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## Surgical treatment of acute cholecystitis in patients with confirmed COVID-19: Ten case reports and review of literature

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### Abstract

#### BACKGROUND

Research concerning postoperative outcomes of confirmed coronavirus disease 2019 (COVID-19) patients revealed unfavorable postoperative results with increased morbidity, pulmonary complications and mortality. Case reports have suggested that COVID-19 is associated with more aggressive presentation of acute cholecystitis. The aim of the present study is to describe the perioperative assessment and postoperative outcomes of ten patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with concomitant acute cholecystitis who underwent cholecystectomy.

#### CASE SUMMARY

We report a total of 10 SARS-CoV-2 positive patients with concomitant acute cholecystitis that underwent cholecystectomy. Six patients were males, the mean age was 47.1 years. Nine patients had moderate acute cholecystitis, and one patient had severe acute cholecystitis. All patients were treated with urgent/early laparoscopic cholecystectomy. Regarding the Parkland grading scale, two patients received a Parkland grade of 3, two patients received a Parkland grade of 4, and six patients received a Parkland grade of 5. Eight patients required a bail-out procedure. Four patients developed biliary leakage and required endoscopic retrograde cholangiopancreatography with biliary sphincterotomy. After surgery, five patients developed acute respiratory distress syndrome (ARDS) and required intensive care unit (ICU) admission. One patient died after cholecystectomy due to ARDS complications. The mean total length of stay (LOS) was 18.2 d. The histopathology demonstrated transmural necrosis ( $n = 5$ ), vessel obliteration with ischemia ( $n = 3$ ), perforation ( $n = 3$ ), and acute peritonitis ( $n = 10$ ).

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## CONCLUSION

COVID-19 patients with acute cholecystitis had difficult cholecystectomies, high rates of ICU admission, and a prolonged LOS.

**Key Words:** COVID-19; SARS-CoV-2; Cholecystectomy in COVID-19; Acute cholecystitis in COVID-19; Case report

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**Core Tip:** Several studies have described multiple gastrointestinal complications in patients with coronavirus disease 2019, including advanced stages of cholecystitis. We found in the present study that patients with confirmed severe acute respiratory syndrome coronavirus 2 infections who presented with acute cholecystitis, tended to have a higher grade on the Parkland grading scale (including gallbladder perforation, empyema and total wall necrosis), had difficult laparoscopic cholecystectomies with an increased need for a bail-out procedure, had high rates of intensive care unit admission, and had a prolonged length of hospital stay.

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## INTRODUCTION

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China, in December 2019, causing a new disease named coronavirus disease 2019 (COVID-19)[1].

Research concerning postoperative outcomes of confirmed COVID-19 patients revealed unfavorable postoperative results with increased morbidity, pulmonary complications and mortality[2-5].

Several studies have described gastrointestinal symptoms in patients with COVID-19, with nearly 25% of patients referring abdominal pain[6]. Association with other gastrointestinal complications for example, liver injury and late cholestasis, have been reported[7]. Concerning the gallbladder, some studies have described the presence of acute ischemic gangrenous cholecystitis, with or without perforation, and with or without associated cholelithiasis[8-30]. Studies have suggested that COVID-19 is associated with more aggressive presentation of acute cholecystitis[15,19,24,27,28].

The guidelines for the treatment of acute cholecystitis before the pandemic recommended early laparoscopic cholecystectomy (Lap-C) for patients with mild acute cholecystitis as the treatment of choice[31-33]. For patients with moderate acute cholecystitis the treatment of choice is urgent/early Lap-C when advanced laparoscopic techniques are available. The indications for urgent Lap-C in confirmed COVID-19 patients should not differ from those without COVID-19[19].

Since the beginning of the pandemic in 2020, several surgical societies have published their recommendations to treat acute cholecystitis[2,34]. The firsts recommendations were to avoid surgeries and to adopt a non-operative management when possible[28,35]. The finding of virus particles in the peritoneal fluid and the idea that pneumoperitoneum could allow the transmission of virus led many surgical societies to publish recommendations for gastrointestinal laparoscopic surgery[34,36-38]. More recent recommendations sustain that laparoscopy is not more likely to spread the COVID-19 infection than open surgery, and minimally invasive surgery provides better outcomes than laparotomy[2].

Since acute cholecystitis represents a very frequent cause of hospital admission worldwide[39], it is important to know the perioperative outcomes of patients with confirmed COVID-19 and cholecystitis, also it is important to know what to expect during surgeries.



The aim of the present study was to describe the perioperative assessment and postoperative outcomes of patients with confirmed SARS-CoV-2 infection with concomitant acute cholecystitis who underwent urgent cholecystectomy.

## CASE PRESENTATION

### **Chief complaints**

We included symptomatic and asymptomatic SARS-CoV-2 positive patients (asymptomatic carriers) who required urgent/early cholecystectomy. During the pandemic all the patients that were admitted to our hospital were screened for SARS-CoV-2 infection.

Regarding the chief complaints, patients presented with the characteristic right upper quadrant pain related to acute cholecystitis.

### **History of present illness**

All patients had concomitant acute cholecystitis with SARS-CoV-2 infection. We included patients with the SARS-CoV-2 infection confirmed either by reverse-transcriptase polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab or a rapid antigenic test. Several variables were recorded including demographic parameters and preoperative quick Sequential Organ Failure Assessment (qSOFA) score[40]. Data is shown in [Table 1](#).

### **History of past illness**

Of the ten patients, four had history of past illness. The most frequent comorbidity was hypertension ( $n = 4$ ). The complete list of comorbidities is presented in [Table 1](#).

### **Personal and family history**

The personal and family history was noncontributory.

### **Physical examination**

On physical examinations patients had right upper quadrant pain ( $n = 10$ ), right upper quadrant mass ( $n = 6$ ), and positive Murphy's sign ( $n = 10$ ).

Demographic data included age (years), gender, body mass index in  $\text{kg}/\text{m}^2$ , comorbidities, smoking status, American Society of Anesthesiology classification. The preoperative qSOFA score was calculated and we divided the patients in high risk ( $> 2$  point) or not high risk patients (0-1 points).

### **Laboratory examinations**

Preoperative laboratory examinations are shown in [Table 1](#). Of relevance, the mean preoperative C-reactive protein level was 20.1  $\text{mg}/\text{dL}$ , the mean total bilirubin was 1.29  $\text{mg}/\text{dL}$ , and the mean ferritin level was 565  $\text{ng}/\text{mL}$ .

### **Imaging examinations**

All patients underwent chest computed tomography (CT) scans prior to surgery. Also, all patients underwent gallbladder ultrasound. We diagnosed acute cholecystitis according to Tokyo Guidelines (TG18) ultrasound criteria (thickened gallbladder wall, enlarged gallbladder, pericholecystic fluid collection)[32,41].

## FINAL DIAGNOSIS

Regarding the timing of COVID-19 diagnosis, nine patients were diagnosed preoperatively and one was diagnosed postoperatively. Of the 10 patients, four were asymptomatic SARS-CoV-2 carriers. The rest of patients ( $n = 6$ ) presented with symptomatic disease and preoperative CT scans with COVID-19 pneumonia (bilateral ground-glass opacities with consolidation).

We diagnosed and graded the severity of acute cholecystitis according to the 2018 TG18[32,41]. All patients were diagnosed with definite acute cholecystitis according to the TG18. Regarding the severity assessment, nine patients had grade II (moderate) acute cholecystitis and one patient had grade III (severe) acute cholecystitis. Additionally, one patient was diagnosed with grade II acute cholangitis, and the other patient had concomitant mild acute pancreatitis. Both patients were operated after

**Table 1** Demographic information of confirmed coronavirus disease 2019 patients with acute cholecystitis (*n* = 10) (mean ± SD)

Classification	<i>n</i> = 10
Sex, <i>n</i> (%)	
Female	4
Male	6
Age (yr), mean (range)	47.1 (20-74)
BMI (kg/m <sup>2</sup> ), mean (range)	28.4 (20-43)
Current Smokers, <i>n</i> (%)	3
ASA classification, <i>n</i> (%)	
I	2
II	4
III	4
Comorbidities, <i>n</i> (%)	
Diabetes	2
Hypertension	4
CRD	2
Lupus	1
No	6
Preoperative qSOFA score, <i>n</i> (%)	
Not high risk (0-1)	4
High risk (> 2)	6
COVID-19 symptoms	
Yes	6
No	4
Preoperative studies	
Hemoglobin (g/dL)	12.8 (2.8)
Platelets (n × 10 <sup>3</sup> /μL)	284 (128.7)
Leucocytes (n/μL)	11.95 (5.6)
CRP (mg/dL)	20.1 (12.5)
Total Bilirubin (mg/dL)	1.29 (1.7)
Gamma-glutamyl transferase (IU/L)	163.1 (198.1)
Alanine aminotransferase (IU/L)	86.1 (102.8)
Aspartate aminotransferase (IU/L)	59.9 (46.7)
Alkaline fosfatase (IU/L)	199 (189.7)
LDH (IU/L)	215.1 (63.3)
Albumin (g/dL)	4.17 (0.4)
Ferritin (ng/mL)	565 (304.5)
Creatinine (md/dL)	1.02 (0.5)

BMI: Body mass index; CRD: Chronic renal disease; qSOFA: Quick Sequential Organ Failure Assessment; CRP: C-reactive protein.

resolution of cholangitis and pancreatitis, respectively.

## TREATMENT

All surgeries were performed at a COVID-19 dedicated operating theater and all the medical staff were equipped with personal protective equipment. Laparoscopic cholecystectomies were performed with a 3 or 4 trocar technique depending the case, using a 12-mm umbilical trocar (optical), a 12-mm trocar in the sub-xiphoid area, and a 5-mm in the right flank. We performed diagnostic laparoscopy and we graded the intraoperative findings according with the Parkland scale. After that, bile and purulent collections were drained and intraabdominal adhesions were taken down. The decision to perform a bail-out procedure was done when the critical view of safety was difficult to achieve. In our hospital, we employ the reconstituting subtotal cholecystectomy or the open conversion as bailout procedures. The reconstituting subtotal cholecystectomy consisted in making an incision in the gallbladder, aspirating the contents including the stones, removing the peritonealized portion of the gallbladder, except the lowest portion (infundibulum and Hartmann's pouch), and partially excising the posterior wall adherent to the liver. After that, the lowest part of the gallbladder is closed with sutures obliterating the cystic duct, leaving a closed gallbladder remnant[15,41].

During laparoscopy we filtered the pneumoperitoneum through filters able to remove most viral particles as suggested by several authors[2,42,43].

Two patients required preoperative endoscopic retrograde cholangiopancreatography (ERCP). One patient had cholestasis and a type I Mirizzi syndrome was found at ERCP. The other patient had grade II acute cholangitis and required early endoscopic treatment (ERCP biliary drainage).

All patients were treated with urgent/early Lap-C. Eight surgeries were completed *via* laparoscopy and two patients required conversion to open cholecystectomy due to operative difficulty.

Regarding the Parkland grading scale, all patients were found to have severe inflammation (grades 3-5): Two patients had pericholecystic fluid, adhesions to the gallbladder body, hyperemia and distended gallbladder (Parkland 3); One patient had adhesions obscuring the majority of the gallbladder and one patient had Mirizzi syndrome (Parkland 4); And six patients had Parkland 5 (six patients with complete necrosis of the gallbladder body infundibulum and cystic duct, three of them with gallbladder perforation) see [Figure 1](#). Six cases were treated with subtotal reconstituting cholecystectomy, because a critical view of safety could not be achieved.

The mean estimated blood loss (EBL) was 258 mL, the mean operative time was 133.5 min, and eight patients required intraabdominal closed drainage.

## OUTCOME AND FOLLOW-UP

Operative outcomes included modality of cholecystectomy (laparoscopic, open or converted), EBL in mL, operative time in minutes, and requirement of intraabdominal drainage. We graded the intraoperative findings according with the Parkland grading scale for cholecystitis[42]. Preoperative or postoperative need for ERCP and findings were registered.

Postoperative complications were classified and presented according with the Clavien-Dindo classification. The need for intensive care unit (ICU), vasopressors and invasive mechanical ventilation were recorded. The hospital length of stay (LOS) in days was registered.

Five patients developed biliary leak after subtotal cholecystectomy. Of these patients, two had low-output leak, while three patients had high-output biliary leak. Patients with low-output leaks were treated with closed suction drainage alone, while patients with high-output leaks needed ERCP with biliary sphincterotomy and biliary stent placement. The complete list of postoperative complications classified according to Clavien-Dindo is shown in [Table 2](#).

After surgery five patients required ICU admission, and one patient was admitted preoperatively and remained in the ICU after surgery. The five patients were on invasive mechanical ventilation and vasopressor therapy. These patients developed acute respiratory distress syndrome (ARDS) related to SARS-CoV-2. One patient died after cholecystectomy and due to ARDS complications.

Considering the complete cohort of patients, the mean total LOS was 18.2 d.

The histopathological diagnosis was performed using hematoxylin-eosin (H&E) stained slides ([Table 3](#)). As demonstrated in [Figure 2](#), H&E slides displayed the inflammatory infiltration ( $n = 10$ ), with transmural necrosis ( $n = 5$ ), hemorrhagic infarction ( $n$

**Table 2** Description of postoperative complications according with the Clavien-Dindo classification (*n* = 10)

Grade	
Grade I	
Hydroelectrolytic imbalance	8
Antiemetics	3
Antipyretic (for fever $\geq 38.3$ )	4
Grade II	
Blood transfusions	3
Total parenteral nutrition	3
Postoperative Ileus	1
Pneumonia	6
Delirium	4
Biliar leak	5
Wound infection	3
Grade IIIb	
Evisceration	1
Bleeding	1
ERCP	3
Grade IVa	
Respiratory	5
Renal	3
Hepatic	2
Cardiovascular	5
Dialysis	2
Grade IVb	
Multiorgan failure	5
Grade V	
Death of a patient	1

ERCP: Endoscopic retrograde cholangiopancreatography.

= 2), mucosal ulcerations (*n* = 1), vessel obliteration with ischemia (*n* = 3), gallbladder wall perforation (*n* = 3), and acute peritonitis (*n* = 10).

## DISCUSSION

We found in the present study that patients with confirmed SARS-CoV-2 infections with concomitant acute cholecystitis tended to have high grades on the Parkland grading scale (including gallbladder perforation, empyema and total wall necrosis), difficult Lap-C with an increased need for a bail-out procedure (open conversion or subtotal cholecystectomy), high ICU admission rates, high rates of postoperative biliary leaks that required ERCP (with biliary stent placement), and prolonged length of hospital stay.

Several studies have described the presentation of acute cholecystitis concomitant with a SARS-CoV-2 infection. A literature review of the research concerning COVID-19 and acute cholecystitis is summarized in [Table 4](#). We have noticed that the majority of studies that have been published during the pandemic are case reports and letters to the editor (see [Table 4](#)). The first case report of histopathological findings of an acute ischemic gangrenous cholecystitis as a late complication in a COVID-19 patient was

**Table 3 Perioperative outcomes of coronavirus disease 2019 patients with acute cholecystitis**

Perioperative outcomes	
ERCP result	
Preop Mirizzi syndrome 1	1
Preop Cholangitis + CBD stones	1
Postoperative Biliary leak	3
ERCP Biliary stent	3
Modality of cholecystectomy, <i>n</i> (%)	
Laparoscopic	8
Lap converted to open	2
Type of cholecystectomy	
Total	4
Sub-total	6
Parkland grading scale, <i>n</i> (%)	
3	2
4	2
5	6
Estimated blood loss (mL), mean (range)	258 (30-500)
Operative time (min), mean (range)	133.5 (70-190)
Intraabdominal drainage, <i>n</i> (%)	8
ICU admission, <i>n</i> (%)	
Yes, Preoperative	1
Yes, Postoperative	4
ICU treatment, <i>n</i> (%)	
Invasive ventilation	5
Vasopressors	5
Hospital LOS (days), mean (range)	18.2 (3-50)
Histopathology results, <i>n</i> (%)	
Ischemic/segmental necrosis	3
Transmural necrosis	5
Perforated	3
Mucosal ulcerations	1
Acute peritonitis	10
GB empyema	4
Hemorrhagic	2

ERCP: Endoscopic retrograde cholangiopancreatography; CBD: Common bile duct; Lap: Laparoscopic; ICU: Intensive care unit; LOS: Length of stay; GB: Gallbladder.

published by Bruni *et al*[21]. Since then, the description of gangrenous cholecystitis in patients with COVID-19 has been found in at least six other studies[15,18,19,24,27,28]. In our series, 3 patients had wall ischemia and segmental necrosis, and 5 patients had complete transmural necrosis. Of note, some of these case reports outlined the presence of gangrenous cholecystitis but without cholelithiasis (acalculous)[18,19,27]. In our series, only one patient presented with acalculous cholecystitis, and the rest of the patients had cholelithiasis. This could represent a different physiopathological pathway that should be further investigated. Nevertheless, patients with both

Table 4 Review of previous studies reporting coronavirus disease 2019 and acute cholecystitis treatment approach

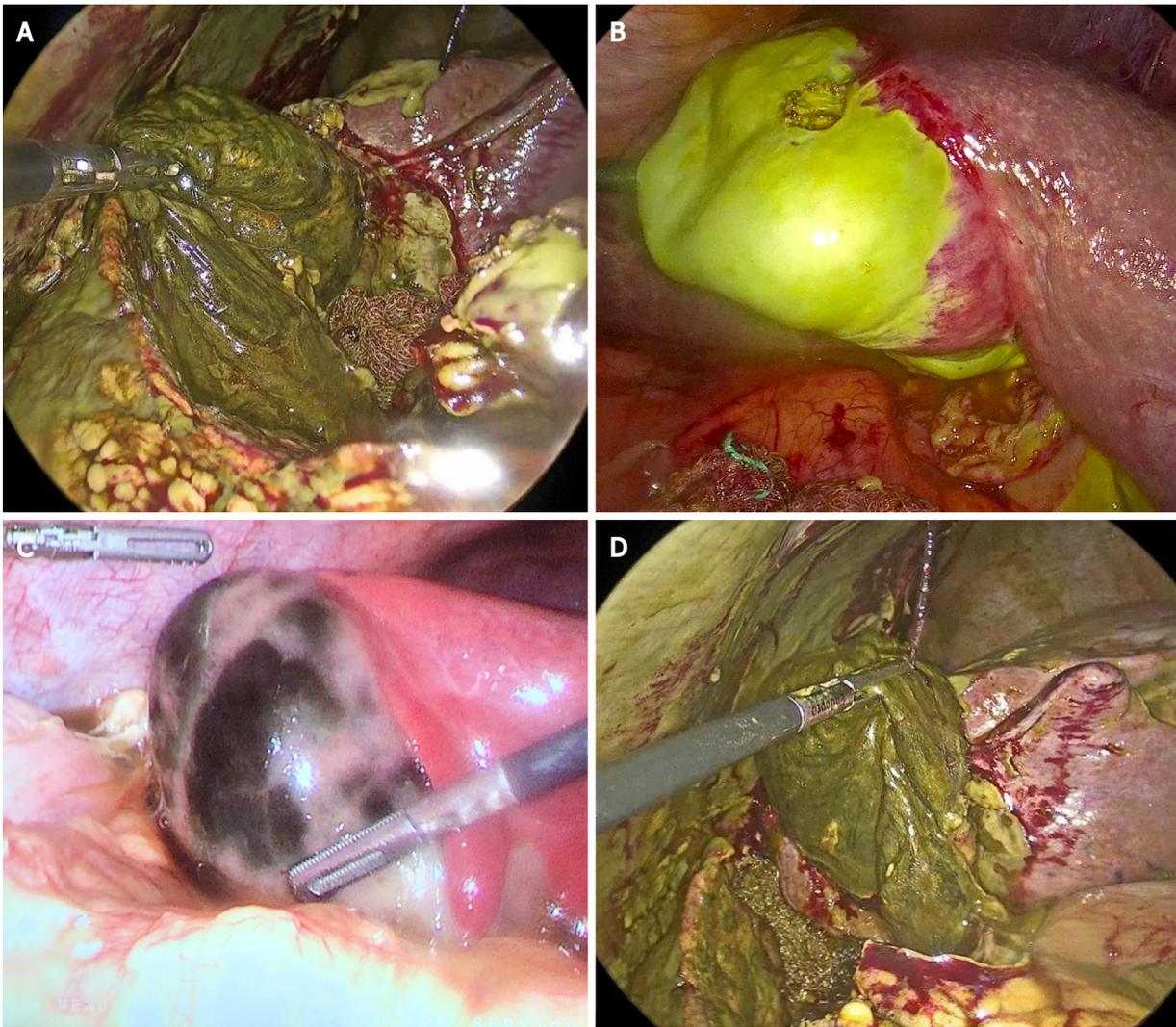
Ref.	Study design	Country	Sample size, n (%)	Age/sex (F:M)	COVID-19 diagnosis	Tokyo class	Treatment	Morbidity/PO complications	ICU, n (%)	LOS (d)	Mortality	Findings/histopathology
Çakır and Kabuli[8], 2021	Retrospective study	Turkey	18	M: 14 (78%); F: 4 (22%); Age: 73.3 (67-81)	RT-PCR	GI: 3 (16.7%); GII: 9 (50%); GIII: 6 (33.3%)	THGD	No complications	3 (16.6%)	16 (3-32)	3 (16.6%)	NR
Barabino <i>et al</i> [9], 2021	Retrospective study	Italy	37: 36 non-COVID; 1 COVID	64 (38-94); Male: 21 (56.7%); Female 16 (43.3%)	RT-PCR	GI: 13 (35.1%); GII: 15 (40.5%); GIII: 8 (21.6%); COVID: GII	Antibiotic only 11 (29.7%); THGD 8 (21.6%); L 18 (48.7%); COVID: THGD 1	Emergency LC 1; Bleeding 1; Cholangitis 2	2	9 (2-12)	-	-
Martínez Caballero <i>et al</i> [10], 2021	Multicentre-combined (retrospective-prospective) cohort study	Spain	42	Age: COVID: 83 (65-87); COVID: 28 M/14 F	Clinics 10.9%; Imaging test 11.3%; RT-PCR 12.5%	GI: 112 (43.6%); GII: 121 (47.1%); GIII: 24 (9.3%)	Antibiotic therapy 47.9%; Surgical treatment 31.5%; THGD 20.6%. COVID: 93.3% non surgical treatment	Gallbladder perforation 8.4%; Biliar setic shock 8.4%	23%	Non-COVID: 5 d (3-8); COVID: 11.0 d (7.5-27.5)	Non-COVID: 3.25%; COVID: 11.9%	-
Çiyiltepe <i>et al</i> [11], 2021	Retrospective study	Turkey	65 non-COVID; 7 COVID	Age: 57.3; F: 40 (55.6)/M: 32 (44.4)		GI: 35 (48.6%); GII: 37 (51.3%)	11 THGD	-	-	9.2 (6-20)	-	-
Somuncu <i>et al</i> [12], 2021	Retrospective study	Turkey	4 COVID; 32 non-COVID	Age: 53 (26-78); M: 17/F: 19	Thorax CT	-	Antibiotic therapy 14; THGD 14 (39%); LC 8	-	-	7 (2-20)	1: Cardiac arrest	-
Puig <i>et al</i> [13], 2021	Case report	Spain	2	M: 65/57	RT-PCR	GIII: 2	Percutaneous cholecystostomy 2	Pulmonary tromboemboly 2	2	34	0	-
Abaleka <i>et al</i> [14], 2021	Case report	United States	1	Age: 76; F	RT-PCR	Grade II	Antibiotics	-	-	-	-	-
Lovece <i>et al</i> [15], 2020	Case report	Italy	1	Age: 42/M	RT-PCR	Grade III	LC	Gallbladder perforation	-	-	-	-
Famularo and Spada [16], 2021	Letter/case report	Italy	1	90/M	RT-PCR +	NR	THGD	No	No	26	No	NR
Vaishnav and Patel [17], 2021	Observational/prospective	India	16	50/F: 7 (29%); M: 17 (70%)	RT-PCR + CT +	GIII	LC	No	NR	4.9	NR	NR
Alhassan <i>et al</i> [18], 2020	Case report	Qatar	1	40/F	Confirmed 14 d prior	AAC	Antibiotics	No	Yes (1, 100%)	NR	No	-

Asti <i>et al</i> [19], 2020	Letter/case report	Italy	3	40-86/F: 1 (33%); M: 2 (66%)	Confirmed	AAC	LC	NR	NR	NR	NR	Acalculous, gangrene
Balaphas <i>et al</i> [20], 2020	Letter/case report	Switzerland	2	83-84/F: 1 (50%); M: 1 (50%)	RT-PCR +	AAC	LC/Antibiotics	NR	Yes (1, 50%)	NR	Yes (1, 50%)	qRT-PCR revealed the presence of SARS-CoV-2 in the gallbladder wall
Bruni <i>et al</i> [21], 2020	Case report	Italy	1	59/M	RT-PCR +	AC/GIII	OC	NR	Yes (1, 100%)	44	No	Gangrenous, Hemorrhagic, vasculitis
Cirillo <i>et al</i> [22], 2020	Letter/case report	Italy	1	79/M	Confirmed	AAC	Cholecystectomy	No	NR	NR	No	Perforated acalculous cholecystitis
Giulio <i>et al</i> [23], 2020	Letter/case report	Italy	1	45/F	RT-PCR +	AC/GI	LC	No	NR	30	No	NR
Gupta <i>et al</i> [24], 2020	Retrospective original article	India	5	53.2/NR	Confirmed	AC	OC	Bile leak	NR	4-9	No	Acute on chronic calculous cholecystitis, gangrenous acalculous cholecystitis
Kabir <i>et al</i> [25], 2020	Letter/case report	Singapore	1	Middle-aged/M	RT-PCR +	Gangrenous cholecystitis	Subtotal reconstituting OC	NR	NR	NR	NR	NR
Lisotti <i>et al</i> [26], 2020	Case report	Italy	1	80/F	CT suspicious	AC/GII	EUS-GBD	No	No	1	NR	NR
Mattone <i>et al</i> [27], 2020	Case report	Italy	1	66/M	RT-PCR +	AAC	Initially THGDLC	No	Yes	NR	No	Gangrenous gallbladder
F Narvaez <i>et al</i> [28], 2020	Brief report/review	United States	1	NR/F	Confirmed	AC	LC	No	No	NR	No	Near-gangrenous gallbladder
Safari <i>et al</i> [29], 2020	Case report	Iran	1	75/F	RT-PCR +CT +	AC/GII	LC	NR	Yes (1, 100%)	9	Yes	NR
Ying <i>et al</i> [30], 2020	Case report	China	1	68/F	RT-PCR +	AC/GII	THGD	No	No	25	No	NR

COVID-19: Coronavirus disease 2019; LOS: Length of stay; RT-PCR: Real-time reverse-transcriptase polymerase-chain reaction; NR: Non-reported; AC: Acute cholecystitis; AAC: Acute acalculous cholecystitis; LC: Laparoscopic Cholecystectomy; OC: Open Cholecystectomy, GI: Tokyo Class Grade I; GII: Tokyo Class Grade II; GIII: Tokyo Class Grade III; qRT-PCR: Quantitative reverse transcriptase PCR; THGD: Trans-Hepatic Gallbladder Drainage; EUS-GBD: Endoscopic ultrasound-guided gallbladder drainage; F: Female; M: Male; ICU: Intensive care unit.

etiologies required cholecystectomy.

An editorial by Cirillo *et al*[22], reported the finding of acalculous hemorrhagic cholecystitis in a patient with a SARS-CoV-2 infection who needed emergent cholecystectomy. In our histopathological analysis we found that 2 patients had hemorrhagic changes in the gallbladder wall after surgery. Our report differs from the report of Cirillo *et al*[22], in the fact that they preoperatively diagnosed the hemorrhage by CT scan with active contrast extravasation around and inside a

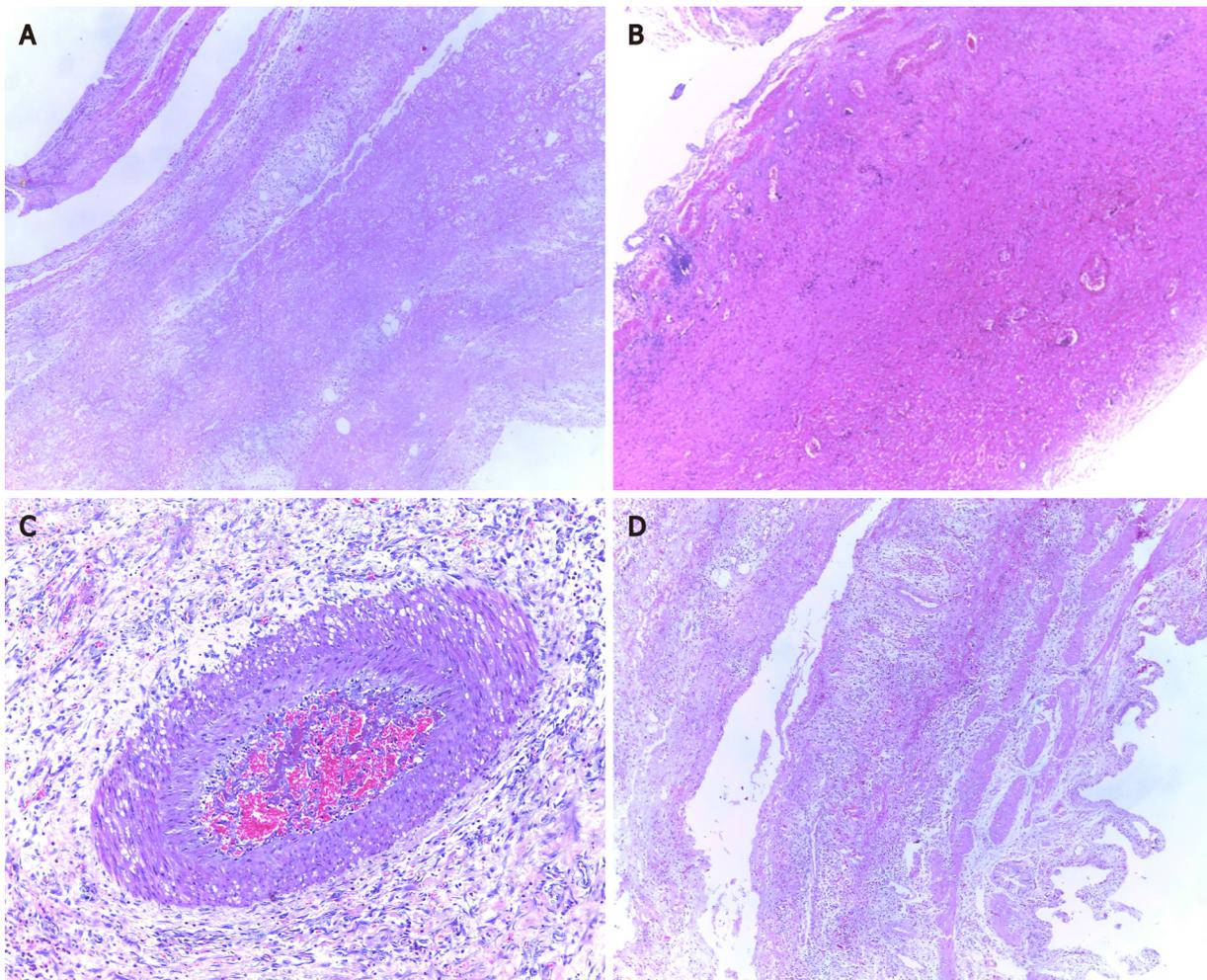


**Figure 1** Intraoperative findings of confirmed coronavirus disease 2019 patients with acute cholecystitis. A: Gangrenous and perforated; B: Fundus and body wall necrosis; C: Wall necrosis; D: Gangrene extended to the infundibulum and cystic duct.

perforated gallbladder. The presence of hemorrhage from an inflamed gallbladder is rare and larger studies are needed to confirm an association with SARS-CoV-2 infection.

Considering the potential association of SARS-CoV-2 with gallbladder disease, several hypothesis have been formulated. One hypothesis is that the systemic inflammation, the immune system changes induced by SARS-CoV-2, and the immunotherapy employed to treat it, may contribute to the late onset of cholecystitis by pro-inflammatory pathways[15]. Also, the findings of small-vessel thrombosis and gallbladder wall ischemia suggested a correlation with the coagulopathy and pro-thrombotic state induced by this coronavirus[21,44]. Furthermore, it has been suggested that due to the expression of angiotensin-converting enzyme 2 receptor in gallbladder epithelial cells, SARS-CoV-2 could target that cells[45]. Taking into account these inflammatory changes, we found on the histopathological examination of our patients, acute peritonitis, acute inflammatory infiltrates, as well as ischemic and necrosis associated with small vessel thrombi, and hemorrhagic changes in the gallbladder wall of our patients.

Regarding the treatment of acute cholecystitis, some authors reported the treatment with antibiotics[46], others reported percutaneous cholecystostomy[16,26], and others published their outcomes after laparoscopic or open cholecystectomy[46,47] (Table 4). The relevance of our study is that we described the outcomes of 10 patients with positive COVID-19 tests who required urgent cholecystectomy. Urgent/early cholecystectomies were performed due to gallbladder perforation ( $n = 3$ ) and gangrenous cholecystitis ( $n = 8$ ), where medical treatment with antibiotics only or cholecystostomy were considered insufficient treatments[19,32,41].



**Figure 2 Histopathological findings (hematoxylin and eosin staining).** A: Total transmural necrosis; B: Gallbladder wall hemorrhage; C: Arterial thrombosis; D: Inflammatory infiltrate.

Concerning the intraoperative findings, we found that patients were operated on at a very advanced stage of acute cholecystitis with severe inflammation (a Parkland score  $> 3$ ); thus, the critical view of safety was very difficult to achieve. The majority of our patients required a bail-out procedure for a safe cholecystectomy. As mentioned in the results section, 2 underwent conversion to laparotomy and 6 required sub-total reconstituting cholecystectomy. Of note, 3 of the 6 patients who needed sub-total cholecystectomy required ERCP due to biliary leak. Leaks developed in patients with complete gangrenous cholecystitis that extended to the infundibulum and to the cystic duct. Therefore, it is important to consider that in patients with suspected gallbladder necrosis, ischemia could extend to the cystic duct, thereby increasing the risk of postoperative biliary leakage or fistula. In our series, patients who develop postoperative bile leakage were treated with ERCP. Endoscopic management of biliary leaks (sphincterotomy with or without biliary stent) is associated with more than 90% of biliary leak healing or closure[48]. ERCP is currently considered the first-line treatment option for biliary leaks, specially cystic stump leaks[48]. Surgeons should be aware that when treating patients with difficult cholecystectomies, the goals are to resolve the septic process and to prevent secondary damage. As reported in previous COVID-19 cases[19,21,24], as well as in our series, operated patients during this pandemic tended to have severe inflammation of the gallbladder thus increasing the risks of postoperative complications including bile duct injury. As suggested by international guidelines[41], choosing a bail-out procedure (subtotal cholecystectomy or open conversion) based on intraoperative findings is recommended to avoid a secondary damage. Both bail-out procedures have been reported to reduce bile duct injury and overall postoperative complications, although it has been recognized that laparoscopic subtotal cholecystectomy is associated with increased rates of postoperative bile leakage in comparison with open conversion[41,49].

There are some limitations to our study that need to be mentioned. The most important limitation is that this was a single-center study with a small sample, which predisposes the study to all the biases inherent to the design (selection, information and confusion biases). Further prospective and multi-center studies should be performed and published, in order to better understand the effects of COVID-19 on acute cholecystitis. However, despite these limitations we consider that the results of this study could help us to describe some of the implications of SARS-CoV-2 infections in patients who require urgent/early Lap-C.

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## CONCLUSION

In conclusion, we found in the present study that patients with confirmed SARS-CoV-2 infections who presented with acute cholecystitis, tended to have a higher grade on the Parkland grading scale (including gallbladder perforation, empyema and total wall necrosis), had difficult laparoscopic cholecystectomies with an increased need for a bail-out procedure, had high rates of ICU admission, and had a prolonged length of hospital stay. As suggested by our case series and previously published literature, we advise to surgeons performing cholecystectomy in confirmed SARS-CoV-2 patients to be prepared for a difficult surgery and to consider a bail-out procedure to prevent secondary damage.

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