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REVIEW

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COVID-19 infection is a significant risk factor for death in patients presenting with acute cholecystitis: a secondary analysis of the ChoCO-W cohort study

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Abstract

Background During the coronavirus disease (COVID-19) pandemic, there has been a surge in cases of acute cholecystitis. The ChoCO-W global prospective study reported a higher incidence of gangrenous cholecystitis and adverse outcomes in COVID-19 patients. Through this secondary analysis of the ChoCO-W study data, we aim to identify significant risk factors for mortality in patients with acute cholecystitis during the COVID-19 pandemic, emphasizing the role of COVID-19 infection in patient outcomes and treatment efficacy."

Methods The ChoCO-W global prospective study reported data from 2546 patients collected at 218 centers from 42 countries admitted with acute cholecystitis during the COVID-19 pandemic, from October 1, 2020, to October 31, 2021. Sixty-four of them died. Nonparametric statistical univariate analysis was performed to compare patients who died and patients who survived. Significant factors were then entered into a logistic regression model to define factors predicting mortality.

Results The significant independent factors that predicted death in the logistic regression model with were COVID-19 infection ($p < 0.001$), postoperative complications ($p < 0.001$), and type (open/laparoscopic) of surgical intervention ($p = 0.003$). The odds of death increased 5 times with the COVID-19 infection, 6 times in the presence of complications, and it was reduced by 86% with adequate source control. Survivors predominantly underwent urgent laparoscopic cholecystectomy (52.3% vs. 23.4%).

Conclusions COVID-19 was an independent risk factor for death in patients with acute cholecystitis. Early laparoscopic cholecystectomy has emerged as the cornerstone of treatment for hemodynamically stable patients.

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Highlights

- Study Objective: Investigated the factors predicting mortality in patients with acute cholecystitis during the COVID-19 pandemic.
- Cohort Size: Analyzed 2,546 patients from 218 centers in 42 countries between October 2020 and October 2021.
- Key Findings:
- COVID-19 infection increased mortality risk by five times in patients with acute cholecystitis.
- Postoperative complications elevated the odds of death sixfold.
- Early laparoscopic cholecystectomy significantly reduced mortality by 86%.
- Surgical Impact: Survivors were more likely to have undergone urgent laparoscopic surgery, suggesting it as a safer intervention during the pandemic.
- Clinical Relevance: COVID-19 was confirmed as an independent predictor of death, highlighting the need for urgent intervention in stable patients with acute cholecystitis.

Keywords Acute cholecystitis, Covid-19, Sars-CoV-2, Mortality, Management, Laparoscopic cholecystectomy, Emergency

Introduction

Acute cholecystitis (AC), a common disease, has an increased incidence during the COVID-19 Pandemic [1, 2]. Two global prospective studies (CHOLECOVID and ChoCO-W) explored the effects of COVID-19 on AC using different approaches. The CHOLECOVID study [3] collected data on 9783 patients with acute cholecystitis admitted to 247 hospitals worldwide during the first wave of the COVID-19 pandemic to assess changes in the management and outcomes of the patients. The Pandemic was associated with (1) reduced availability for surgery, (2) more severe disease, and (3) increased use of conservative management. The "Risk factors for necrotic **Cho**lecystitis during the **CO**VID-19 pandemic (ChoCO) study [4, 5] enrolled 2893 patients from 42 countries (218 centers) during the second wave of the COVID-19 pandemic to compare the clinical findings and outcomes of acute cholecystitis in patients having COVID-19 infection compared with those who did not. The results showed that: (1) COVID-19 patients had significantly higher postoperative complications, longer mean hospital stay, and mortality rate compared with the non-Covid patients; (2) the incidence of gangrenous cholecystitis was doubled in COVID-19 patients with increased mortality [4, 5].

Despite the initial findings, it remains unclear whether COVID-19 is an independent risk factor for mortality or a confounding factor linked to frailty and comorbidities in those who died. This issue was highlighted following the publication of the ChoCO-W study [5].

Consequently, the aim with this secondary analysis of the ChoCO-W trial is to identify and analyze independent risk factors for mortality in patients presenting with acute cholecystitis during the COVID-19 pandemic. This analysis provides valuable insights that were not part of the primary study, focusing on specific clinical variables that could potentially impact outcomes and guide future management strategies in similar scenarios.

Materials and methods

Ethical considerations

Ethical committee approval for this ChoCO-W study was obtained from CPP Sud-Méditerranée 3, University Hospital of Nîmes-France (2021.03.05 ter _ 21.01.16.09406). The ChoCO-W global prospective study met and followed the standards outlined in the World Medical Association Declaration of Helsinki [6].

Study protocol

This ChoCO-W study was registered at ClinicalTrials.gov.(**ID: NCT04542312).** The details of the protocol have been published previously [4]. This is a global collaborative, prospective cohort study that included consecutive adult patients admitted to emergency departments with AC who were screened for SARS-CoV-2 on October 1, 2020, to April 30, 2021. The prospectively collected data were reported according to the **STROBE guidelines** [7].

Study design

This was a post-hoc analysis of the ChoCO-W study data. Data were collected prospectively during the COVID-19 Pandemic (October 2020 to 31st October 2021) about patients admitted to the emergency department with acute cholecystitis. We planned to analyse data about survivors and non-survivors patients to evaluate differences in outcomes. The clinical and biological variables of 2893 patients who were admitted with acute cholecystitis from 218 centers and 42 countries were collected. The decision for laparoscopic cholecystectomy versus conservative management was based on local hospital protocols, patient stability, and the severity of the infection.

Study population

Two thousand eighty-three patients diagnosed with AC during the study period were enrolled in the study. Patients who did not undergo a COVID-19 test or whose final in-hospital outcomes were missing were excluded from the analysis. Accordingly, 2546 patients were analyzed, of whom 64 died.

Data collection

Demographic, clinical, laboratory, radiological, surgical, microbiological, histopathological, and in-hospital outcome data were collected prospectively. The clinical severity of the disease was assessed using the qSOFA score [8], PIPAS severity score [9], WSES sepsis severity score [10], and Tokyo severity classification for acute cholecystitis [11]. COVID-19 infection was assessed at admission to the emergency department using the COVID-19 PCR swab test [12]. Data were stored in a database.

Definitions

Immunodeficiency was defined as immunosuppression induced by chronic treatment, including glucocorticoids, immunosuppressive agents or chemotherapy, immunohematological diseases, and virus-related immunosuppression, such as Human Immunodeficiency Virus (HIV).

Malignancy was defined by the presence of a neoplastic active disease.

Severe cardiovascular disease refers to a clinical history of ischemic heart disease, heart failure, and severe valvular disease according to the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Non-cardiac Surgery [13].

Diabetes mellitus refers to patients with a clinical diagnosis of diabetes documented in their medical records who are receiving pharmacological treatment for diabetes (oral hypoglycemic agents or insulin).

Severe chronic kidney disease was defined as kidney failure during preparation for or permanent renal replacement therapy.

Severe chronic obstructive pulmonary disease refers to a clinical history of severe chronic pulmonary disease, which is different from COVID-19 pneumonia.

Postoperative complications were defined as Immediate post-operative complications (within 72 h) and early postoperative complications that occurred 72 h after the surgical procedure. Complications were assessed using the Clavien-Dindo classification [14].

Adequate source control refers to an effective and timely intervention aimed at eliminating the source of infection and preventing ongoing contamination. This includes any surgical, procedural, or medical measures required to achieve these objectives [15].

Microangiopathy in COVID patients refers to the pathological condition affecting the small blood vessels (microcirculation), typically characterized by damage to the endothelial cells lining these vessels, leading to compromised blood flow, thrombosis, and tissue ischemia [16].

Adequate empirical antibiotics refer to the initial antibiotic therapy administered to a patient based on the most likely pathogens and local antibiogram data before specific culture results are available [15].

Statistical analysis

Continuous data are presented as mean (SD), ordinal data as median (IQR), and categorical data as numbers (%). Nonparametric statistical univariate analysis was used to compare those who died and those who survived. This included the Mann–Whitney U test for continuous or ordinal data and Fisher's exact test for categorical data. Variables with a p-value of less than 0.05 were then entered into a backward likelihood binary logistic regression model to define the significant independent risk factors for mortality. Statistical analysis was performed using IBM Statistical Statistics for Windows, version 28. (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was accepted as significant.

Results

Out of the 2893 patients, 301 were excluded from the analysis because of inconclusive data. Out of 2592 patients, 47 (1.8%) missed the outcome variable (alive or dead). Out of the remaining 2546 patients, 2482 (98%) survived and 64 (2.5%) died.

Those who died were assessed significantly more with CT scan 39/64 (60.9%) compared with those who survived, 816/2469 (33%) ($p<0.001$), and less ultrasound 25/64 (39.1%) compared with 1653/2469 (67%) of patients undergone US evaluation ($p<0.001$, Fisher's Exact test).

There was no statistical difference in the time between the onset of the symptoms till the admission at the Emergency Department between those who died and those who survived (mean (SD) days 5.17 (9.17) compared with 3.66 (7.47), $p=0.011$, Mann Whitney test) neither in the delay to treatment (mean (SD) hours 37.1 (58.6) compared with 49.84 (109.6), $p=0.22$, Mann Whitney test), respectively.

There was a statistically significant difference in the thickness of the wall of the gallbladder between those who died and those who survived (mean (SD) mm 6.24 (2.59) compared with 5.44 (3.42 mm), $p=0.007$, Mann Whitney test).

Acalculous cholecystitis constituted 3.9% (114/2857) of the patients while 96.1% had gallstones. The diagnosis of acalculous cholecystitis was similar between those who died and those who survived 6.3% compared with 3.8% ($p = 0.3$, Fisher's Exact test).

Table 1 compares the demographics of patients who died and those who survived. Patients who died were significantly older (mean difference of 13 years, $p < 0.001$), had significantly more COVID-19 infection ($p < 0.001$), had significantly more immunodeficiency ($p = 0.02$), malignancy ($p = 0.04$), severe cardiovascular disease ($p < 0.001$), diabetes ($p < 0.001$), severe chronic kidney disease ($p = 0.003$), severe chronic obstructive pulmonary disease ($p < 0.001$), ARDS ($p < 0.001$), PIPAS score ($p < 0.001$), and WSES score ($p < 0.001$).

Table 2 compares the clinical findings of the dead and surviving groups. Those who died had significantly more severe clinical findings (< 0.001 in all variables), including more diffuse abdominal pain, higher temperature, increased heart rate, lower systolic blood pressure despite the increased age, tachypnea, reduced oxygen saturation, and more severe acute cholecystitis (56.7% compared with 9.8%).

Table 3 compares the laboratory investigation results of the 2 groups of patients. Patients who died had significantly higher serum lactate (< 0.001) and C-reactive protein (< 0.001) levels.

The Activated Partial Thromboplastin Time (aPTT) was longer in patients who died than in those who survived ($p < 0.007$).

Table 4 compares the surgical management of the patients who died and those who survived. The surgical management was significantly different ($p < 0.001$). Those who died had a significantly higher urgent open cholecystectomy (31.3% compared with 8.1%) and cholecystostomy/percutaneous drainage (25% compared with 7.3%), while those who survived had significantly earlier (in the first 3 days) laparoscopic cholecystectomy (52.3%

Table 1 Demographic data about the patients treated for acute cholecystitis during the COVID-19 pandemic comparing those who survived (n = 2482) and those who died (n = 64)

Variable	Alive N = 2482	Dead N = 64	*p*
Age	61.84 (17.2)	74.6 (14.8)	< **0.001**
Gender			0.21
Male	1294 (52.2%)	39 (60.9%)	
Female	1184 (47.8%)	25 (39.1%)	
Setting of acquisition			0.004
Community based	2098 (89.4%)	44 (75.9%)	
Hospital based	248 (10.6%)	14 (24.1%)	
Delay in ED visit (from the onset of symptoms to ED admission)	Mean 3.66 (days) SD 7.4	Mean 5.17 (days) SD 9.1	
COVID-19 infection	155 (6.2%)	24 (37.5%)	**< 0.001**
Immunodeficiency	103 (4.2%)	7 (10.9%)	0.02
Malignancy	167 (6.8%)	9 (14.1%)	0.04
Severe cardiovascular disease	510 (20.6%)	33 (51.6%)	**< 0.001**
Diabetes			**< 0.001**
No diabetes	1910 (77%)	37 (57.8%)	
Prediabetes	45 (1.8%)	2 (3.1%)	
History of diabetes	134 (5.4%)	3 (4.7%)	
Diabetes without complications	318 (12.8%)	14 (21.9%)	
Diabetes with complication	74 (3%)	8 (12.5%)	
Severe CKD	90 (3.6%)	8 (12.5%)	0.003
Severe COPD	159 (6.4%)	16 (25%)	**< 0.001**
ARDS	35 (1.4%)	16 (25.4%)	**< 0.001**
PIPAS score	0 (0–1)	2.5 (1–4)	**< 0.001**
WSES sepsis severity score	1 (0–3)	5 (2–8)	**< 0.001**

CKD chronic kidney disease; *COPD* Chronic Obstructive Pulmonary Disease, *ARDS* Acute Respiratory distress syndrome; *PIPAS* core: Physiological Indicators for Prognosis in Abdominal Sepsis score [https://wjes.biomedcentral.com/articles/10.1186/s13017-019-0253-2/tables/5]; WSES sepsis severity score: World Society of Emergency Surgery sepsis severity score [https://wjes.biomedcentral.com/articles/10.1186/s13017-015-0055-0/tables/5], ED: Emergency Department

Table 2 Clinical findings of the patients treated for acute cholecystitis during the COVID-19 pandemic comparing those who survived (n = 2482) and those who died (n = 64)

Variable	Alive, n = 2482	Dead, n = 64	*p*
Abdominal findings			**< 0.001**
No pain	53 (2.1%)	1 (1.6%)	
Localized pain	1545 (62.5%)	23 (35.9%)	
Localized pain and rigidity	568 (23%)	12 (18.8%)	
Diffuse abdominal pain	307 (12.4%)	28 (43.8%)	
Radiological assessment (US/CT)	1653/2469 (66% US)	25/64 (39% US	**< 0.001**
	816/2469 (33% CT)	39/64 (60% CT)	
Core temperature (°C)	37.16 (4.55)	37.31 (0.98)	**< 0.001**
Heart rate (bpm)	84.9 (27.5)	94.8 (19.2)	**< 0.001**
Systolic blood pressure (mmHg)	131.4 (23.1)	115.4 (31.2)	**< 0.001**
Respiratory rate (breaths/min)	17.4 (4.9)	20.6 (4.4)	**< 0.001**
SpO2 (%)	94.5 (13.8)	92.8 (5.6)	**< 0.001**
Acalcular cholecystitis	94/2465 (3.8%)	4/63 (6.3%)	
Severity of acute cholecystitis			**< 0.001**
Mild	1141 (47.9%)	4 (6.7%)	
Moderate	1008 (42.3%)	22 (36.7%)	
Severe	233 (9.8%)	34 (56.7%)	
Gallbladder wall thickness (mm)	5.4 (SD 3.4)	6.24 (SD 2.5)	**< 0.001**

US ultrasound exam; *CT* abdominal computed tomography

Table 3 Laboratory tests of the patients treated for acute cholecystitis during the COVID-19 pandemic comparing those who survived (n = 2482) and those who died (n = 64)

Variable	Alive, n = 2482	Dead, n = 64	*p*
WBC count/ mm3	7540 (18,430)	8156 (8266)	0.06
C Reactive Protein mg/L	80.66 (111.8)	152 (149.3)	**< 0.001**
AST U/L value	90.2 (171)	104.2 (147.3)	0.004
ALT U/Lvalue	95.7 (150)	88 (107.2)	0.22
Total bilirubin mg/dL	5.38 (26)	9.21 (20.1)	0.08
Lactate mmol/L	15.82 (76.4)	19.5 (70.7)	**< 0.001**
Prothombinetime time sec	18.1 (20.5)	16.4 (12.2)	0.013
APTT sec	26.6 (11.4)	31.19 (14.5)	0.007

WBC white blood cell count; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase; *APTT* activated partial thromboplastin time

compared with 23.4%). Those who survived had significantly higher rates of adequate source control ($p < 0.001$), adequate empirical antibiotics ($p < 0.001$), and fewer complications ($p < 0.001$). Those who died had significantly more complications ($p < 0.0001$).

Table 5 shows the details of these complications.

Table 6 shows the results of the binary backward likelihood logistic regression model for predicting mortality. The model was highly significant ($p < 0.001$) having a Nagelkerke R Square of 0.3, indicating that these factors explained more than 30% of the variation in the model. The significant factors that increased death were COVID-19 infection ($p < 0.001$), complications ($p < 0.001$), and type of surgical intervention ($p = 0.003$). The odds of death increased 5 times with the COVID-19 infection, 6 times in the presence of complications, and reduced by 86% with adequate source control. The odds of death from cholecystostomy/percutaneous drainage decreased by 64% compared with urgent open cholecystectomy.

Discussion

The current ChoCO-W study post-hoc analysis showed that the independent significant risk factors for death of patients admitted with AC during the COVID-19 Pandemic were COVID-19 infection, inadequate source control, post-operative complications, and lack of urgent laparoscopic cholecystectomy. The odds of death increased 5 times with the COVID-19 infection, 6 times in the presence of complications, and reduced by 86% with adequate source control. Survivors predominantly underwent urgent laparoscopic cholecystectomy (52.3% vs. 23.4%).

The ChoCO-W observational study [5], which was carried out when Delta SARS-CoV-2, with higher transmission, decreased vaccine effectiveness, and higher secondary attacks was present, showed that the incidence of gangrenous cholecystitis was doubled in COVID-19 patients compared with that

Table 4 Surgical management of the patients treated for acute cholecystitis during the COVID-19 pandemic comparing those who survived (n = 2482) and those who died (n = 64);

Variable	Alive, n = 2482	Dead, n = 64	*p*
Surgical treatment			**< 0.001**
Conservative	335 (13.6%)	9 (14.1%)	
Conservative and delayed Laparoscopic Cholecystectomy	290 (11.7%)	4 (6.3%)	
ERCP ± sphincterotomy and delayed laparoscopic cholecystectomy	173 (7%)	0 (0%)	
Cholecystostomy/percutaneous drainage	180 (7.3%)	15 (25%)	
Urgent laparoscopic cholecystectomy	1293 (52.1%)	20 (23.4%)	
Urgent open cholecystectomy	200 (8.1%)	64 (31.3%)	
Delay in treatment (hours)	49.84 (SD 109.6)	37.10 (SD 58.6)	
Adequate source control	2285 (95.1%)	54 (87.1%)	**< 0.001**
Adequate empirical antibiotics	2396 (98%)	169 (95.5%)	**< 0.001**
Postoperative Complications	302 (12.2%)	37 (59.7%)	**< 0.001**
Hospital stay (days)	6.8 (6.2)	13.91 (14.04)	**< 0.001**

ERCP endoscopic retrograde cholangiopancreatography

Table 5 Details of the complications of the studied population

Complication	Survived n = 2482	%	Death n = 64	%	Total n = 2546	%
Localized biliary peritonitis	57	2.3	3	4.7	60	2.4
Pulmonary infection	44	1.8	6	9.4	50	2
Surgical site infection	41	1.7	1	1.6	42	1.6
Bleeding	34	1.4	3	4.7	37	1.5
Biliary fistula	21	0.8	0	0	21	0.8
Intra-abdominal abscess	15	0.6	1	1.6	16	0.6
Sepsis	8	0.3	8	12.5	16	0.6
Hyperbilirubinemia	13	0.5	0	0	13	0.5
Diffuse biliary peritonitis	8	0.3	4	6.3	12	0.5
Hypertension	10	0.4	1	1.6	11	0.4
Cardiovascular complications	8	0.3	2	3.1	10	0.4
Fever	8	0.3	1	1.6	9	0.4
Common bile duct injury	7	0.3	1	1.6	8	0.3
Bowel injury	5	0.2	2	3.1	7	0.3
Ileus	6	0.2	1	1.6	7	0.3
Pancreatitis	5	0.2	0	0	5	0.2
Post-operative bile collection	3	0.1	1	1.6	4	0.2
Renal impairement	4	0.2	0	0	4	0.2
Delirium	4	0.2	0	0	4	0.2
Pulmonary embolism	1	0	0	0	1	0.04
Clostridial difficile Colitis	1	0	0	0	1	0.04

non-COVID-19 patients (40.7% compared with 22.3%; $p < 0.0001$) and that the gallbladder wall was significantly thicker in with COVID-19 patients (Fig. 1). Acute gangrenous cholecystitis is related to COVID-induced microangiopathy and hypercoagulability, causing hemorrhagic infarction and increased gallbladder wall [16–18]. The Cholecovid study [3] showed a decreased number of cholecystectomies during the pandemic compared with the pre-pandemic period without a difference in mortality after cholecystectomy.

This post-hoc analysis highlights a statistically significant difference in gallbladder wall thickness between patients who died and those who survived [6.24 mm (SD 2.59) vs. 5.44 mm (SD 3.42); $p = 0.007$, Mann–Whitney test]. Gallbladder wall thickness is a well-recognized marker of disease severity in acute

Table 6 Backward logistic regression model predicting death of patients having acute cholecystitis during the COVID-19 Pandemic

Selected Variables	Coefficient	SE	Wald	P value	OR	LL CI 95%	UL 95% CI
COVID-19 Disease	1.65	0.33	24.67	< 0.001	5.21	2.72	9.99
Malignancy	0.75	0.46	2.99	0.08	2.12	0.9	4.98
PIPAS severity score	0.02	0.01	3.69	0.06	1.03	1	1.05
Treatment			18.08	0.003			
Conservative treatment	– 0.93	0.69	1.81	0.18	0.39	0.10	1.53
Conservative treatment and delayed LC	– 17.39	3099.5	0	0.99			0
ERCP ± sphincterotomy and delayed LC	0.46	0.54	0.72	0.40	1.58	0.55	4.555
*Cholecystostomy/ percutaneous drainage of gallbladder	– 1.01	0.51	3.96	0.047	0.36	0.135	0.985
Urgent LC	0.31	0.54	0.33	0.57	1.364	0.474	3.925
Adequate source control	– 1.96	0.38	27.38	< 0.001	0.14	0.07	0.29
Postoperative Complications	1.85	0.32	33.68	< 0.001	6.34	3.40	11.82
Constant	– 2.54	0.50	25.67	< 0.001	0.079		

LC Laparoscopic Cholecystectomy; *ERCP* endoscopic retrograde cholangiopancreatography; *PIPAS score* Physiological Indicators for Prognosis in Abdominal Sepsis score [https://wjes.biomedcentral.com/articles/10.1186/s13017-019-0253-2/tables/5]

*Compared with urgent open cholecystectomy

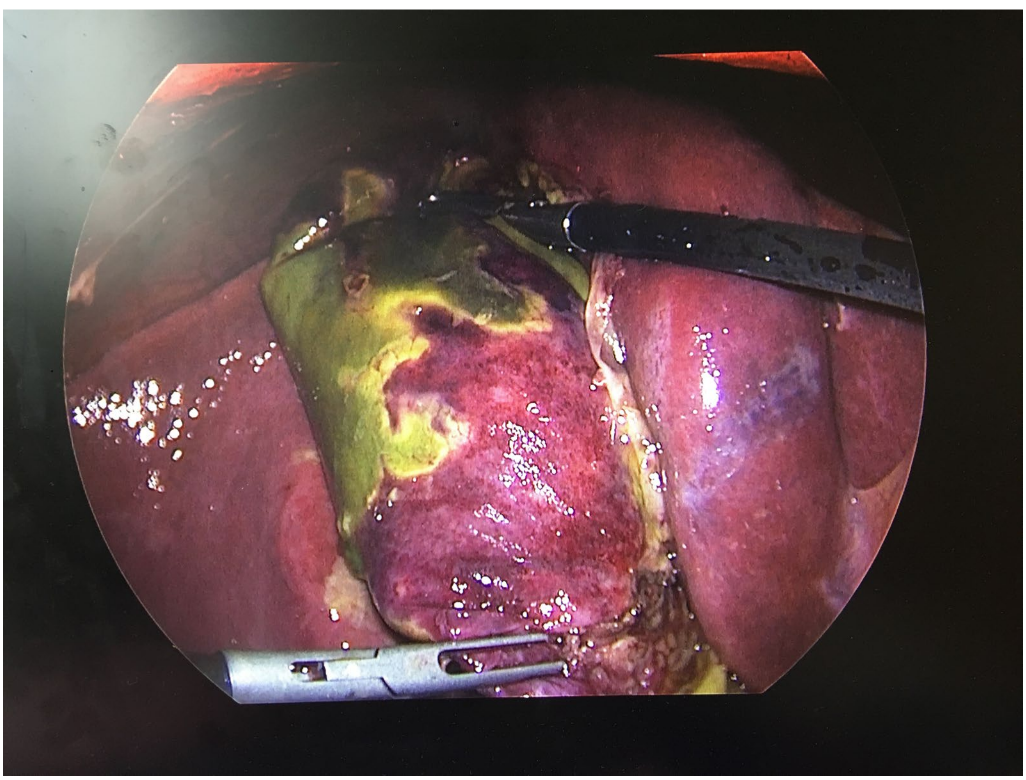

Fig. 1 Gangrenous cholecystitis

cholecystitis and was strongly associated with worse outcomes and increased mortality in this study. These findings emphasize the need for early recognition of high-risk patients with thickened gallbladder walls, particularly in the context of COVID-19, to optimize clinical management and improve outcomes.

Furthermore, the ChoCO-W post-hoc analysis showed that patients admitted with AC who died had the following features: (1) they had significantly more severe clinical findings, (2) they were older, and (3) they underwent more open cholecystectomy and cholecystostomy/percutaneous drainage than those in the survival group. In comparison, the group of survivors had more early laparoscopic cholecystectomy (52.3% compared with 23.4% in non-survivors), higher adequate source control, adequate empirical antibiotics, and fewer complications.

In our study, the Covid infection was found to be an independent risk factor for death. This finding was supported by an Italian cohort study in which COVID-19 was the main factor associated with complications and death [19]. Furthermore, although age was significantly higher in those who died in the univariate analysis, in the current study, age was not an independent risk factor in the logistic regression model, indicating that it may be correlated with other significant factors, such as PIPAS score and malignancy. A previous retrospective study showed that elderly patients (>65 years old) had significantly higher rates of acute [17.9% vs. 58.8%; $p=0.001$] and gangrenous cholecystitis [0 vs. 7; $p=0.013$] during the COVID-19 Pandemic [1].

In the early Covid pandemic, surgeons initially tried to manage patients admitted with AC conservatively, as strongly recommended by several international surgical organizations [20–22], because of the risk of in-hospital spread of Covid infection due to smoking and artificial pneumoperitoneum during the laparoscopic approach, and as a response to the limited hospital resources. In the current study, urgent LC resulted in better survival. The WSES Expert Panel recommended that early laparoscopic cholecystectomy was the gold standard for managing acute cholecystitis, even during the COVID-19 Pandemic in hemodynamically stable patients, despite the risk of infection [16, 23–25].

Patients who died had a higher rate of cholecystostomy/percutaneous gallbladder drainage. Percutaneous drainage of the gallbladder was largely adopted during the first period of the COVID-19 Pandemic to avoid surgery. Barabino et al. performed percutaneous cholecystostomy (PC) in 7 cases among 37 patients (19.4%) who had acute cholecystitis. The success rate of PC was 87.5%, and the mean postprocedural hospitalization length of stay was 9 days [26]. The Tokyo Guidelines [27] suggest the use of percutaneous transhepatic gallbladder drainage (PTGBD) as a safe alternative to early cholecystectomy for acute cholecystitis, especially in surgically high-risk patients, in high-volume institutes by skilled endoscopists. The WSES Guidelines [23] recommend performing gallbladder drainage in patients with acute calculous cholecystitis who are not suitable for surgery, as it converts a septic patient with ACC into a non-septic patient. Nassar et al. [28] showed that early laparoscopic cholecystectomy may be a preferred treatment option over PTGBD in AC. However, patient- and disease-specific factors should be considered in decision-making to avoid poor outcomes in early laparoscopic cholecystectomy. Cirocchi et al. [29] reported that PTGBD is inferior in the treatment of acute cholecystitis in high-risk patients and that early laparoscopic cholecystectomy should be considered as the treatment of choice, even in very high-risk patients.

In our study, patients who survived had significantly higher rates of adequate source control ($p<0.001$) and adequate empirical antibiotics ($p<0.001$). Source control pillars in managing septic patients include (1) antibiotic/anti-infective therapy, (2) adequate surgery, (3) minimally invasive nonsurgical/radiological procedures, and (4) proper hemodynamic support and restoration [30].

This study has several strengths. The large sample size across 42 countries and 218 centers provided strong statistical power and generalizability to the findings. The ChoCO study's large prospectively collected dataset enabled a comprehensive analysis of the outcomes associated with different management strategies adopted during the pandemic. Using strict non-parametric statistical methods and the advantages of binary logistic regression to compare survivors and non-survivors provides insights into the factors influencing mortality. Additionally, the focus on urgent laparoscopic cholecystectomy and its association with improved outcomes underscores a clear and actionable recommendation for clinical practice, particularly in the context of a pandemic.

Limitations of the study

The current study had several limitations. *First*, the retrospective nature of the post hoc analysis may introduce bias related to data collection and reporting accuracy. The lack of outcome data for 47 patients (1.8%), although small, may potentially affect the overall findings because missing data are usually more in those who die. *Second*, there are multiple confounding factors that may explain the increased death in COVID-19 patients, such as delay in surgery, lack of operating theatres and ICU beds, delayed presentation due to the lockdown, and recommendations for conservative management to reduce COVID-19 infection [16–18]. The low R square of the logistic regression model of 0.3 indicates that the model explains only 30% of the variation, and the increased death can be due to uncaptured factors. This is not related to the number of entered independent factors in the logistic regression model. It is advised to have ten deaths for each variable included in the logistic regression model [31]. We had only six variables and 64 deaths in the model (Table 6) which fullfills this criteria. Nevertheless, other statisticians [32] thought that "the rule of ten" can even be relaxed. This post-hoc analysis, although providing very useful information, has the natural nature of missing important factors. Moreover, the study did not account for all potentially confounding variables, such as variations in healthcare systems, resource availability, and differences in COVID-19 treatment protocols across the included centers. The emphasis on early laparoscopic cholecystectomy, while supported by the data, may not be feasible in all settings, particularly in those with limited surgical capacity or during peak pandemic periods when healthcare resources are stretched thin.

Furthermore, since this is a post-hoc analysis, some interesting variables were not been collected like, using a drain, the number, size, and location of the gallstones, COVID-19 vaccination status, the experience of the operating surgeon, the ethical or regional factors. We could not use the Clavien-Dindo classification to predict mortality because class V is death, and we cannot use death to predict death. The evidence does not support the use of drains [33, 34]. Moreover, during the early phase of the COVID pandemic, the use of drains was strongly discouraged due to the high risk of in-hospital contamination. Vaccination was not globally available at the start of this clinical study.

Despite these limitation, and despite the numerous studies that have examined the relationship between COVID-19 and acute cholecystitis, we think that our study is unique for these reasons: (1) it was useful in defining other factors predicting mortality besides COVID-19 infection, (2) its large global prospective cohort of patients studied during the Pandemic increases its generalizability, (3) we have studied only the management of acute cholecystitis per se during this unique infectious Pandemic. By doing so, we hope to enhance the understanding and improve treatment protocols for surgeons facing similar surgical challenges in future pandemics.

Conclusions

COVID-19 is an independent risk factor for death in patients with acute cholecystitis. Early laparoscopic cholecystectomy has emerged as the cornerstone of treatment in hemodynamically stable patients, even during the pandemic.

Abbreviations

AC	Acute cholecystitis
GC	Gangrenous cholecystitis
WSES	World Society of Emergency Surgery
PCR	Polymerase chain reaction
ChoCO	Cholecystitis during the COVID-19 pandemic

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Author contributions
BDS conceived, designed, and coordinated the project and collected the data. FAZ performed statistical analysis of data. BDS and FAZ wrote the manuscript. All authors have read, commented, and suggested modifications. BDS revised the manuscript based on expert opinions. FC read and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

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