective method for identifying high-risk patients isolating the discrete risk factors that predict mortality after ACC to select the patients best suited for NST.

## Methods

This was a retrospective study carried out in a single center with a dedicated surgical emergency unit, from January 2011 to December 2016, in a Metropolitan University Hospital in Barcelona, Spain. The data were reviewed and completed by 2018, and the analysis was completed in March 2020.

The study candidates comprised 963 consecutive patients with a diagnosis of acute cholecystitis.

## Inclusion and exclusion criteria

All patients were selected if they had acute cholecystitis according to the Tokyo Guidelines of 2018 (TG18) and/or received a diagnosis of ACC in the Pathology report (Table I). The study case definition was a 'Pure Acute Cholecystitis'; therefore, patients with any other concomitant diagnosis potentially influencing outcome (postoperative cholecystitis, acute cholangitis, acute pancreatitis, post-endoscopic retrograde pancreato-cholangiography, or neoplasia) were excluded from the final analysis (Fig. 1).

## Variables

Primary data were available from a prospective database maintained in File Maker v.12 (Mountainview, CA, USA), which included basic demographic data, type of interventions, sex, days of admission, and complications. Every record was completed by browsing the electronic patient record, adding laboratory and microbiology data, as well as antibiotic therapy, duration of procedure, additional procedures, and grade of acute cholecystitis according to the TG18 diagnostic criteria (Table 2).

Preoperative comorbidities were assessed using the CCI<sup>16</sup> and surgical risk by ASA classification<sup>17</sup>. The type of initial treatment was classified as surgical treatment (ST; cholecystectomy either by laparoscopy

or laparotomy) or NST, which was either percutaneous cholecystostomy (PC) or intravenous antibiotics alone.

The main outcome measure was the mortality after the diagnostic of ACC (30 days if the patient is discharged from the hospital, or at any time during the same admission if not discharged).

## Interventions

All patients received intravenous antibiotic therapy from the moment the diagnosis was formulated, according to a fixed protocol.

Ultrasound-guided cholecystostomy was performed percutaneously with an 8-Fr catheter (SKATER™, Argon Medical Devices, Rochester, NY, USA) by either transhepatic or transperitoneal insertion, at the discretion of the radiologist.

LC was performed according to the French technique using 4 trochars. The content of the gallbladder was evacuated by Veress needle puncture when necessary.

## Statistical Analysis

The normal distribution of the quantitative variables was assessed using the Kolmogorov–Smirnov test, which showed that none of the variables were normally distributed; therefore, their values were expressed as median and interquartile ranges. The Mann–Whitney U non-parametric test was used to assess the significance of differences between means.

The association between qualitative variables was assessed with the chi-square test or Fisher's exact test, as required. The increased risk of an event associated with a variable was reported as the odds ratio (OR) and 95% confidence interval (CI).

Additionally, as this was a retrospective observational study and the treatment groups were markedly asymmetric, we used the propensity score matching method<sup>20</sup> to select and compare two subgroups of patients evenly balanced by severity according to the TG18 criteria and by comorbidity according to the CCI.

A model for predicting mortality was built using binomial logistic regression with stepwise progressive conditional entry and standard baseline conditions for admission and rejection of variables with significant differences in the univariate analysis. The discrimination power of the model was assessed by receiver operating characteristic (ROC) curves and was compared with the DeLong methods.

## Results

This study was based on a group of 963 patients with acute cholecystitis, from whom 725 patients with pure ACC were selected (Fig. 1). Of these, 689 underwent initial ST and 36 (5%) underwent NST. Among ST patients, the median time from onset of symptoms to surgery was 3 days (<sup>25-75</sup>IQR: 2–5). Among the NST patients, 27 initially received only antibiotics and 9 received PC. Subsequently, 4 patients of the only

antibiotics initial treatment received PC due to unfavorable evolution, totaling 13 patients with PC, 5 of whom were finally cholecystectomized owing to a worsening clinical course. Overall, 698 urgent cholecystectomies were performed.

The median age of patients was 69 years (interquartile range, 53–80 years), and the elderly ( $\geq 80$  years) represented 26% of the total.

The prevalence of diabetes mellitus and heart failure was noteworthy, followed by kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), and acute myocardial infarction. Most of the patients were classified as ASA II (52.3%) or ASA III (32.8%) (Table 1).

Table 1

Differences between Survivors and Non-Survivors in Pre-Operative and Post-Operative variables

*(An additional file shows this in more detail: Additional File 1.)*

VARIABLE		ODDS RATIO <sup>b</sup>	95% IC	P
<b>Gender</b> (M vs. F)		0.898	0.41–1.97	0.791
<b>ASA Score<sup>c</sup></b>	II	1.03	0.99–1.08	0.666
	III	1.08	1.04–1.12	0.019
	IV	1.21	1.04–1.42	0.001
<b>Tokyo International Guidelines Severity Grading<sup>d</sup> (TGSG)</b>	II (Moderate)	3.19	0.38–26.78	0.258
	III (Severe)	10.3	1.36–77.7	0.005
<b>TGSG PAFI &lt; 300</b>		0.39	0.042–3.58	0.390
<b>TGSG Oliguria</b> (diuresis < 0.5mL/kg/h)		18.19	7.47–44.29	0.001
<b>TGSG Marked Local Inflammation</b>		2.26	0.811–6.29	0.109
<b>TGSG WBC &gt; 18,000/mm<sup>3</sup></b>		3.73	1.63–8.52	0.001
<b>TGSG PT-INR &gt; 1.5</b>		3.83	1.6–9	0.001
<b>TGSG Renal dysfunction</b> (Creatinine > 2 mg)		12.65	5.58–28.65	0.001
<b>TGSG Neurological Dysfunction</b>		1.65	0.67–4.06	0.269
<b>TGSG Cardiovascular Dysfunction</b> (Amines)		18.94	7.44–48.18	0.001
<b>TGSG Murphy's Sign</b>		0.5	0.23–1.11	0.082
<b>TGSG Palpable tender mass in RUAQ</b>		1.4	0.62–3.4	0.399
<b>TGSG Tachypnea</b> (> 20 bpm)		9.46	4–22.4	0.001
<b>TGSG Duration of complaints &gt; 72h</b>		2.15	0.96–4.82	0.056
<b>SIRS</b>		10.21	3.45–30.27	0.0001

a) N (%) or Median (IQR); b) Odds-Ratio for mortality; c) ASA score 1 has been used to calculate the Odds-Ratio for the remaining groups; ASA score V is not reported as there was only one patient in this group; d) Tokyo Guidelines Classification Year 2013<sup>33</sup> TG I was used to calculate the Odds-Ratio for the remaining groups.

PAFI: PaO<sub>2</sub>/FiO<sub>2</sub>; WBC: White Cells Blood Count; PT-INR: Prothrombin Time International Normalized Ratio; SIRS: Systemic Inflammatory Response Syndrome ≥ 2 points; RUAQ: Right Upper Abdominal Quadrant; bpm: Breaths per Minute; CPR: C-Reactive Protein. \* ≥ Clavien-Dindo IIIb.

VARIABLE		ODDS RATIO <sup>b</sup>	95% IC	P
		EXITUS <sup>a</sup>	SURVIVORS <sup>a</sup>	P
		N = 26 (3.6)	N = 699 (96.4)	
<b>Charlson Comorbidity Index</b>		3.50 (5.3)	0 (2)	0.001
<b>Age (y)</b>		83.0 (5.5)	68.0 (27)	0.001
<b>Bilirubin (mg/dL)</b>		1.64 (0.9)	0.86 (1.1)	0.002
<b>Creatinine (gr/dL)</b>		1.7 (2.2)	0.80 (0.4)	0.001
<b>Alkaline phosphatase (UI/L)</b>		142 (152)	93 (72)	0.001
<b>Gamma-glutamyl-transpherase UI/L)</b>		71 (71)	123 (239)	0.317
<b>Glutamil oxaloacetic transaminase (UI/L)</b>		57 (167)	27 (41)	0.005
<b>PT-INR</b>		1.43 (0.3)	1.19 (0.2)	0.001
<b>Lactate (gr/dL)</b>		2.20 (3)	1.5 (1.1)	0.008
<b>Temperature (°C)</b>		37.0 (1.7)	36.3 (1)	0.289
<b>WBC &gt; 1000/mm<sup>3</sup></b>		17 (13)	14 (7)	0.016
<b>Partial oxygen pressure (mmHg)</b>		98 (10)	99 (1)	0.010
<b>CRP (gr/dL)</b>		23.7 (22)	14 (26)	0.110
<b>Platelets (1000/mm<sup>3</sup>)</b>		162 (162)	210 (129)	0.210
<b>OPERATIVE</b>				
	<b>N (%)</b>	<b>OR</b>	<b>95% IC</b>	<b>P</b>
<b>Cholecystectomy as first treatment</b>	689 (95)	0.149	0.056–0.399	0.001
<b>Cholecystectomy as last treatment</b>	9 (1.2)	4.181	0.499–35.041	0.242
<b>Laparotomy as initial approach</b>	75 (10)	25.708	9.618–68.71	0.001
<b>Converted laparoscopy</b>	93 (13)	0.678	0.155–2.959	1.000
a) N (%) or Median (IQR); b) Odds-Ratio for mortality; c) ASA score 1 has been used to calculate the Odds-Ratio for the remaining groups; ASA score V is not reported as there was only one patient in this group; d) Tokyo Guidelines Classification Year 2013 <sup>33</sup> TG I was used to calculate the Odds-Ratio for the remaining groups.				
PAFI: PaO <sub>2</sub> /FiO <sub>2</sub> ; WBC: Withe Cells Blood Count; PT-INR: Prothrombin Time International Normalized Ratio; SIRS: Systemic Inflammatory Response Syndrome ≥ 2 points; RUAQ: Right Upper Abdominal Quadrant; bpm: Breaths per Minute; CPR: C-Reactive Protein. * ≥ Clavien-Dindo IIIb.				

VARIABLE		ODDS RATIO <sup>b</sup>	95% IC	P
Additional procedures	164 (23)	3.087	1.28–7.40	0.015
Cholecystostomy as first treatment	9 (1.2)	1.643	0.247–10.95	0.627
Cholecystostomy as rescue treatment	4 (0.5)	1.800	0.154–20.99	0.535
Antibiotics as primary treatment	27 (3.7)	0.609	0.091–4.056	0.627
<b>POST-OPERATIVE</b>				
		<b>EXITUS</b>	<b>SURVIVORS</b>	<b>P</b>
		<b>N = 26</b> <b>(3.6)</b>	<b>N = 699</b> <b>(96.4)</b>	
Reoperation		0 (0)	2 (0.3)	1.000
Postoperative hospital stay (d)		13 (19)	3 (5)	0.001
Postoperative complications		26 (100)	287 (41)	0.001
<b>POSTOPERATIVE COMPLICATIONS</b>	<b>No</b>		412 (59)	
<b>(CLAVIEN-DINDO)</b>	<b>I</b>		105 (15)	
	<b>II</b>		88 (12.6)	
	<b>IIIa</b>		45 (6.4)	
	<b>IIIb</b>		17 (2.4)	
	<b>IVa</b>		16 (2.3)	
	<b>IVb</b>		15 (2.1)	
	<b>Severe*</b>		48 (7)	
a) N (%) or Median (IQR); b) Odds-Ratio for mortality; c) ASA score 1 has been used to calculate the Odds-Ratio for the remaining groups; ASA score V is not reported as there was only one patient in this group; d) Tokyo Guidelines Classification Year 2013 <sup>33</sup> TG I was used to calculate the Odds-Ratio for the remaining groups.				
PAFI: PaO <sub>2</sub> /FiO <sub>2</sub> ; WBC: White Cells Blood Count; PT-INR: Prothrombin Time International Normalized Ratio; SIRS: Systemic Inflammatory Response Syndrome ≥ 2 points; RUAQ: Right Upper Abdominal Quadrant; bpm: Breaths per Minute; CPR: C-Reactive Protein. * ≥ Clavien-Dindo IIIb.				

The grade of cholecystitis according to TG18 was mild in 21%, moderate in 39%, and severe in 40% of patients. The severity factors for each group are shown in Table 1.

In 689 (95%) patients, ST was initially indicated, which was by laparotomy in 75 (11%), and laparoscopic in 623 (89%) of which 93 (13%) were converted to open cholecystectomy.

# Mortality

Overall, the mortality rate of the series was 3.6%. The mortality of each treatment type, including treatments applied as rescue, are detailed in Fig. 1.

The patients excluded from the analysis because they developed a non-pure ACC exhibited a wide variation in mortality rates (from 0–28%) depending on the precise etiology (Fig. 2)

Patients with pure AAC who died were almost 20 years older, had higher ASA scores and CCI, and had the same distribution of individual comorbidities (Table 1). Each discrete comorbidity factor of the CCI carried a disparate relative risk for mortality (OR from 1 to 12), as depicted in Fig. 3.

The mortality rate of patients with severe cholecystitis (Grade III of the TG18) was nine times greater than that of patients with mild cholecystitis. The clinical and biological variables of patients with associated ORs for mortality are detailed in Table 1.

Patients with an initial NST experienced a mortality six times higher than those with initial ST. Differences in mortality between patients initially ascribed to exclusive antibiotics or PC were not significant (15% vs. 22%;  $P = 0.62$ ). The open cholecystectomy approach was followed by a 20-fold higher mortality than the laparoscopic cholecystectomy approach (20% vs. 1%;  $P = 0.001$ ). However, the laparoscopic converted procedures had similar mortality than non-converted cholecystectomies (2.2% vs 3.1%;  $P = 1$ ). Patients who switched from NST to ST ( $n = 9$ ) had an overall mortality of 11%.

## Propensity Score Matching: Comparison among subgroups of similar severity

From the 689 patients with ST, a subgroup of 36 patients with ACC was pair-matched for identical severity (TG18) to the 36 patients with NST using the propensity score matching method. Mortality in the NST group was twice that of the ST group, although this difference was not statistically significant owing in part to the low prevalence (Table 2).

**Table 2. Differences between iST and iNST with the PSM analysis.**

VARIABLE		iST <sup>a</sup> (19)	iNST <sup>a</sup> (19)	P
<b>Complications</b>		63.2% (12)	63.2% (12)	0.631
<b>Severe complications*</b>		26.3% (5)	42.1% (8)	0.248
<b>POSTOPERATIVE COMPLICATIONS (Clavien-Dindo)</b>	<b>No</b>	36.8% (7)	36.8% (7)	
	<b>Grade I</b>	10.5% (2)	5.3% (1)	
	<b>Grade II</b>	15.8% (3)	5.3% (1)	
	<b>Grade IIIa</b>	10.5% (2)	10.5% (2)	
	<b>Grade IIIb</b>	5.3% (1)	10.5% (2)	
	<b>Grade IV</b>	10.5% (2)	5.3% (1)	
	<b>Grade V</b>	10.5% (2)	26.5% (5)	

a)% (Patients). iST: initial surgical treatment. iNST: initial Non-Surgical Treatment.

\* Clavien-Dindo Classification  $\geq$  IIIb.

## Predictive model

A multivariate model predicting mortality, the Acute Cholecystitis Mortality Estimation (ACME), retained a set of four variables: COPD (OR 4.66; 95% CI: 1.7–12.8; P = 0.001), dementia (OR 4.12; 95% CI: 1.34–12.7; P = 0.001), age  $\geq$  80 years (OR 1.12; 95% CI: 1.02–1.21; P = 0.001), and preoperative vasoactive amines (OR 9.9; 95% CI: 3.5–28.3; P = 0.001), which accurately predicted mortality in 92% of cases. The ROC curve yielded an area under the curve of 88%, well above the 68% (P = 0.003) from the TG18 classification (Fig. 4).

## Discussion

A distinctive feature of this study is the strict selection of patients. Some 238 patients were discarded to obtain a homogeneous cohort of pure AAC<sup>21,22</sup>. Many source papers used by the TG18 suffer from multiple etiologies pooling<sup>10,19–21</sup> or only exclude the chronic cholecystitis subgroup<sup>8</sup>, undoubtedly being a source of statistical noise. Some reports on ACC perform some intents of refined patient selection<sup>23</sup>, but a strict approach has not been used before, and we believe it is essential.

The current study reports on the experience meticulously registered in a surgical emergency unit where NST has not been adopted as recommended by TG18. In fact, we opted for NST in 5% of patients, whereas 40% of the series were classified as TG grade III. This attitude has been adopted by a significant number of groups with ample clinical experience in ACC management<sup>13,24–27</sup>.

In the current series, the distributions of TG18 severity classification were clearly more slanted toward severity than the majority of other series of non-selected ACC where the severe proportion oscillates between 5% and 19%<sup>3,12,27,28</sup>. This plethora of severe is mainly due to higher proportions of Kidney and Neurological dysfunction, and/or international normalized ratio  $\geq 1.5$  among our patients.

## Mortality

According to the TG18, the accepted mortality for acute cholecystitis should be  $< 1\%$ <sup>7</sup>. In the current study, the 30-day mortality was substantially higher (3.6%). Large multicenter studies reported a mortality rate from 0.6–13.5%<sup>4,10,29,30</sup>. Nevertheless, a fifth of the 26 patients who died in our series did so after the standardized 30 days to calculate postoperative mortality. The mortality rate not including these patients would drop to 2.8%. Furthermore, if chronic cholecystitis and post-endoscopic retrograde cholangiopancreatography cases were included in the total count, as is routinely done in many series, the mortality would have been wrongly reported at 1.8%, missing almost half of the deceased due to complications after ACC was diagnosed and treated. In contrast, our series did not include acalculous or postoperative cholecystitis; two etiologies with very low prevalence but higher mortality and morbidity<sup>33</sup>.

Advanced age, high ASA score, and CCI are almost universally cited as mortality risk factors, not only for ACC but for any emergency procedure<sup>12,34,35</sup>. However, not every discrete comorbidity factor of the CCI carries the same relative risk for mortality, their ORs ranging from 1 to 12, as depicted in Fig. 3. That is why we chose to “deconstruct” the CCI and calculate the contribution of each component of the specific population of ACC patients.

## Identifying the high-risk patient

Regarding reducing mortality, surgeons have been struggling to identify patients too frail and/or too severely affected, who will be better served without surgery. In this context, we label this patient as a high-risk patient. The standardization and use of therapeutic algorithms that include the preoperative assessment of surgical risk mortality rate of patients admitted with a diagnosis of acute cholecystitis is essential. Hypothetically, in some high-risk patients at admission, their general condition may be improved with medical treatment, and a risk evaluation carried out 24–48 h after admission could reassign the patient to the group of early ST.

Some authors consider high-risk patients as those with failure of at least one organ or multiple organ dysfunction<sup>36</sup>. Patients with an ASA III or IV score have an expected postoperative mortality of 5–27%, are considered high risk for cholecystectomy<sup>37</sup>, and have higher morbidity<sup>9,38</sup>. In contrast, in a prospective observational study, González-Muñoz et al. found that patients with ASA  $> II$  and only medical treatment had a mortality of 17%, whereas those operated upon early had no mortality<sup>8,11</sup>.

In the current series, nearly 40% of patients would have been labeled as high risk. However, we believe that we should not exclude them from early surgery.

Age alone appears in some studies as an independent surgical risk<sup>39</sup>. However, age by itself does not increase mortality. Decreased functional reserve capacity in addition to comorbidities, usually but not always linked to age, are the main risk factors for mortality<sup>39</sup>. Consequently, although age *per se* is not regarded as a contraindication for early cholecystectomy, it has been widely recognized that the use of frailty and surgical risk scores could contribute to achieving the best clinical judgment in elderly people.

There is no consensus on which of the already available surgical risk scores better predicts postoperative mortality in acute cholecystitis. APACHE II > 15<sup>40</sup>, CCI > 6<sup>12</sup>, and P-POSSUM > 40<sup>10,11</sup> have all been used to support ST. None of them were specifically created for ACC; therefore, none of them are particularly advantageous over the others, and none of them offer an outstanding prediction ability.

We found that the individual weight of each variable included in the CCI was quite different when studied in a cohort of ACC patients (Fig. 3).

## Acute Cholecystitis Mortality Estimation

By selecting variables with a greater impact on the univariate analysis, we devised the Acute Cholecystitis Mortality Estimation (ACME). The model retained a set of four variables which accurately predicted mortality better than the TG classification (Fig. 4). Using a similar approach, Fagenson et al. chose the modified Frailty Index to identify patients with the worst prognosis after cholecystectomy. They also opted for extracting the more significant CCI components and ended up with a very similar AUC of 83% for predicting mortality<sup>14</sup>.

## Treatment modalities

Patients with initial NST experienced a mortality six times higher than those initially selected for initial ST. Differences in mortality between patients initially ascribed to exclusive antibiotic therapy or cholecystostomy were not significant. Patients who switched from NST to ST (n = 9) had an overall mortality of 11%. Likewise, a massive observational prospective study by Endo et al., compared four strategies (antibiotic therapy, cholecystostomy either as a definitive treatment or as a bridge to surgery, and early cholecystectomy). Their results supported early cholecystectomy over any other strategy, with or without cholecystostomy<sup>41</sup>. ST is the first option in the management of ACC crystallized in the CHOCOLATE trial, which encouraged early laparoscopy cholecystectomy over cholecystostomy<sup>40</sup>.

The complexity of the course of treatment, with subgroups of NST patients requiring rescue cholecystostomy and those in turn that finally required rescue cholecystectomy is reflected in Fig. 1. In every non-randomized trial, there are patients migrating from the four initial treatment groups (to be analyzed by intention-to-treat) to treatments finally received (to be analyzed per protocol). This circumstance undoubtedly contributed to the long period of uncertainty surrounding the best therapy option for high-risk patients with ACC.

## Propensity Score Matching: Comparison among subgroups of similar severity

This technique has been used occasionally in the cholecystectomy series<sup>42,43</sup>. In the current study, when comparing high-risk subgroups with the same preoperative morbidity and ACC severity selected by PSM, the mortality was higher in the NST group than in the ST group (26.2% vs. 10.5%), probably reflecting that we reserved the NST for patients with more severe ACC.

## Limitations of the study

The retrospective nature of this study is undoubtedly its main limitation. In contrast, the limited application of NST makes this cohort valid to determine risk factors for postoperative complications but less solvent when determining the best strategy for severe ACC in the common range for a series of consecutive patients in a single center<sup>10,38</sup>.

The patients in this study had more advanced disease, the severe ACC is being overrepresented in comparison with most other series which can bias the conclusions toward a higher mortality estimation. However, we believe that this population composition makes this analysis more robust in assessing risk factors for mortality.

The follow-up was limited to 30 days after the intervention or until the patient's discharge. More extensive monitoring would likely discover a greater number of complications<sup>9</sup>. Nevertheless, we reported mortality directly related to the ACC taking place beyond the 30th day of admission, which is routinely missing from other reports circumscribed to 30-day mortality.

## Conclusion

Laparoscopic Cholecystectomy is the recommended treatment for acute calculous cholecystitis, but not all patients benefit from initial surgical treatment.

The Tokyo Guidelines classification would probably be as effective using only 2 groups: Mild (Mild and Moderate) and Severe ACC.

Not all the factors of Charlson Comorbidity Index carry the same risk of mortality in ACC. A new simplified, highly predictive model of mortality (ACME) included a different set of variables that included age  $\geq$  80 years, COPD, dementia, and administration of amines in the preoperative period.

The mortality risk ACME could promptly identify the high-risk patient with ACC and its validation could allow us to create new guidelines alternatives to TG for the treatment of ACC.

## List Of Abbreviations

ACC  
Acute Calculous Cholecystitis  
ST  
Surgical Treatment

NST  
Non-Surgical Treatment  
PC  
percutaneous Cholecystostomy  
ATB  
antibiotics  
CCI  
Charlson Comorbidity Index  
ASA  
American Society Anesthesiologist score  
TG  
Tokyo Guidelines  
OR  
odds ratio  
CI  
confidence interval  
ROC  
Receiver operating characteristic  
IQR  
interquartile range  
COPD  
chronic obstructive pulmonary disease  
AMI  
acute myocardial infarction

## **Declarations**

### **Ethics approval and consent to participate**

This study was approved by the clinical research ethical committee of the Hospital del Mar and was classified as a non-clinical trial. Approval Number: 2016/6973/I. Board Name: CEIm-PSMAR. Affiliation: Institut Hospital del Mar d'Investigacions Mèdiques. Email: [ceic-psmar@imim.es](mailto:ceic-psmar@imim.es)

### **Availability of data and materials**

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request, but the results are going to be able to consult in ClinicalTrials.gov for a year.

### **Competing Interest**

The authors declare that they have no competing interest.

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## Author's contributions

Each author of this work has contributed to the design, the acquisition, analysis, interpretation of the data and have revised the article before submitting.

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Not applicable

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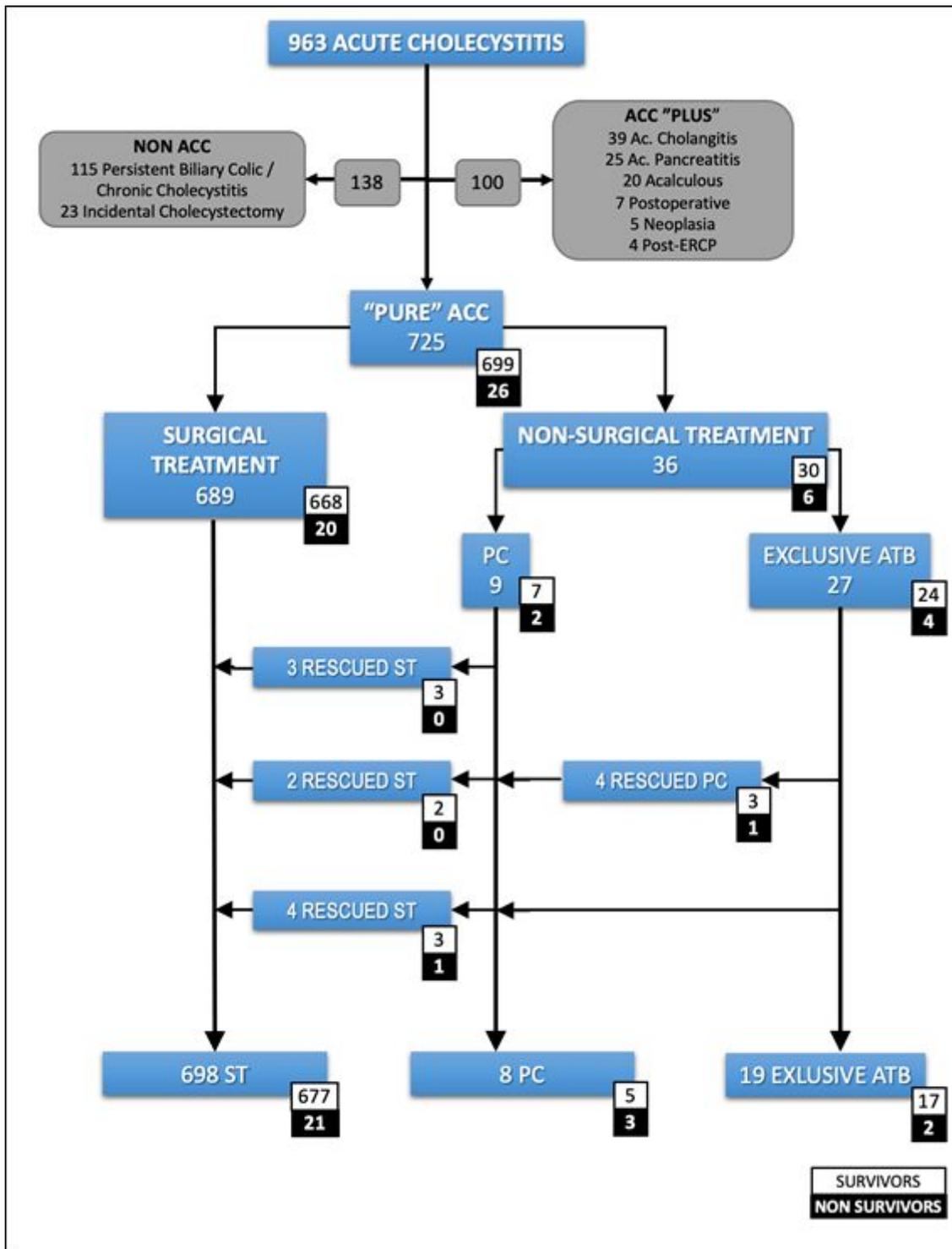
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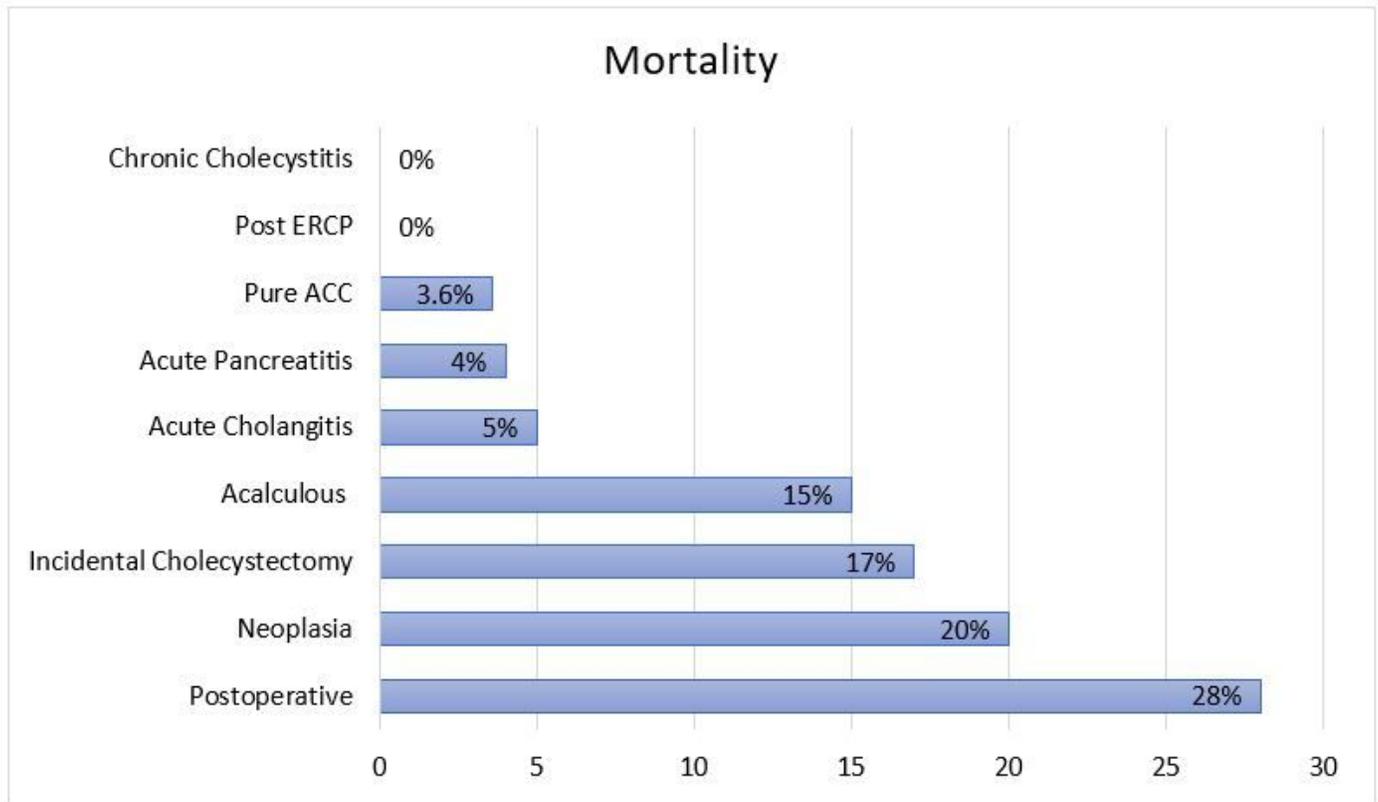
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## Figures



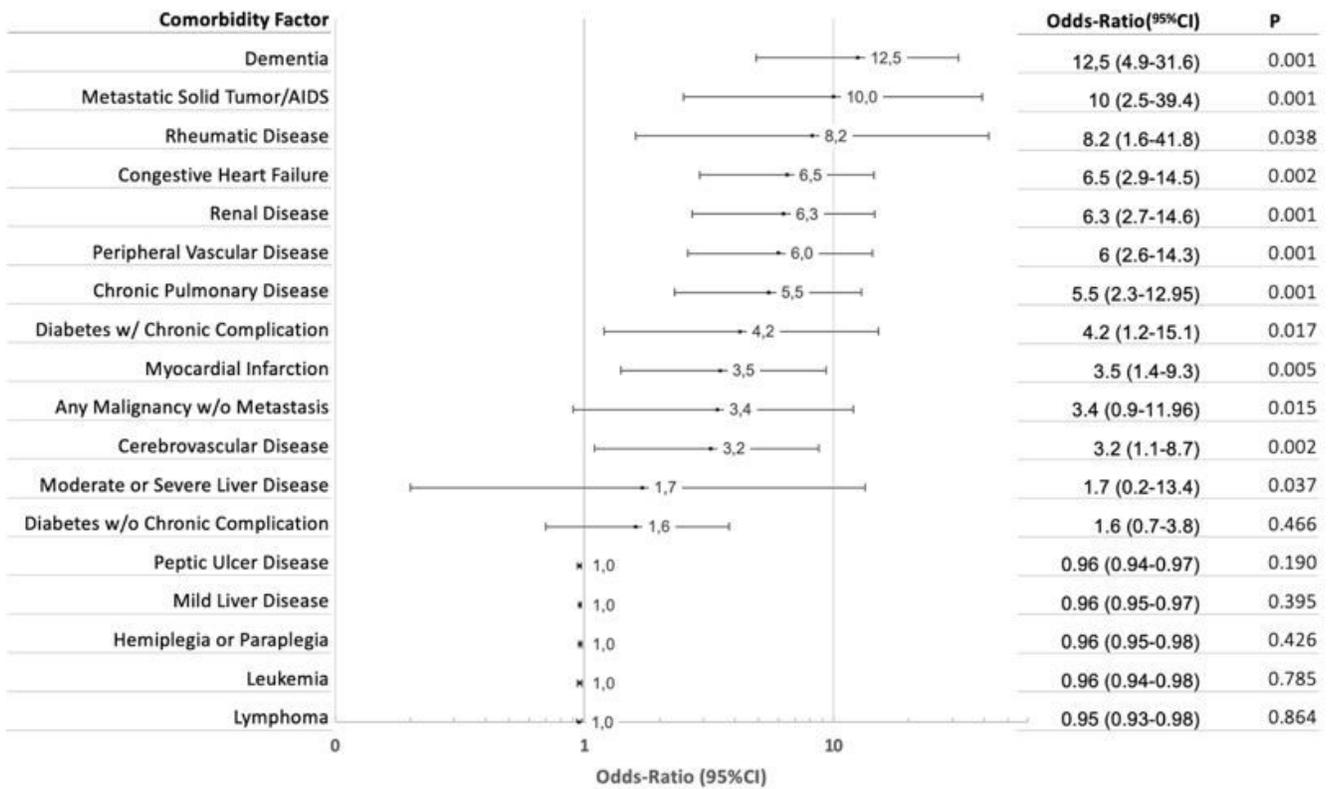
**Figure 1**

Patient selection and patient flow diagram. (An additional file shows this in more detail: Figure 1) Legend: ACC: Acute Calculous Cholecystitis. ST: Surgical Treatment. NST: Non-Surgical Treatment. PC: Percutaneous Cholecystostomy. ATB: antibiotics.



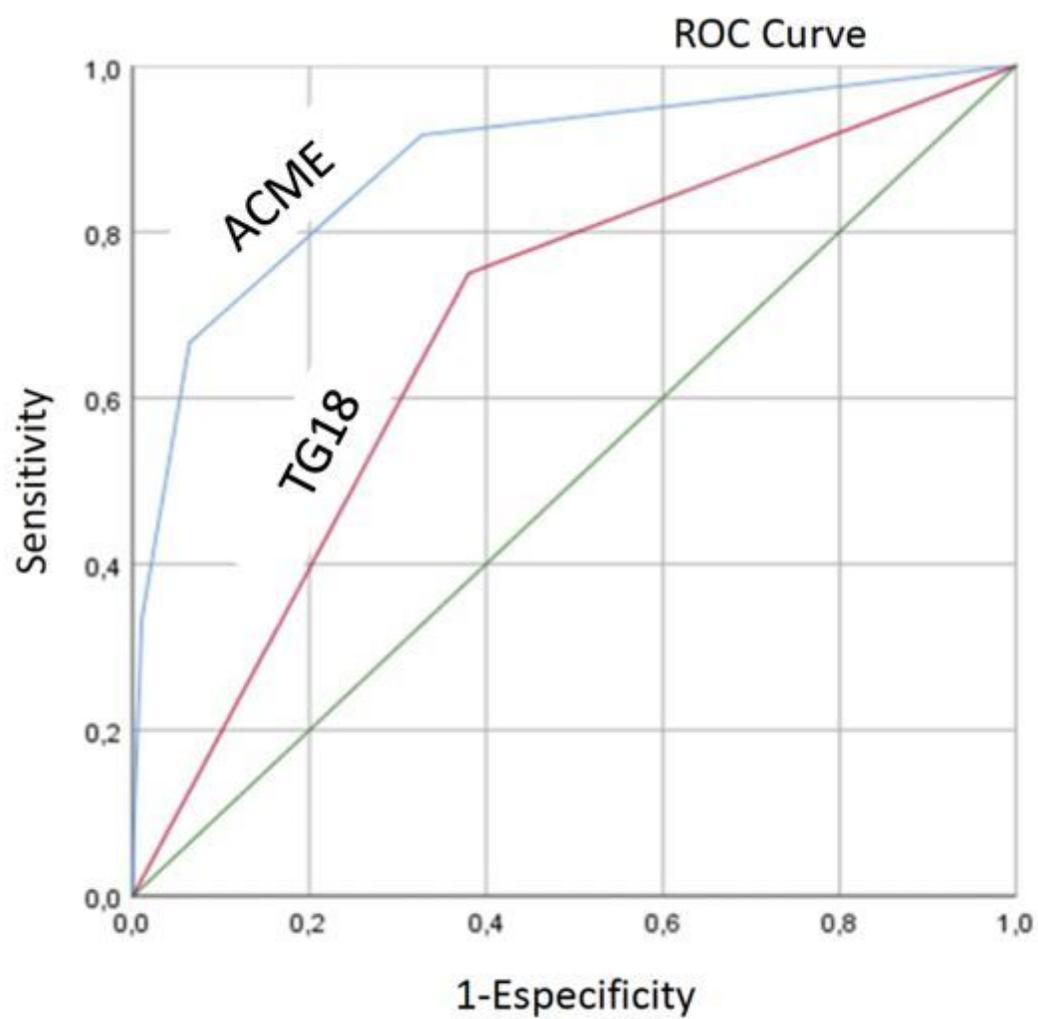
**Figure 2**

Mortality depending the precise etiology of ACC. (An additional file shows this in more detail: Figure 2)



**Figure 3**

Charlson Comorbidity Index components as risk for mortality in acute cholecystitis. (An additional file shows this in more detail: Figure 3)



**Figure 4**

ROC Curve for Mortality: ACME vs TG18. (An additional file shows this in more detail: Figure 4)