

Title:

**RISK FACTORS FOR NECROTIC CHOLECYSTITIS DURING
COVID-19 PANDEMIC: THE ChoCO WSES PROSPECTIVE
MULTICENTER OBSERVATIONAL STUDY**



Short title:

**The ChoCO (Cholecystitis under COVID-19 pandemic) WSES STUDY
PROTOCOL**

ID number: NCT04542512

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Introduction

Gangrenous cholecystitis (GC) is the most common complication of acute cholecystitis (AC), affecting around 15% (range 2-30%) of patients and it occurs as a result of ischemia with necrosis of the gallbladder walls [1].

It is related to increased mortality rate (mortality rate ranging between 15 and 50%) compared with non necrotic AC [2].

Retrospective studies which investigated risk and predictive factors related to GC showed that males, older patients with diabetes, coronary artery disease, and other co-morbidities are at risk to have GC. [1-3]

Another study identified longer delay time prior to hospital admission and low white blood cell count as independent risk factors affecting mortality and indicated the presence of diabetes mellitus, higher blood levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total bilirubin, pericholecystic fluid in abdominal ultrasonography, and conversion from laparoscopic surgery to open surgery as risk factors increasing mortality [2]

In any case, the treatment of GC is similar to that of patients with AC but in presence of GC, cholecystectomy can be difficult because of adhesions, insufficient anatomic control, complications like bleeding and injury to bile ducts.

There is a high variability in reported conversion rate to be 30% to 50% [4], down to 8.7% [5]. These results are probably due to careful preoperative selection of patients for laparoscopic cholecystectomy and to an early surgery [6].

Hunt et al [7] reported a decreased morbidity and mortality rates with the implementation of laparoscopic cholecystectomy for GC.

Onder et al [2] showed that mortality was higher in cases in which conversion to open surgery occurred.

Recently, many authors reported necrotic and perforated cholecystitis as the most common complication of COVID-19 pneumonia [8-9-10].

A recent multi-societary position paper suggested to consider percutaneous drainage of the gallbladder after the failure of conservative therapy with antibiotics but highlighted that advanced age, or other factors of higher COVID-19 risk, cannot be regarded as sufficient to indicate this alternative treatment except in real conditions of the impracticability of cholecystectomy [11].

In the lack of evidence and guidelines about the management of patient with acute cholecystitis during COVID-19 pandemic, laparoscopic cholecystectomy, at most preceded by percutaneous trans-gall bladder drainage (PTGBD) in high surgical risk patients, remains the gold standard for the treatment of acute cholecystitis on COVID-19 patients, with high morbidity rate and length of hospital stay that increases the risk of spreading the virus among health care staff and negative COVID-19 patients.



Our aim is to study all patients, Covid-19 (+) and Covid-19 (-) presenting cholecystitis, including those having GC, to improve their management.

Rationale for the trial:

Investigate the risk factors to develop necrotic cholecystitis.

To evaluate the management of acute (complicated) cholecystitis focusing on diagnosis, timing for surgical treatment and outcomes of operative or non-operative management in COVID (+) and COVID (-) patients with the aim to improve the results, reducing morbidity and mortality rates related to emergency setting and high risk patients.

Objectives:

- (1) Evaluate the prevalence of cholecystitis, in female and male patients during COVID-19 pandemic.
- (2) Evaluate the risk factors for necrosis or gangrenous cholecystitis in COVID-19 patients.
- (3) Evaluate the clinical outcomes of early (<72h from the onset of symptoms) versus delayed (>72h from the onset of symptoms) cholecystectomy, and of cholecystostomy in terms of mortality and morbidity.

Primary objectives

Our hypothesis is that COVID-19 patients should not be treated conservatively (antibiotics only/ percutaneous drainage of gallbladder) for the high risk of progressing to necrotic and then perforated cholecystitis. It was reported that COVID-19 disease predisposes to both venous and arterial thromboembolism, explained by excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation. In particular, critically ill patients with SARS-CoV-2 showed a high risk to present thromboembolic events.

To investigate risk factors and high risk patients to develop necrotic cholecystitis.

To assess the best timing for surgery in high risk patients, during COVID-19 pandemic.

Secondary objective

To assess the management of acute cholecystitis in emergency setting during COVID-19 pandemic.

Study Design:

Prospective Multicenter Observational Study.

Study population:

All patients admitted to the surgical department with clinical and radiological diagnosis of acute cholecystitis (with and without gangrenous cholecystitis).

Inclusion criteria



Patients of all age and sex admitted in emergency department for acute cholecystitis, aged ≥ 18 yo.

Exclusion criteria

Patients aged < 18 yo.

Period: 2020/10/01 to 2021/05/31

Data collection

All epidemiological, clinical and surgical data will be collected on a CFR that will be sent by mail to the participating centres.

Statistical analysis:

Prevalence study and univariate and multivariate analysis of each scheduled parameter. In the statistical analysis the investigator will differentiate data also by gender. The main aim of this study to assess all patients having cholecystitis including those having gangrenous cholecystitis. Previous WSES prospective studies on sepsis (Sartelli et al, WJES, 2019; 14: 34; Sartelli et al, 2015; 10: 61) show that this is feasible and the aim is getting exactly the numbers of these two studies. The COVID-19 patients group will be obviously smaller than the group of negative patients for two reasons:

- 1) the incidence of COVID-19 infection;
- 2) trial to treat them conservatively (antibiotics only) outside the hospitals.

Nevertheless, even if the numbers of COVID-19 patients are very small, the investigator can use non-parametric methods which work even if the groups are less than 20 patients and analyse the ranks and not the crude numbers.

Ethical Aspects

This is an observational study, it will not attempt to change or modify the clinical practice of the participating physicians. The study will meet and conform to the standards outlined in the Declaration of Helsinki and Good Epidemiological Practices. Every clinical centres attending the study is responsible for Ethics Committee approval. All surgeons involved in the patients' recruitment will be included in the research authorship.

Methods and assessments:

Every clinical centres will be identified by a number assigned before starting to enter data. In each centre, the coordinator will collect and compile data in an online case report system.

Safety Considerations

There are not safety issues. This study will be conducted under the supervision of WSES board.

Informed consent

This observational study will not attempt to change or modify the laboratory or clinical practices of the participating physicians, consequently informed consent will not be required.

Data Management and Statistical Analysis

Every local investigator is responsible for entering data on an on line case report form for every patient included in the study.

Expected Outcomes of the Study

To demonstrate the correlation between necrotic cholecystitis and predisposition to thromboembolism in COVID-19 patients.

To assess risk factors and high risk patients for necrotic cholecystitis and timing for surgery to decrease morbidity and mortality correlated with this disease.

Dissemination of Results and Publication Policy

The outcomes of this study will be analysed and published on a The World Journal of Emergency Surgery in 2021.

Duration of the Project

1 year

Budget

No budget study

Financing and Insurance

Not applicable

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